AWARD NUMBER: W81XWH-22-2-0016

TITLE: 2021 Prostate Cancer Clinical Consortium Clinical Research Site: University of Washington

PRINCIPAL INVESTIGATOR: Heather Cheng, MD, PhD

CONTRACTING ORGANIZATION: University of Washington, Seattle, WA

REPORT DATE: Oct 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE
Oct 2023

2. REPORT TYPE
Annual

3. DATES COVERED
30Sep2022-29Sep2023

4. TITLE AND SUBTITLE

2021 Prostate Cancer Clinical Consortium Clinical Research Site:
University of Washington

5a. CONTRACT NUMBER
W81XWH-22-2-0016

5b. GRANT NUMBER
NA

5c. PROGRAM ELEMENT NUMBER
NA

6. AUTHOR(S)
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5d. PROJECT NUMBER
NA

5e. TASK NUMBER
NA

5f. WORK UNIT NUMBER
NA

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Washington
4333 Brooklyn Ave NE
Seattle, WA 98195-0001

8. PERFORMING ORGANIZATION REPORT NUMBER

NA

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

NA

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

NA

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Purpose: Participate as an active and productive member of the Prostate Cancer Clinical Trial Consortium (PCCTC) throughout the funding period.

Scope: This report summarizes total site activities for the University of Washington (UWash) for the funding period 30Sep2022-29Sep2023.

Major Progress: UWash was the lead/co-lead site on 15 trials in which we participated during this funding period.

Results: UWash accrued 120 patients to PCCTC trials, proposed 4 LOIs, and accrued 15 patients (12.5%) from a DAP.

Significance: The PCCTC provides a mechanism for participation in early clinical development of novel agents and rapid testing of these agents for the treatment of prostate cancer. Many of the PCCTC trials have challenging entry criteria such as a biopsy of metastatic tissue or complicated pharmacokinetics/pharmacodynamics, and collection of correlative biomarkers. The PCCTC is well positioned to conduct such trials that might not be possible outside of sites that specialize in prostate cancer translational research. Shortening drug development time with better trial design, patient selection, and validation of biomarkers will bring new agents to prostate cancer patients faster, optimize treatment for the individual patient, and avoid treating others with ineffective therapies.

15. SUBJECT TERMS
Prostate cancer, castration resistant, phase I/II, immunotherapy, novel agent, androgen receptor, biopsy, circulating tumor cells, germline genetics

16. SECURITY CLASSIFICATION OF: NA			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
Unclassified	Unclassified	Unclassified	Unclassified	751	

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. **INTRODUCTION:**
The University of Washington (UWash) has been a member of the Department of Defense Prostate Cancer Clinical Trials Consortium (PCCTC) since 2006. The purpose of the PCCTC is to provide a mechanism for collaboration among institutions with specialized expertise in prostate cancer in order to develop new agents and combinations of drugs in phase 1 and 2 trials. The mission of the PCCTC is aligned with that of the CDMRP: to eliminate deaths from prostate cancer and to enhance the well-being of men experiencing the impact of prostate cancer.

2. **KEYWORDS:**
Prostate cancer, castration resistant, phase I/II, immunotherapy, novel agent, androgen receptor, biopsy, circulating tumor cells, germline genetics

3. **ACCOMPLISHMENTS:**
   a. **What were the major goals of the project?**
      i. Accrue at least 25 patients per year to PCCTC trials
      ii. Accrue at least 5% patients from disproportionately affected populations per year
      iii. Propose a minimum of two trials per year or eight trials over 4 years, which may include biomarker studies
      iv. Participate in a minimum of eight trials initiated by other sites over 4 years
      v. Ensure timely submission of quality data
      vi. Participate in ≥1 PCCTC committee
      vii. Attend all face-to-face meetings of the PCCTC
      viii. Participate in scheduled consortium conference calls
      ix. Participate in review meetings/evaluation by the External Advisory Board (EAB)
      x. Compliance with the operations manual of the Consortium regarding tasks such as (but not limited to): publication of major findings, intellectual and material property issues, quality assurance and control procedures, data submission and management plans

   b. What was accomplished under these goals?
      i. Site accrued 120 patients to PCCTC trials, 28 patients to therapeutic and 91 patients to non-therapeutic trials. See Appendix 1 for details.
      ii. 15 of 120 patients (12.5%) accrued during this reporting period were members of disproportionately affected populations, including 2 (1.6%) Vietnam era veterans.
      iii. Site submitted the following LOIs (4) in this award period: c23-317 (jointly with Karanos), c21-295 (jointly with Columbia), c23-297, c23-331
      iv. Site participated in 15 PCCTC trials: 5 trials initiated by other PCCTC sites, 4 initiated by UWash with another site, and 6 initiated by UWash. In addition, 1 trial initiated by UWash is in start-up at the end of the award period.
      v. Site met requirements of timely submission of quality data.
      vi. Dr. Cheng [PI] is the Chairperson and Dr. Yu [co-PI] is a member of the Germline Genetics Working Group. Drs. Cheng and Yu are also members of the Recognizing/Tackling Disparities Working Group.
      vii. PCCTC meetings at GU ASCO, ASCO, and PCF were attended by Drs. Cheng, Yu and Schweizer.
      viii. Coordinator participates in site conference calls. PI and/or co-I and sub-investigators participate in all monthly PI conference calls.

ix. All EAB meetings were attended by PI Cheng. Co-PIs Dr. Schweizer also attended the EAB meetings.
x. Procedures are in place and the UWash site is in compliance with the operations manual of the PCCTC.

c. **What opportunities for training and professional development has the project provided?**

Junior faculty members have had the opportunity to meet senior leaders of the PCCTC and to benefit academically from these contacts. The PI, Dr. Cheng, continues to chair the PCCTC Germline Genetics Working Group. Dr. Cheng's participation in the PCCTC helped accelerate her reputation as a recognized international expert in germline genetics in prostate cancer. She is also partnering with Dr. Channing Paller at Johns Hopkins, together with PCCTC, to lead the PROMISE prostate cancer genetics registry, which has also included numerous publication and career development opportunities for junior investigators.

Dr. Schweizer is the Genitourinary Oncology Clinical Research Director at UW/FHCC. In this capacity he oversees the group's clinical trial portfolio and acts as PI for multiple studies. UW/FHCC has a robust translational pipeline, which affords trainees the opportunity to develop novel clinical trials. These include "A Phase II Trial of Durvalumab and Olaparib for treatment of biochemically-recurrent prostate cancer in men predicted to have a high neoantigen load". The study is ongoing and was originally designed by Dr. Alexandra Sokolova (UWash former mentee, now faculty at OHSU). Dr. Schweizer is also activating a pilot study to assess the HDAC inhibitor vorinostat as a novel therapy to enhance PSMA expression and augment the clinical activity of 177Lutetium-PSMA-617. This study was co-developed with his mentee and current oncology fellow, Dr. Ruben Raychaudhuri. These projects not only provide valuable hands-on experience designing clinical trials, but also provide an opportunity to publish and present original work at scientific meetings.

Since starting in September 2021, Dr. Jessia Hawley, in her role as assistant professor at UW/FHCC, has opened several clinical trials. She is co-lead with other PCCTC/DOD participating institutions on two of these trials (Vaccitech w/ Columbia, c21-295; Macrogenics w/ Karmonos, c23-317). To date she has opened 4 clinical trial studies. Dr. Hawley has successfully completed a translational project that interrogates the TME in metastatic HSPC and will be published by Cancer Cell later this week. In addition, she successfully competed for a DOD Physician Research Award, mentored by Drs. Yu and Nelson and has received other internal funding for pilot studies assessing the stool microbiome in conjunction with FHCC investigators. Dr. Hawley is a co-I on Project #3 of our Prostate Cancer SPORE Award that is centered around bringing a novel STEAP1 CAR T cells to patients with CRPC.

Dr. Hiba Khan is a medical oncologist recently recruited to UWash (started 10/2023) from UW/FHCC, where she has been mentored by Dr. Heather Cheng (PI) and Dr. Veena Shankaran (Professor, Co-Director of the FHCC Institute for Cancer Outcomes Research and expert in cancer care delivery; https://www.fredhutch.org/en/research/institutes-networks-ircs/hutchinson-institute-for-cancer-outcomes-research.html). Dr. Khan has expertise in prostate cancer outcomes research and is especially interested in equitable care delivery, including access to clinical trials, cancer disparities and cost effectiveness. Dr. Khan was

awarded an ASCO YIA and she presented on her research ideas at the July 2023 DOD/PCCTC teleconference call. Drs. Yu, Schweizer, Cheng and Shankaran will continue to help her find and develop research interests and career opportunities.

Moreover, recent UWash fellows have gone on to accept prestigious academic faculty positions at other institutions, including PCCTC site OHSU (Dr. Sokolova), University of Colorado (Dr. Laura Graham), University of Pittsburg (Dr. Risa Wong), Baylor College of Medicine (Dr. Rafee Talukder) and Stanford (Dr. Ali Khaki). Thus, PCCTC participation has fostered both collaboration and academic growth for trainees and junior faculty at our institution, the larger PCCTC and prostate cancer research community.

d. **How were the results disseminated to communities of interest?**
We believe that informed patients make the best decisions, are more satisfied, and have the best outcomes. To that end, we have a long history of educating patients about prostate cancer, the role of clinical research, and new treatments available, not only at our institution, but around the country. We have typically two annual meetings directed at men with prostate cancer:

The Institute for Prostate Cancer Research (IPCR) at UWash was founded to develop interdisciplinary institutional programs for prostate cancer research. In addition to fund-raising, the meeting reports on the status of research endeavors in prostate cancer to the lay public.

Dr. Yu is the Director of the Clinical Core of the PC SPORE grant and continues the SPORE Advocates Committee. This committee is engaged in numerous outreach activities in the Pacific Northwest and includes consumer advocates from Vancouver, BC, Seattle, WA and Portland, OR. Members of this committee participate in the SPORE lecture series as well as the SPORE external advisory board meetings where they hear results from SPORE related clinical trials and basic research.

Drs. Cheng, Schweizer and Yu, as well as their colleagues Drs. Montgomery, Nyame, Gore, Lin, Wright, and others are also actively engaged in educational and CME activities, particularly around their research topics of interest and clinical trials. Faculty at UWash are regularly invited to speak at monthly prostate cancer support groups in Washington (Seattle, Tacoma, Olympia, Shelton, Centralia), Oregon (Portland), and British Columbia (Vancouver).

In September of 2023, Fred Hutchinson Cancer Center and the University of Washington Medical Center in collaboration with the Black and African-descent Collaborative for Prostate Cancer Action (BACPAC) provided a free, education event, BACPAC Prostate Cancer Community Research Symposium. This event aimed to bring together community members, advocates, researchers, and clinicians in a forum expressly designed to meet the needs of the Black community for education and action around prostate cancer equity. The symposium also provided an annual opportunity to engage these constituent groups in co-learning designed to facilitate greater awareness and understanding between patients, clinicians, and researchers.

e. **What do you plan to do during the next reporting period to accomplish the goals?**
Nothing to Report.

4. **IMPACT:**
   a. **What was the impact on the development of the principal discipline(s) of the project?**
   Investigators at UWash and other PCCTC institutions continue to focus on the evolving role of genetics and genomics in prostate cancer. Our group has driven changes in NCCN guidelines since 2019 and published extensively with the PCCTC Germline Genetic Working Group and through efforts such as the PROMISE registry. In addition, our efforts also include developing better diagnostic strategies for precision oncology, including recent publication led by Dr. Schweizer on concordance between primary prostate tumor and metastases that will inform testing for PARPi candidacy.

   To provide needed genetics expertise in the clinic, Dr. Cheng organized a unique prostate cancer genetics clinic at UWash, and leads both UWash and PCCTC efforts in this area. She chairs the PCCTC Prostate Cancer Genetics Working Group and is PI of the GENTleMEN study that enables men with prostate cancer to enroll on the trial to receive free germline testing.

   b. **What was the impact on other disciplines?**
   - Provide guidance to primary care physicians and urologists on the importance of complete family history and education about germline genetic testing.
   - Educate oncologists, urologists and radiation oncologists about germline genetic testing for understanding cancer risk versus tumor biomarker testing for treatment decisions.
   - Developing more education in radiation oncology (with help of Dr. Weg).
   - Address the critical role for genetic counseling of prostate cancer patients with pathogenic germline mutations.
   - Provide a model of care to meet the need for genetics expertise in prostate cancer in the clinic.
   - Develop infrastructure to help identify more rare germline variants with prostate cancer.

   c. **What was the impact on technology transfer?**
   Nothing to Report.

   d. **What was the impact on society beyond science and technology?**
   NCCN guidelines for prostate cancer therapy were amended based on work that came out of PCCTC involvement in early development of enzalutamide, abiraterone, radium-223, rucaparib and Olaparib, Lutetium (177Lu) vipivotide tetraxetan and input from members of the PCCTC, including the PI, who are on the Prostate Panel of the NCCN. In addition, guidelines around germline genetic testing and tumor sequencing and liquid biopsies have also arisen from work from our group. We are also focused on therapeutic strategies to address treatment emergent disease, further developing immunotherapeutic approaches, and incorporating novel imaging and theranostics, each of which has potential to reduce the impact of suffering from prostate cancer.

5. **CHANGES/PROBLEMS:**
   a. **Changes in approach and reasons for change**
   Nothing to Report.

   b. **Actual or anticipated problems or delays and actions or plans to resolve them**
   Nothing to Report.

c. **Changes that had a significant impact on expenditures**
Nothing to Report.

d. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
Nothing to Report.

6. **PRODUCTS:**
   a. **Publications, conference papers, abstracts, and presentations (UWash author)**

Journal Articles

Yu EY, Piulats JM, Gravis G, Fong PCC, Todenhöfer T, Laguerre B, Arranz JA, Oudard S, Massard C, Heinzelbecker J, Nordquist LT, Carles J, Kolinsky MP, Augustin M, Gurney H, Tafreshi A, Li XT, Qiu P, Poehlein CH, Schloss C, de Bono JS. Pembrolizumab plus Olaparib in Patients with Metastatic Castration-resistant Prostate Cancer: Long-term Results from the Phase 1b/2 KEYNOTE-365 Cohort A Study. Eur Urol. 2023 Jan;83(1):15-26. doi: 10.1016/j.eururo.2022.08.005. Epub 2022 Aug 30. Erratum in: Eur Urol. 2023 Mar;83(3):e87. PMID: 36055895.

Yu EY, Kolinsky MP, Berry WR, Retz M, Mourey L, Piulats JM, Appleman LJ, Romano E, Gravis G, Gurney H, Bögemann M, Emmenegger U, Joshua AM, Linch M, Sridhar S, Conter HJ, Laguerre B, Massard C, Li XT, Schloss C, Poehlein CH, de Bono JS. Pembrolizumab Plus Docetaxel and Prednisone in Patients with Metastatic Castration-resistant Prostate Cancer: Long-term Results from the Phase 1b/2 KEYNOTE-365 Cohort B Study. Eur Urol. 2022 Jul;82(1):22-30. doi: 10.1016/j.eururo.2022.02.023. Epub 2022 Apr 6. PMID: 35397952.

Smith MR, Scher HI, Sandhu S, Efstathiou E, Lara PN Jr, **Yu EY**, George DJ, Chi KN, Saad F, Ståhl O, Olmos D, Danila DC, Mason GE, Espina BM, Zhao X, Urtishak KA, Francis P, Lopez-Gitlitz A, Fizazi K; GALAHAD investigators. Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2022 Mar;23(3):362-373. doi: 10.1016/S1470-2045(21)00757-9. Epub 2022 Feb 4. PMID: 35131040; PMCID: PMC9361481.

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(mCRPC). J Immunother Cancer. 2023 Mar;11(3):e005702. doi: 10.1136/jitc-2022-005702. PMID: 36948505; PMCID: PMC10040068.

Su CT, Nizialek E, Berchuck JE, Vlachostergios PJ, Ashkar R, Sokolova A, Barata PC, Aggarwal RR, McKay RR, Agarwal N, McClure HM, Nafissi N, Bryce AH, Sartor O, Sayegh N, **Cheng HH**, Adra N, Sternberg CN, Taplin ME, Cieslik M, Alva AS, Antonarakis ES. Differential responses to taxanes and PARP inhibitors in ATM- versus BRCA2-mutated metastatic castrate-resistant prostate cancer. Prostate. 2023 Feb;83(3):227-236. doi: 10.1002/pros.24454. Epub 2022 Nov 16. PMID: 36382533; PMCID: PMC10099873.

Seibert TM, Garraway IP, Plym A, Mahal BA, Giri V, Jacobs MF, **Cheng HH,** Loeb S, Helfand BT, Eeles RA, Morgan TM. Genetic Risk Prediction for Prostate Cancer: Implications for Early Detection and Prevention. Eur Urol. 2023 Mar;83(3):241-248. doi: 10.1016/j.eururo.2022.12.021. Epub 2023 Jan 4. PMID: 36609003.

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Reed-Perino DE, Lai M, **Yu EY**, et al. *Re-sensitization to pembrolizumab following PSMA-CD3 T-cell redirection therapy with JNJ-081 in a patient with mismatch repair-deficient metastatic castration-resistant prostate cancer: a case report*. Journal for ImmunoTherapy of Cancer 2023;11:e006794. doi:10.1136/jitc-2023-006794

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Higano CS, **Cheng HH**. *Poly-ADP ribose polymerase inhibitor and androgen receptor signaling inhibitor for all comers for first-line treatment of metastatic castration-resistant prostate cancer: is gene sequencing out?* Curr Opin Urol. 2023 Sep 1;33(5):396-403. doi: 10.1097/MOU.0000000000001114. Epub 2023 Jul 25. PMID: 37497748.

Paller, C.J.*, Barata, P.C., Lorentz, J., Appleman, L.J., Armstrong, A.J., DeMarco, T.A., Dreicer, R., Elrod, J.B., Fleming, M., George, C., Heath, E.I., Hussain, M.H., Mao, S., McKay, R.M., Metwalli, A.R., Morgans, A., Stadler, W.M., Tran, C., Macario, N., Vinson, J., Green, R., Cheng, H.H.* *PROMISE Registry: A Prostate Cancer*

Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness (in press, The Prostate)

Zhao, J.L., Antonarakis, E.S., Cheng, H.H., George, D., Aggarwal, R., Riedel, E., Sumiyoshi, T., Schonhoft, J., Mao, N., Haywood, S., Decker, B., Curley, T., Abida, A., Feng, F.Y., Knudsen, K., Carber, B., Lacouture, M.E., Wyatt, A., Rathkopf, D., *Phase 1b Study of Enzalutamide plus CC-115, a dual mTORC1/2 and DNA-PK inhibitor, in Men with Metastatic Castration-Resistant Prostate Cancer*. (in press, British Journal of Cancer)

Abstracts

Lorentz, J., Appleman, L., Armstrong, A.J., Barata, P., DeMarco, T.A., Dreicer, R., Elrod, J.B., Fleming, M., George, C., Heath, E.I., Hussain, M.A., Mao, S., McKay, R.R., Metwalli, A., Morgans, A., Orton, M., Pili, R., Saraiya, B., Sigmond, J., Sokolova, A.O., Stadler, W.M., Tran, C., Macario, N., Vinson, J., Green, R., Paller, C.J., **Cheng, H.H.** *Utilization of a decentralized national genetic registry to address informational needs caused by expanded testing recommendations and recently approved treatments for prostate cancer: the PROMISE Registry*. National Society for Genetic Counseling (2022) [Abstract]

Paller, C.J.*, Barata, P.C., Lorentz, J., Appleman, L.J., Armstrong, A.J., DeMarco, T.A., Dreicer, R., Elrod, J.B., Fleming, M., George, C., Heath, E.I., Hussain, M.H., Mao, S., McKay, R.M., Metwalli, A.R., Morgans, A., Stadler, W.M., Tran, C., Macario, N., Vinson, J., Green, R., **Cheng, H.H.*** *PROMISE Registry: A Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness*. Prostate Cancer Foundation Annual Retreat (2022). [Poster abstract]

Giri, V.N., Gross, L., Hartman, R., Reader, A.E., Whang, Y.E., Couvillon, A., **Cheng, H.H.,** Paller, C.J., Loeb, S., Karsh, L.I., Friedman, S., Beer, T.M., Keith, S. *Factors Impacting Men's Experience with Prostate Cancer Germline Testing: Results from PROGRESS Registry.* ASCO Genitourinary Cancer Symposium (2023). [Abstract]

Wong, R.L., **Cheng, H.H.,** Fann, J.R., Hnida, J., Chakoian, M., Jannat, S., Schenker, Y., Yu, E.Y., Gore, J.L. *Longitudinal variability in symptom burden for men with prostate cancer (PC).* ASCO Annual Meeting (2023). [Abstract]

Loeb, S., **Cheng, H.H.,** Leader, A., Gross, L., Sanchez Nolasco, T., Byrne, N., Wise, D.R., Hollifield, L., Brown, L.H., Pieczonka, C., Gomella, L.G., Kelly, W.K., Trabulsi, D.J., Handley, N., Lallas, C.D., Mille, P., Mann, M., Mark, J.R., Brown, G., Chopra, S., Wasserman, J., Phillips, J., Giri, V.N. *Technology-enhanced AcceleRation of Germline Evaluation for Therapy (TARGET): Results of a randomized controlled trial of a pretest patient-driven webtool vs. genetic counseling for prostate cancer germline testing.* ASCO Annual Meeting (2023). [Abstract]

John Shen, Richard Pachynski, Luke Nordquist, Nabil Adra, Mehmet Bilen, Rahul Aggarwal, Zachary Reichert, **Michael Schweizer**, Dong Xu, Manan Patel, Jin Zhang, Wenge Shi, Darryl Z. L'Heureux, Scott Tagawa; *Abstract CT121: ARX517, an anti-PSMA ADC targeting mCRPC resistant or refractory to standard therapies: A phase 1 dose escalation and dose expansion study* (ARX517-2011, NCT04662580). Cancer Res 15 April 2023; 83 (8_Supplement): CT121. https://doi.org/10.1158/1538-7445.AM2023-CT121

Orme, J.J., Taza, F., De Sarkar, N., Tewari, A., Naqvi, S.A., Riaz, I.B., Childs, D.S., Omar, N., Adra, N., Ashkar, R., Cheng, H.H., Hwang, J., Shi, Q., Fleischmann, Z., Sokol, E.S., Elliott, A., Huang, H., Bryce, A., Marshall, C.H., Antonarakis, E.S. *Co-occurring BRCA2/SPOP mutations predict exceptional PARP inhibitor sensitivity in metastatic castration-resistant prostate cancer*. ASCO Genitourinary Cancer Symposium (2024). [Abstract]

b. **Books or other non-periodical, one-time publications**
Nothing to report.

c. **Other publications, conference papers, and presentations**
Nothing to report.

d. **Website(s) or other Internet site(s)**
The following site is publicly accessible and includes presentations of the IPCR educational conferences for patients described above in section 3.d.
Institute for Prostate Cancer Research
https://www.fredhutch.org/en/research/institutes-networks-ircs/institute-for-prostate-cancer-research.html

e. **Technologies or techniques**
Nothing to Report.

f. **Inventions, patent applications, and/or licenses**
Nothing to Report.

g. **Other Products**
Nothing to Report

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**
   a. **What individuals have worked on the project?**

Name:	Heather Cheng, MD, PhD
Person months worked:	5
Project Role:	Principal Investigator
Contribution to project:	Responsible for site's overall performance, assure site's goals are met as outlined in the SOW, participate as a senior PCCTC member and mentor.

Name:	Evan Yu, MD
Person months worked:	5
Project Role:	Co-Principal Investigator
Contribution to project:	Conduct and recruit to PCCTC clinical trials, participate in weekly research and monthly PCCTC protocol meetings, attend face-to-face PCCTC meetings.

Name:	Michael Schweizer, MD
Person months worked:	5
Project Role:	Co-Principal Investigator

Contribution to project:	Conduct and recruit to PCCTC clinical trials, participate in weekly research and monthly PCCTC protocol meetings, attend face-to-face PCCTC meetings.

Name:	Jessica Hawley, MD
Person months worked:	2
Project Role:	Sub- Investigator
Contribution to project:	Conduct and recruit to PCCTC clinical trials, participate in weekly research and monthly PCCTC protocol meetings, attend face-to-face PCCTC meetings.

Name:	Patrick Panlasigui
Person months worked:	6
Project Role:	Clinical Research Manager
Contribution to project:	Participate in PCCTC conference calls. Oversee research team in management of protocol adherence and timeliness/quality of data collection. Support data and regulatory coordinators, ensuring data collection is accurate and timely, and that all regulatory procedures meet local IRB requirements.
Project Role:	PCCTC CRC
Contribution to project:	Track trial accruals, LOI submissions, and provide updates to PCCTC. Serve as point person for PCCTC activities. Participate in PCCTC coordinator conference calls. Manage consortium budget and contract process, provide monthly reports, oversee start-up process for PCCTC clinical trials, and post award accounting of DOD contract. Assist PI and co-PIs with preparation and submission of required semi-annual and annual reports.

Name:	Nathan Conrad
Person months worked:	3
Project Role:	Data Coordinator
Contribution to project:	Track and enter data, including enrollment demographics, for PCCTC studies. Set up research charts and work-flow plans, and ensure timely submission of quality data for all UWash PCCTC trials.

Name:	Hannah Loesch
Person months worked:	3
Project Role:	Clinical Trial Specialist
Contribution to project:	Develop site budgets for PCCTC studies, and negotiate amendments based on protocol modifications as needed.

Name:	Sarah Finkelstein
Person months worked:	1
Project Role:	Budget/Contract Manager (30Sep2017-31Jan2021)

Contribution to project:	Manage consortium budgets and contracts, provide monthly reports to PI and PCCTC CRC, oversee start-up process for PCCTC clinical trials, and post-award accounting of DOD contract. Assist PI and co-PI with preparation and submission of required semi-annual and annual reports.
Project Role:	PCCTC CRC (01Jul2020-31Jan2021)
Contribution to project:	Track trial accruals, LOI submissions, and provide updates to PCCTC. Serve as point person for PCCTC activities. Participate in PCCTC coordinator conference calls.
Project Role:	Operations Support (01Feb2021-29Sep2022)
Contribution to project:	Support PCCTC CRC in tracking accruals and LOI submissions. Serve as resource to UWash team with respect to DOD award requirements. Assist PI, co-PI and PCCTC CRC with preparation and submission of semi-annual and annual reports.

Name:	Amanda Barela
Person months worked:	3
Project Role:	Research Assistant
Contribution to project:	Assist with filing and managing of regulatory documentation, subject demographic data, and report preparation.

Name:	Martha Lee
Person months worked:	1
Project Role:	Administrative Support (thru 15Mar2020)
Contribution to project:	Provide administrative support for consortium related activities for the PI and research team.

Name:	Jane Romani
Person months worked:	2
Project Role:	Research Coordinator
Contribution to project:	Serve as a resource for the conduct of protocol specified laboratory correlative projects and overall protocol coordination for PCCTC studies.

Name:	Brianna Woo
Person months worked:	2
Project Role:	Research Coordinator
Contribution to project:	Serve as a resource for the conduct of protocol specified laboratory correlative projects and overall protocol coordination for PCCTC studies.

b. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
Nothing to Report

c. **What other organizations were involved as partners?**
Nothing to Report

8. **SPECIAL REPORTING REQUIREMENTS**
   Not applicable.

9. **APPENDICES:**

   Appendix 1 – PCCTC trials, status and accruals at UWash clinical research site during funding period

   Appendix 2 – Copies of original publications

   Appendix 3 – Curricula vitae for Cheng (PI), Yu (co-PI) and Schweizer (sub-I)

APPENDIX 1

PCCTC trials, status, and accruals at UWash clinical research site

30Sep2022-29Sep2023**Table A UWash PCCTC Trials, Open and in Start-Up**

9/30/2022-9/29/2023

(abbreviation mCRPC = metastatic castration resistant prostate cancer)

PCCTC# (UW#)	Trial Title	UWash Accrual	Status	Lead Site
c16-181 (UW16081)	Phase Ib/II Trial of Pembrolizumab (MK-3475) Combination Therapies in… (mCRPC) (KEYNOTE-365)	1	Open	UWash
c19-248 (UW18002)	A Phase I… Study of PF-06821497 in the Treatment of Adult Patients with… Castration Resistant Prostate Cancer (CRPC)…	5	Open	UWash
c20-252 (RG1121714)	DASL-HiCaP: Darolutamide Augments Standard Therapy for Localised Very High-Risk Cancer of the Prostate (ANZUP1801). A randomised phase 3 double-blind, placebo-controlled trial of adding darolutamide to androgen deprivation therapy and definitive or salvage radiation in very high risk, clinically localised prostate cancer.	2	Closed	MSKCC
c21-275 (RG1007001)	Durvalumab (MEDI4736) and Olaparib (AZD2281) for treatment of biochemically recurrent prostate cancer in men predicted to have a high neoantigen load: a pilot study	4	Open	UWash
c21-276 (RG1121689)	A Phase 1, Open-Label, Study Evaluating the Safety, Pharmacokinetics, and Clinical Effects of Intravenously Administered PT-112 Injection in Patients with Advanced Solid Tumors and Subsequent Expansion Cohorts	4	Open	Weill Cornell
c21-295 (RG1007001)	A Phase 1/Phase 2 Trial… of VTP-850 Prostate Cancer Immunotherapeutic in Men with Biochemical Recurrence after Definitive Local Therapy for Prostate Cancer	2	Open	UWash Columbia
c22-297 (RG1122235)	A Phase 1 Study of JNJ-78278343, a T-Cell-Redirecting Agent Targeting Human Kallikrein 2 (KLK2), for Advanced Prostate Cancer	6	Open	UWash Columbia
c22-303 (RG1122292)	A Phase 2 Trial of SRF617 in Combination With AB928 (Etrumadenant) and AB122 (Zimberelimab) in Patients With Metastatic Castration-Resistant Prostate Cancer	1	Open	UWash
c23-317 (RG1123101)	A Phase 2/3, Randomized, Open-label, Study of MGC018 Versus Androgen Receptor Axistargeted Therapy (Abiraterone or Enzalutamide) in Participants with Metastatic Castrationresistant Prostate Cancer	2	Open	UWash Karanos

c23-326 (RG1121517)	A Phase 1/2, Multicenter, Open-label, Dose-escalation, and Dose-expansion Study to Evaluate the Safety, Pharmacokinetics, and Anti-tumor Activity of ARX517, with Randomized Comparison to Investigator's Choice of Treatment, in Subjects with Metastatic Castration-resistant Prostate Cancer who are Resistant or Refractory to Prior Standard Therapies	2	Open	Weill Cornell
C23-331 (RG1123898)	Phase 1/2 Study of Onct-534 In Subjects with Relapsed or Refractory Metastatic Castration Resistant Prostate Cancer		Pending	UWash
	Total Therapeutic accruals:	***29***		

PCCTC# (UW#)	Trial Title	UWash Accrual	Status	Lead Site
c16-170 (CC9853)	Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men with Advanced Prostate Cancer (IRONMAN)	2	Open	Duke MSKCC DFCI
c19-235 (RG1006494)	PROMISE: A Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness	63	Open	UWash JHU
c20-258 (RG1006011)	The impact of DNA repair pathway alterations identified by circulating tumor DNA on sensitivity to Radium-223 in bone metastatic castration-resistant prostate cancer	1	Open	UWash
c21-271 (RG1006494)	Darolutamide Observational Study in non-metastatic castration-resistant prostate cancer patients	2	Closed	UWash
c23-237 (RG1122272)	NCI Multi-Center Natural History Study of Precision-Based Genomics in Prostate Cancer	23	Open	DFCI
	Total non-therapeutic accruals	***91***		

Appendix 2

Copies of original journal articles

Appendix 3

Curricula vitae:

Heather H. Cheng – PI

Evan Y. Yu - co-investigator

Michael T. Schweizer - co-investigator

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Prostate Cancer

Genetic Risk Prediction for Prostate Cancer: Implications for Early Detection and Prevention

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Article info

Article history:
Accepted December 20, 2022

Associate Editor:
Giacomo Novara

Keywords:
Ancestry
Disparities
Early detection
Genetics
Genomics
Lifestyle
Prevention
Prostate cancer
Race
Screening

Abstract

Context: Prostate cancer (PCa) is a leading cause of death and partially heritable. Genetic risk prediction might be useful for strategies to reduce PCa mortality through early detection and prevention.
Objective: To review evidence for genetic risk prediction for PCa.
Evidence acquisition: A collaborative literature review was conducted using PubMed and Google Scholar. Search terms included genetic, risk, prediction, and "prostate cancer". Articles addressing screening, early detection, or prevention were prioritized, as were studies involving diverse populations.
Evidence synthesis: Rare pathogenic mutations (RPMs), especially in DNA damage repair genes, increase PCa risk. RPMs in *BRCA2* are most clearly deleterious, conferring 2–8.6 times higher risk of PCa and a higher risk of aggressive disease. Common genetic variants can be combined into genetic risk scores (GRSs). A high GRS (top 20–25% of the population) confers two to three times higher risk of PCa than average; a very high GRS (top 1–5%) confers six to eight times higher risk. GRSs are not specific for aggressive PCa, possibly due to methodological limitations and/or a field effect of an elevated risk for both low- and high-grade PCa. It is challenging to disentangle genetics from structural racism and social determinants of health to understand PCa racial disparities. GRSs are independently associated with a lethal PCa risk after accounting for family history and race/ancestry. Healthy lifestyle might partially mitigate the risk of lethal PCa.
Conclusions: Genetic risk assessment is becoming more common; implementation studies are needed to understand the implications and to avoid exacerbating healthcare disparities. Men with a high genetic risk of PCa can reasonably be encouraged to adhere to a healthy lifestyle.
Patient summary: Prostate cancer risk is inherited through rare mutations and through the combination of hundreds of common genetic markers. Some men with a high genetic

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https://doi.org/10.1016/j.eururo.2022.12.021
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risk (especially *BRCA2* mutations) likely benefit from early screening for prostate cancer. The risk of lethal prostate cancer can be reduced through a healthy lifestyle.
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1. Introduction

Prostate cancer (PCa) represents a complex clinical spectrum, ranging from an indolent to a rapidly lethal disease course. The benefit of population-based screening with prostate-specific antigen (PSA) testing is controversial largely due to frequently finding indolent cancers that can lead to anxiety and/or initiation of curative-intent treatments that do not render a clear survival benefit [1,2]. Nevertheless, PCa remains a leading cause of cancer death despite excellent outcomes when detected in its early stages [3,4]. Strategies are needed to identify men at the highest risk of developing aggressive PCa for targeted screening and consideration of preventive measures, as well as early detection and treatment.

As PCa is partially heritable, genetic risk stratification is an appealing approach. Genetic predisposition to PCa is associated with both rare pathogenic mutations (RPMs; eg, in *BRCA2*) and common variants. Individually, common variants may have a small effect size; however, a combined analysis of multiple variants can offer a genetic risk score (GRS) that represents a combined cancer risk. Although rare mutations display larger effect sizes and have more direct clinical implications (due to their potential as drug targets and importance for familial cancer risk), broad validation of GRS impact on overall risk has led to significant interest in clinical implementation (Fig. 1). PCa is included in a rapidly expanding list of conditions where both RPMs and GRSs appear clinically meaningful. Similar to individual rare variants, GRSs may indicate predisposition to a wide range of diseases, including those of a cardiovascular, metabolic, neurological, and malignant nature [5]. Genotyping is highly accurate and is becoming widely available.

As of early 2021, over 30 million people have purchased direct-to-consumer genotyping [6], typically at <100 USD. Some of these customers received genetic risk reports from these data, and early commercial products are now available specifically to estimate the PCa risk. A number of prospective studies that include calculation of GRSs have been reported [7,8], raising the real possibility that many men will soon have access to genotype data and GRSs for PCa. Meanwhile, germline sequencing is also occurring with increased frequency, due to precision-oncology–focused patient testing, cascade testing in the setting of family members with known mutations in high-penetrance genes, and abundance of consumer-facing commercial laboratory tests. Here, we review the state of the evidence of germline genetic risk prediction for PCa and the implications for screening, early detection, risk stratification, and prevention strategies.

2. Evidence acquisition

We performed a systematic literature search and a collaborative narrative review. We searched PubMed and Google Scholar using the following terms: genetic, risk, prediction, and "prostate cancer". The literature review was limited to studies of genetic risk prediction or genetic influence on PCa in humans. Articles addressing screening, early detection, or prevention were prioritized for inclusion, as were studies involving diverse populations. Results of this search were

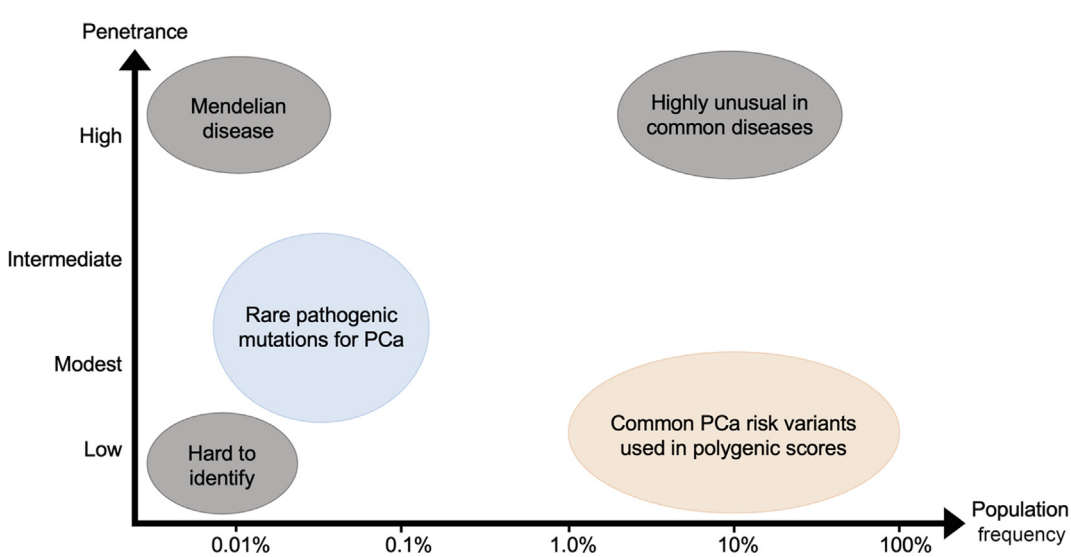

Fig. 1 – Schematic demonstrating the relationship between population frequency and penetrance for rare pathogenic mutations (RPMs) and common risk variants predisposing to prostate cancer (PCa). RPMs include *BRCA2* and *HOXB13*. Common risk variants generally have low penetrance, but when combined in "polygenic" genetic risk scores, the net effect is comparable with that of prominent RPMs.

Table 1 – Genetic risk factors for prostate cancer (PCa), including rare pathogenic mutations, as well as genetic risk scores (GRSs) comprising common variants

	Genetic risk factor	Population affected	Increased risk of PCa	Associated with worse prognosis
Rare pathogenic mutations	*BRCA2* [17,18,21,73]	0.07%	3–8.5	Yes
	BRCA1 [14,21,73]	0.05%	1–3	Probably
	HOXB13 G84E [10,21,74]	0.1% (1.3% in Sweden)	2–6	No
	MLH1, MSH2, MSH6 [20,21]	0.04–0.4%	2–3.5	No
Genetic risk scores	Very high GRS [30,32–34]	1–5%	3.5–9	No
	High GRS [29–31,33,34]	20–25%	2–3	No

For GRSs, the risk increase is reported relative to men with an average GRS.

curated and summarized in collaboration, with all authors contributing to the consensus review below.

3. Evidence synthesis

3.1. *Rare pathogenic mutations*

The importance of RPMs in driving PCa risk has increasingly been recognized over the past decade (Table 1). Most of the clinically relevant genes function in DNA damage repair (DDR), such as homologous recombination (eg, *BRCA1*, *BRCA2*, and *ATM*) or mismatch repair (eg, *MLH1*, *MSH2*, and *MSH6*). In addition, *HOXB13* is a gene expressed in urogenital development for which specific variants are strongly associated with PCa risk [9,10]. In the seminal study by Pritchard and colleagues [11], 11.8% of patients with metastatic PCa were found to have a pathogenic mutation in one of 16 genes involved in DDR. *BRCA2* mutations accounted for 44% of the pathogenic germline mutations identified in this cohort. The observed prevalence of these germline DDR mutations in patients with localized disease is lower than that in patients with metastatic cancer.

Importantly, there may be ancestry-specific mutational landscapes, and a reliance on European samples to classify variants has likely confounded many studies. For example, men with Ashkenazi Jewish ancestry are more likely to have specific RPMs in *BRCA1* or *BRCA2*, and Black men with RPMs may harbor different mutational profiles than White men [12]. In one study, Lee and colleagues [13] assessed 17 genes involved in DDR and demonstrated mutation rates of 4.0% and 1.4% in individuals with localized PCa of European and African descent, respectively. *BRCA2* mutations were the most common, being present in 0.82% of patients, followed by *BRCA1* (0.63%) and *ATM* (0.44%). When restricting to patients with more aggressive PCa, the most common mutations were in *BRCA2*, *ATM*, and *PALB2*. RPMs in *BRCA2* have repeatedly been demonstrated to drive aggressive PCa risk to a greater degree than RPMs in any other DDR gene [14,15].

RPM status currently has direct clinical impact in four domains: (1) early cancer detection (prostate and other), (2) risk stratification for patients with localized PCa, (3) treatment of advanced PCa, and (4) cascade testing of family members. For this review, we focus on PCa early detection and risk stratification. From the standpoint of PCa early detection, it is helpful to keep in mind that men with *BRCA1* mutations have a lifetime risk of PCa of 7–26% by the age of 80 yr [16], compared with a substantially higher risk of 19–61% in men with *BRCA2* mutations. Overall, individuals with *BRCA2* mutations are approximately 3–8.6 times more likely to develop PCa than those in the general population [17]. Not all mutations confer similar levels of risk, and PCa risk is impacted by family history even in individuals with RPMs (Table 1) [18].

Current data strongly support tailored screening and early detection strategies that account for genetic risk. This is best illustrated by the IMPACT trial, where men aged 40–69 yr from families with *BRCA1* or *BRCA2* mutations underwent PSA screening [19]. Men with a *BRCA2* mutation were diagnosed with PCa more often and at a younger age than men from these same families who did not personally have a *BRCA2* mutation. *BRCA2* carriers were also more likely to have aggressive PCa. The increase in PCa among men with *BRCA1* mutations was not statistically significant in the published interim analysis. In a parallel cohort, men with RPMs in *MSH2* and *MSH6* were similarly found to have an increased risk of PCa [20].

RPM status has been incorporated into early detection guidelines, including from the National Comprehensive Cancer Network (NCCN) and European Association of Urology. Both guidelines point specifically to the importance of initiating screening at age 40 in *BRCA2* carriers, with the NCCN guidelines also suggesting that it is reasonable to initiate shared decision-making around screening starting at age 40 for men with RPMs in a broader set of genes (eg, *BRCA1*, *ATM*, and *HOXB13*) [21]. The Philadelphia Prostate Cancer Consensus Conference 2019 also endorsed earlier PCa screening among male *BRCA2* carriers, with a consideration of the same for carriers of mutations in *BRCA1*, *HOXB13*, DNA mismatch repair genes, and *ATM* [22].

There is also growing consensus regarding indications for genetic testing to detect RPMs. In general, patients with metastatic or high-grade localized PCa should be counseled about genetic testing [22–24]. For patients with less aggressive localized PCa, genetic counseling/testing can be considered if they have a family history of a high-risk RPM; a strong family history of breast, ovarian, pancreatic, and/or PCa; Ashkenazi Jewish ancestry; or intraductal/cribriform PCa histology. When testing for RPMs (vs testing for common germline variants used in GRSs), thorough pretest counseling is required, as testing for rare variants could have implications for insurance (for health, disability, life, or long-term care) and for family members through cascade testing [25,26]. While pretest education can be performed by clinicians knowledgeable about the risks/benefits of germline testing, all patients found to have pathogenic or likely pathogenic mutations should be referred to a certified genetic counselor.

3.2. Common germline variants and polygenic risk

Powerful risk stratification for PCa has been demonstrated in a number of studies using GRSs [27–34]. Unlike diagnostic tests used for risk stratification (eg, PSA and magnetic resonance imaging [MRI]), assessment of a GRS is required only once in a man's lifetime. Moreover, since the GRS is static, it can be calculated at an early age when the risk is potentially modifiable through lifestyle modifications. While current guidelines recommend early screening for men with certain RPMs and have not incorporated GRSs, men with high GRSs have a comparable—and in some cases, higher—risk of developing PCa (Table 1). Compared with men with an average risk, men with a high GRS (eg, top 20–25% of population) have an approximately two to three times greater risk of developing PCa [29–31,33,34]. Conversely, men in the lowest 20–25% of GRSs have an approximately two to three times lower risk than average [29–31,33,34]. Application of GRS stratification improves the positive predictive value of screening PSA testing in the data from the diagnostic phase of the ProtecT trial [27,33]. At the extremes of polygenic risk (eg, top 5% or 1% of GRSs), men have approximately six to eight times greater risk and are likely to develop clinically significant PCa approximately 10 yr earlier than the population average [32–35]. Importantly, more men in the general population fall into these extreme GRS quantiles than have RPMs.

3.3. GRS and aggressive PCa

The most meaningful endpoints for PCa prediction and detection include development of aggressive disease, metastasis, and PCa mortality. It is important for risk-stratified early detection strategies to focus on preventing these devastating outcomes. This focus is challenging in most existing datasets because men diagnosed with low-grade cancers have historically undergone radical treatment at high rates, and long-term follow-up data are not always available. It is thus generally unknown which men have experienced poor outcomes at a time point beyond what is captured in the dataset.

Time-to-event analyses can be one effective way to evaluate existing data for key oncological endpoints, as men treated for low-risk PCa or who were not followed long term can be censored. Polygenic hazard scores are a type of GRSs developed via a model optimized for these time-to-event analyses [27]. Additionally, polygenic risk scores, technically developed based on models for binary outcomes (eg, cancer vs no cancer), have also been used successfully in a time-to-event analysis. Using this approach, a GRS has been associated with the age at the development of metastatic disease [34] and with PCa mortality [29,32–34]. Compared with men with an average risk, men with a high genetic risk (top quartile or quintile of GRSs) have approximately two to three times greater risk of death from PCa.

Despite the strong associations of GRSs with key oncological endpoints, no GRS has been shown to be *specific* for aggressive PCa (vs low-grade PCa) [30,32]. This is an important issue, since an ideal risk classifier would predict the development of aggressive cancers without also capturing men likely to develop indolent cancers. With genome-wide association studies now including hundreds of thousands of cases and controls, we need to consider why common PCa risk variants that are specific for aggressive or lethal disease have not been found. Partly, this may reflect a lack of power, as case-control datasets frequently lack detailed information on the aggressiveness of disease at diagnosis or long-term follow-up. Alternate approaches and other datasets may yield insights. For example, there is intriguing evidence that germline genetic composition influences cancer evolution and tumor gene expression [36]. Another study found that men initially started on active surveillance for PCa were more likely to convert to treatment if they had a higher PCa GRS (patients who converted because of anxiety were censored from the analysis) [37].

There is also a potential biological explanation for the observed lack of strong specificity. PCa genesis typically occurs in the context of a *field effect* of genetic and environmental risk factors affecting the entire prostate [38,39]. Men with PCa are overwhelmingly likely to have multifocal disease (and even more likely if they have a higher GRS) [40], with tumors arising independent of each other and having both distinct genomic profiles and distinct Gleason scores [41–43]. This means that men with aggressive disease in one part of the prostate very likely *also have a low-grade tumor* elsewhere in the prostate. Moreover, men initially diagnosed only with low-grade PCa are still at a high risk of being diagnosed with high-grade PCa in the future; pathological upstaging occurred within just 3 yr in 48% of men in one prospective study [4]. Most of this reclassification likely represents undersampling with systematic biopsy (and will change further in the era of MRI-targeted biopsy), but it nonetheless illustrates the point that the population at risk of developing low-grade PCa is also the population at risk of developing clinically significant PCa.

These challenges notwithstanding, identifying men at an elevated genetic risk (ie, higher genetic field effect) for developing PCa, GRSs can still contribute to individualized screening. As has been shown, GRS stratification improves the positive predictive value of screening for clinically significant PCa [27,33]. Even more importantly, GRSs are strongly associated with a man's lifetime PCa-specific mortality, and thus could identify men most likely to benefit from early detection and prevention [29,32–34].

3.4. Family history

Current guidelines recommend considering early detection strategies for men with an affected first-degree relative. Family history is obtained without cost, although it can be unreliable or not available [44]. A recent study revealed clinician knowledge gaps and errors in taking PCa family history and suggested that digital tools might improve results [45].

Although sometimes posited as a surrogate for an inherited risk, family history is not an adequate substitute for genetics. Both RPMs and GRSs have a strong independent association in multivariable models that included family history [27,29,30,32,34,46]. Adding GRSs to family history doubled the number of men accurately identified as having

a high risk of clinically significant PCa in a prospective trial with biopsy of all participants [47].

At the same time, family history captures an additional risk of aggressive or fatal PCa beyond GRSs and RPMs, suggesting that the combination is better than either alone [27,29,30,32,34,46]. This may reflect heritability not yet accounted for using the current knowledge of genetic risk assessment but may also reflect shared environmental exposures.

3.5. *Race, ethnicity, and genetic ancestry*

Troubling disparities in health outcomes are well documented for PCa, especially for self-identified Black men from western countries [48,49]. Through thoughtful and socially conscious approaches to studying these disparities, there is an opportunity to better elucidate the drivers of disparities, while leading to a better understanding of PCa risk factors and ultimately translation of culturally appropriate interventions. It is important to emphasize that disparities associated with self-identified race/ethnicity are a result of a multitude of factors, including social determinants of health, structural racism, possible genetic contributors linked to ancestry, and the interaction of genes and the environment [50–52]. It is also important to make the distinction between race/ethnicity and genetic ancestry (including local vs global ancestry). Genetic studies sometimes consider genetic ancestry instead of self-identified race/ethnicity (which is a social and cultural identifier) using common genetic markers to consistently identify groups associated with continental ancestry (eg, African or European). While arguably objective, genetic ancestry groups are still suboptimal since ancestry informative markers are identified under the assumption that arbitrarily defined continental groups are clinically meaningful or even appropriate at all. Considering known heterogeneity within each continent and the prevalence of admixture, many have questioned the assumption that the effects of ancestry on PCa risk are best accounted for by continental groups [9,32]. Agnostic ancestry designations may be a better approach and should be explored further [32]. Early evidence also suggests incorporation of local ancestry may be useful in admixed populations. For example, one study of 6253 men of African genetic ancestry found that performance of a GRS for PCa varied widely depending on genetic principal components of local ancestry in the 8q24 band of the genome [53].

Owing to the above limitations, it is critical to examine the implications of race/ethnicity and genetic ancestry when integrating GRSs into early PCa detection guidelines. Current guidelines explicitly recommend considering early detection strategies for men who self-identify as Black or have African ancestry, as these men are known to have a substantially increased risk of PCa and an approximately two-fold risk of dying from PCa compared with White men [48,49]. Importantly, much of the work on PCa genetic risk has focused on largely White populations. As a result, it is unclear whether the prevalence and impact of RPMs differ meaningfully across the full spectrum of racial/ethnic groups, with research in this area stunted by selection bias and sparsity of data [9,13,54,55] (meanwhile, the presence of variants of unknown significance appears to be higher in non-White men [12]). Early GRS work was similarly marred by exclusive focus on men of European ancestry [27,28], leading to fears that implementing a GRS might exacerbate existing health disparities [56,57]. There is consensus that more data are needed from non-European populations, although it is not clear whether a single GRS can be optimal for all people or whether population-specific scores will be required [30,53,58].

Available genetic datasets continue to be heavily weighted toward European ancestry, but recent efforts have begun to address this problem by training and testing GRSs in more diverse datasets, improving GRS performance in a broader population and demonstrating risk stratification within each ancestry group [30,32–34,58]. Evaluations of GRSs have now been performed in independent datasets of men with African [30–32,34,53], Asian [32–34], and Hispanic ancestry [34], demonstrating good risk stratification within each group. In a cohort of over half a million US veterans, family history, race/ethnicity, and GRSs were each independently associated with age at diagnosis of metastatic PCa and with lifetime PCa-specific mortality [34]. Similar results were found when using genetic ancestry or the top ten genetic principal components instead of self-reported race/ethnicity. When accounting for family history and race/ethnicity, men in the highest quintile of GRSs (compared with men in the lowest quintile) were four times more likely to die of PCa. As discussed above, genetic testing is recommended in individuals with a significant family history of cancer to determine an appropriate PCa early detection evaluation algorithm. However, it has been demonstrated that PCa patients without a family history also carry rare germline variants [59]. Consequently, integrating rare germline variation with GRSs may improve targeted screening strategies with the added clinical benefit of identifying genes specifically linked to a higher risk of aggressive disease [60]. This would inform management decisions for early-stage disease focused on improving survival in those with poorer prognosis and reducing overtreatment for indolent disease.

When considering the contribution of GRSs in the context of racial/ethnic health disparities, the degree to which the use of GRSs will exacerbate or mitigate the overall PCa risk remains unclear. However, as a nonmodifiable factor, future studies that incorporate GRSs could illuminate the relative contributions of adverse social determinants (relatively lower socioeconomic status, reduced access to care, residing in neighborhoods with increased environmental exposures, relatively increased life stressors, etc.) that are often over-represented in specific racial/ethnic populations. Taken together, the current guideline recommendation of assessing an individual's risk by race/ethnicity and family history may be substantially improved by incorporating a quantitative, objective GRS.

3.6. *Lifestyle*

Lifestyle and environmental factors could be particularly relevant for men at a high genetic risk. An analysis of

men in two prospective US cohort studies with 27 yr of follow-up showed the highest lifetime risk of metastatic or fatal PCa among men in the top GRS quartile [61]. However, the risk of metastatic or fatal disease among men in the top GRS quartile was 50% lower for those adhering to a healthy lifestyle than men with an equivalent genetic risk not adhering to a healthy lifestyle. Those with a high GRS adhering to a healthy lifestyle had a comparable risk of metastatic or fatal PCa to the population average. A healthy lifestyle in that study was defined by not smoking, vigorous physical activity, a healthy weight, and three healthy diet components, although the findings suggest that adhering to a few of these factors may also be beneficial for men at an increased genetic risk. A subsequent study evaluated the impact of healthy lifestyle—defined by not smoking, vigorous physical activity, and a healthy weight—in a racially diverse, population-based cohort of over 280 000 US military veterans [62]. Even when accounting for race/ethnicity and family history of PCa, those with a healthy lifestyle had reduced incidence of fatal PCa and metastatic PCa. This association was observed in the full cohort, but the largest absolute reduction in risk was observed in those with the highest inherited PCa risk. Similar findings have been reported for lifestyle factors and GRSs of other diseases and cancer types, including colorectal and breast cancers [63–65]. While further studies are needed to refine our understanding, this suggests that modifiable factors related to a healthy lifestyle could attenuate the impact of a high genetic risk.

3.7. Chemoprevention

Beyond lifestyle changes, there has been longstanding interest in preventing PCa with medication. In two randomized trials, 5α-reductase inhibitors have been shown to reduce the risk of PCa by approximately 25% [66,67]. At a median follow-up of 18 yr, men randomized to take finasteride (vs placebo) for 7 yr also had a point estimate (not statistically significant) of 25% less PCa mortality (hazard ratio 0.75, 95% confidence interval: 0.50–1.12). The lack of statistical significance is not surprising given that the absolute rate of PCa death was only 0.60% in the placebo arm. As men with high GRSs have higher absolute risks of PCa and PCa death [29,30,33,34], it is conceivable that they could have the largest absolute benefit from chemoprevention. This could be true even if germline variants are not predictive of a larger *relative* benefit, as was suggested in one recent study [68]. Finally, if early detection is pursued in men with a high genetic risk, chemoprevention may be beneficial in reducing overdiagnosis by reducing the overall risk of PCa in men undergoing careful screening. All these ideas require prospective study before they could be widely recommended; however, the recent improvements in our understanding of genetic risk could go a long way toward refining the target populations for these studies. Future trials of candidate preventive medications would do well to enrich their study population with men at a high genetic risk of aggressive PCa.

3.8. Where does assessing genetic risk best fit into an early detection pipeline?

Germline genetic risk does not change and can be calculated at any point in a man's life. Its clinical utility may vary with age, though. For example, early genetic assessment could encourage healthy lifestyle patterns that could reduce the risk of PCa (and of other health problems). Disadvantages to early genetic assessment could be increased anxiety or a temptation to initiate prostate screening at a young age when low-risk disease is more common than clinically significant PCa [33,69]. As the science of genetic risk progresses, the interpretation of an individual's results may also change, with a consequent impact on recommended actions.

In terms of early detection, current evidence supports assessing each person's individual risk to help guide decisions about whether and when to begin screening—that is, before PSA testing is started. Genetic risk assessment represents one important avenue for guiding early detection decisions, with a clear influence on the pretest probability and positive predictive value of PSA testing [27,33,35]. Less is understood about how genetic risk should be interpreted within the context of other results—for example, when a man has already undergone prior PSA testing, multiparametric MRI, or biopsy. Early studies suggest that there may be a role for integrating genetic risk with diagnostic test results, but more research is needed to clarify optimal integration [7,37].

3.9. Perspectives for the future

Germline risk prediction will be widespread in both oncological and nononcological settings in the next 5–10 yr. Whether this will happen because genetic tools are embraced by the medical community, because direct-to-consumer products are embraced by the public, or because of a combination of these remains unclear, but it will undoubtedly happen. Over 30 million people (and counting) have already obtained direct-to-consumer germline genotyping. Currently recommended clinical genetic testing is underutilized [70,71], suggesting opportunities for future growth and the need to identify new delivery methods to meet the increasing demand [72]. The medical community must consider how we are going to manage patients who present to our clinics with GRS results in hand, with a variant of unknown significance or with an RPM detected on a direct-to-consumer platform.

4. Conclusions

A rigorous, prospective study of germline genetic tools is essential, including careful calibration of GRSs for diverse prostate screening populations to determine preferred thresholds to guide early detection decisions. These studies should also seek to clarify how genetic risk should be integrated with other risk factors (family history and ancestry) and tools (early midlife PSA and other blood tests). Clear evidence and guidelines are likewise needed when germline

sequencing should be offered and the extent of such testing: panel testing, whole exome, or whole genome, as well as the role of epigenetic testing. Cost-effectiveness considerations will be important for any population-level sequencing efforts and need to be studied further. Finally, prospective studies are needed to test whether pragmatic interventions can mitigate risk for men found to be at high genetic susceptibility for PCa.

For now, we recommend that men with a high GRS or who harbor a relevant RPM adopt a healthy lifestyle, including avoiding smoking, maintaining a healthy weight, exercising regularly, and eating a healthy diet. Utilization of these "teachable moments" may have important benefits well beyond PCa risk, impacting patients' overall health and longevity.

***Author contributions*:** Tyler M. Seibert had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Seibert, Garraway, Plym, Mahal, Giri, Jacobs, Cheng, Loeb, Helfand, Eeles, Morgan.
Acquisition of data: Seibert, Garraway, Plym, Mahal, Giri, Jacobs, Cheng, Loeb, Helfand, Eeles, Morgan.
Analysis and interpretation of data: Seibert, Garraway, Plym, Mahal, Giri, Jacobs, Cheng, Loeb, Helfand, Eeles, Morgan.
Drafting of the manuscript: Seibert, Garraway, Plym, Mahal, Morgan.
Critical revision of the manuscript for important intellectual content: Plym, Mahal, Giri, Jacobs, Cheng, Loeb, Helfand, Eeles, Morgan.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: None.
Other: Systematic review: Seibert, Garraway, Plym, Mahal, Giri, Jacobs, Cheng, Loeb, Helfand, Eeles, Morgan.

Financial disclosures: Tyler M. Seibert certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Tyler M. Seibert reports honoraria from Varian Medical Systems and WebMD; has an equity interest in CorTechs Labs, Inc. and serves on its Scientific Advisory Board; and has received in-kind research support from GE Healthcare via a research agreement with the University of California San Diego. Veda Giri reports stock and other ownership interests in Novopyxis. Heather H. Cheng receives research funding for her institution from Astellas, Clovis, Color Genomics, Janssen, Medivation, Phosplatin, and Sanofi; and she has been a consultant to AstraZeneca. Brian T. Helfand is an employee of North-Shore University HealthSystem, which has an agreement with GoPath Labs for genetic tests of polygenic risk score. Rosalind A. Eeles reports the following: GUASCO meeting, San Francisco, CA, USA, January 2016, honorarium as a speaker; the Royal Marsden NHS Foundation Trust, Genetics and prostate cancer, November 2017, support from Janssen, honorarium as a speaker; University of Chicago, Chicago, IL, USA, May 2018, honorarium as an invited speaker; ESMO Meeting, Barcelona, Spain, Treatment sequencing for mCRPC patients within the changing landscape of mHSPC-GU connect, September 2019, educational honorarium paid by Bayer and Ipsen; and AstraZeneca UK Limited, UK, Prostate Dx Advisory Panel, June 30, 2020, a member of the external expert committee, May 2021. Todd M. Morgan reports institutional research funding from Veracyte, and personal fees from Blue Earth Diagnostics and Myriad Genetics Inc.

***Funding/Support and role of the sponsor*:** None.

Peer Review Summary

Peer Review Summary to this article can be found online at https://doi.org/10.1016/j.eururo.2022.12.021.

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Genetic and Genomic Testing for Prostate Cancer: Beyond DNA Repair

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overview

Significant progress has been made in genetic and genomic testing for prostate cancer across the disease spectrum. Molecular profiling is increasingly relevant for routine clinical management, fueled in part by advancements in testing technology and integration of biomarkers into clinical trials. In metastatic prostate cancer, defects in DNA damage response genes are now established predictors of benefit to US Food and Drug Administration–approved poly (ADP-ribose) polymerase inhibitors and immune checkpoint inhibitors, and trials are actively investigating these and other targeted treatment strategies in earlier disease states. Excitingly, opportunities for molecularly informed management beyond DNA damage response genes are also maturing. Germline genetic variants (eg, *BRCA2* or *MSH2/6*) and polygenic germline risk scores are being investigated to inform cancer screening and active surveillance in at-risk carriers. RNA expression tests have recently gained traction in localized prostate cancer, enabling patient risk stratification and tailored treatment intensification via radiotherapy and/or androgen deprivation therapy for localized or salvage treatment. Finally, emerging minimally invasive circulating tumor DNA technology promises to enhance biomarker testing in advanced disease pending additional methodological and clinical validation. Collectively, genetic and genomic tests are rapidly becoming indispensable tools for informing the optimal clinical management of prostate cancer.

INTRODUCTION

Prostate cancer management has undergone substantial transformation within the past decade. Genetic and genomic testing has rapidly matured from a research tool to standard practice across multiple clinical settings, with importance reinforced via inclusion in key practice guidelines. Opportunities for genomic testing in routine practice are continually being refined and expanded, cultivating excitement about precision oncology among patients and prostate cancer health care providers. However, this sea change also emphasizes the importance of having a solid foundational understanding of the data to support clinical practice changes. End users must be aware of testing nuances and potential pitfalls, which transect not only clinical decision making but also patient education and medical resource stewardship. Here, we review key updates in genetic and genomic testing for prostate cancer, including clinical implications of testing for advanced disease, the role of RNA expression tests with emphasis on localized and recurrent disease, and emerging opportunities for minimally invasive plasma circulating tumor DNA (ctDNA) technology to affect the clinical management of advanced prostate cancer.

CLINICAL AND THERAPEUTIC IMPLICATIONS OF GENETIC AND GENOMIC TESTING IN PROSTATE CANCER

Implications of germline genetic testing (ie, testing for inherited alterations) and genomic testing (ie, testing a tumor for somatic and germline alterations) have precipitated major practice changes in the care of patients with prostate cancer, particularly in advanced disease. These changes were heralded by a series of key discoveries beginning in 2015. First, The Cancer Genome Atlas Research Network evaluated 333 primary prostate cancers and found that 19% harbored mutations in DNA repair genes.[1] This was followed up by a Stand Up to Cancer/Prostate Cancer Foundation/American Association for Cancer Research–lead effort sequencing 150 metastatic tissue biopsies collected from patients with castration-resistant disease, revealing that 23% had alterations in DNA repair pathway genes—most commonly within genes *BRCA2*, *ATM*, and *BRCA1*.[2] Shortly thereafter, another pioneering study reported that approximately one in 10 patients with metastatic prostate cancer carried a heritable (ie, germline) mutation in a DNA repair gene.[3] These and subsequent confirmatory studies[4-8] have demonstrated that the DNA damage response pathways—particularly homologous recombination repair (HRR) and mismatch repair—are recurrently altered in a large subset of patients and can drive aggressive prostate cancer biology. Clinically, DNA damage response alterations can confer therapeutic sensitivity to novel targeted agents and potentially constitute life-saving information in the context of navigating familial cancer risk.

DNA Damage Response Defects as Prognostic Biomarkers

Patients with prostate cancer who carry germline *BRCA* mutations are more likely to have poor clinical

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on April 1, 2023 and published at ascopubs.org on May 19, 2023: DOI https://doi.org/10.1200/EDBK_390384

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PRACTICAL APPLICATIONS

- Defects in DNA damage response genes (eg, *BRCA1/2*, *ATM*, *MSH2/6*) are prevalent in approximately 15%-25% of patients with metastatic prostate cancer and confer treatment candidacy for poly (ADP-ribose) polymerase inhibitors and immune checkpoint inhibitors.
- Germline *BRCA2* pathogenic variants are linked to elevated risk of prostate cancer and have implications for intensified early cancer screening and familial risk management. Polygenic risk scores are poised to improve risk evaluation in future.
- RNA expression tests (using prostate tissue) can help inform treatment options for patients with localized disease, including decisions surrounding definitive local treatment and salvage therapy.
- Minimally invasive circulating tumor DNA (ctDNA) tests are used to identify treatment-predictive and prognostic biomarkers in advanced prostate cancer. Newer generations of tests are rapidly augmenting the biological resolution that can be gleaned from ctDNA but require further clinical validation.

outcomes, intraductal and cribriform morphology, and higher Gleason grades compared with their non-*BRCA* carrying counterparts.[9,10] Moreover, evidence suggests that *BRCA2*-defective localized prostate cancers have singularly aggressive biology resembling treatment-refractory metastatic disease. This is evidenced by greater genomic instability and increased (epi)genomic dysregulation of the WNT-pathway mediator complex (ie, *MED12L*/*MED12*) in *BRCA2*-defective localized disease, which are common molecular hallmarks of castration-resistant prostate cancer.[11]

The link between germline *BRCA1/2*-defective disease and clinical aggression is also supported by studies from Castro et al, who observed that germline *BRCA1/2* mutation carriers were more likely to have Gleason score ≥ 8 ($P = .00003$), T3/T4 stage ($P = .003$), nodal involvement ($P = .00005$), and metastases at initial prostate cancer diagnosis ($P = .005$). Germline *BRCA1/2* carriers also had shorter prostate cancer–specific survival (CSS)[12] and metastasis-free survival (MFS) after curative intent therapy: *BRCA1/2* carriers (n = 67) had 3-, 5-, and 10-year MFS rates of 90%, 72%, and 50%, compared with 90%, 94%, and 84% for non-*BRCA1/2* patients ($P < .001$), respectively.[13] Multivariable analysis incorporating standard clinical risk metrics for localized disease demonstrated that *BRCA1/2* mutations were independently prognostic for MFS (hazard ratio [HR], 2.36; 95% CI, 1.38 to 4.03; $P = .002$) and CSS (HR, 2.17; 95% CI, 1.16 to 4.07; $P = .016$).[13] Finally, a retrospective analysis of the Consortium of Investigators of Modifiers of BRCA1/2 cohort of 6,902 men reported an elevated prostate cancer risk for patients with germline pathogenic variants in *BRCA1/2*, affirming the relevance of germline *BRCA1/2* status for familial risk management.[14]

DNA Damage Response Defects as Biomarkers for Response to Poly (ADP-ribose) Polymerase Inhibitors

Recognition of DNA damage response defects as a core molecular driver of metastatic prostate cancer led to multiple clinical trials therapeutically exploiting these defects. Poly (ADP-ribose) polymerase inhibitors (PARPi) are a key targeted drug class developed initially in the context of breast and ovarian cancer. One of the first trials of PARPi in metastatic prostate cancer was the single-arm, phase II, TOPARP-A study, where patients with alterations in DNA damage response genes *BRCA2*, *ATM*, and *BRCA1* achieved significantly higher response rates to olaparib than biomarker-negative patients.[15] This observation fueled several important PARPi studies culminating in US Food and Drug Administration (FDA) approvals for patients with metastatic castration-resistant prostate cancer (mCRPC). The phase III PROfound study enrolled patients with mCRPC harboring DNA repair alterations who had progressed on at least one AR-pathway inhibitor (ARPI) and randomly assigned them to olaparib versus a second ARPI.[16] Patients in the olaparib arm had improved progression-free survival and overall survival,[16,17] leading to olaparib being the first FDA-approved PARPi for prostate cancer in 2020. The strongest signal was seen in patients with *BRCA1*, *BRCA2*, and *ATM* mutations, although rarer DNA repair gene alterations in *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L* are also included within the approval label. In the same year, the phase II TRITON2 study of rucaparib showed a 51% radiographic response rate for docetaxel-refractory patients with *BRCA1/2*-altered mCRPC,[18] leading to FDA-accelerated approval. Recently, multiple phase III studies have investigated the combination of PARPi plus ARPI for mCRPC,[19-21] consistently showing the greatest magnitude of PARPi benefit in patients whose tumors have germline or somatic DNA damage response defects. Several clinical-genomic registries are underway exploring novel biomarkers of PARPi response, including the PROMISE germline-focused registry (NCT04995198)[22] and the PRECISION PARPi-focused registry.[23]

Germline (ie, Inherited) DNA Damage Response Defects as Cancer Risk Genes

Given the relatively high prevalence of germline cancer risk genes and their growing significance in both familial and

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therapeutic contexts, the National Comprehensive Cancer Network (NCCN) Prostate Cancer and American Urological Association/American Society for Therapeutic Radiology and Oncology/Society of Urologic Oncology Advanced Prostate Cancer guidelines advise genetic counseling and genetic testing for patients with metastatic or high-risk localized prostate cancer.[24-26] Identification of germline cancer risk genes in patients enables blood relatives to learn if they share the same cancer risk gene and could potentially benefit from cancer screening and/or risk-reducing and prevention options.

There are recognized and established early detection and risk-reducing options to mitigate breast and ovarian cancer risk, but the implications for male carriers of *BRCA1/2* and other prostate cancer risk genes are less widely recognized. On the basis of the associations of increased prostate cancer risk and aggressiveness overviewed above—as well as findings from the ongoing international United Kingdom–led Identification of Men with a Genetic Predisposition to Prostate Cancer study—there is a strong rationale for offering men with germline *BRCA2*, *BRCA1*, *MSH2*, and *MSH6* mutations intensified prostate cancer screening.[27,28] NCCN Prostate Cancer early detection guidelines currently recommend consideration of family history, Black ancestry and familial cancer risk genes (such as *BRCA2*) in prostate cancer screening decisions, and advise initiating screening at age 40 years for *BRCA2* carriers. Additional trials exploring screening and early detection are ongoing at the National Cancer Institute (ClinicalTrials.gov identifier: NCT03805919), Yale (ClinicalTrials.gov identifier: NCT02154672), University of Michigan, Israel (ClinicalTrials.gov identifier: NCT02053805), Sunnybrook (ClinicalTrials.gov identifier: NCT01990521), and University of Washington/Fred Hutch (ClinicalTrials.gov identifier: NCT04472338) and are expected to help clarify screening/interventional strategies for at-risk carriers.

In the foreseeable future, it is likely that further incorporation of genetic risk into screening optimization will occur across at least two domains. The first domain is refining risk prediction beyond the rare variants in genes such as *BRCA2*, *BRCA1*, *MSH2*, *MSH6*, and *HOXB13*. This combined approach involves simultaneously evaluating rare but higher penetrance genes (eg, *BRCA2*) together with more common but lower-risk variants (so-called polygenic risk scores), as recently reported.[29,30] This combined approach is promising due to its potentially broader applicability but will require additional study and validation in larger diverse populations.[31] The second domain is improving cancer early detection methods beyond prostate-specific antigen (PSA) and current imaging modalities. Excitingly, early cancer detection is a highly active research area precipitating advancements in novel DNA, transcription, methylation, and other genomic profiling technologies. These methodological developments will be reviewed (mostly in the context of biomarker profiling for advanced disease) in the section on ctDNA technology below. Overall, enhanced genetic risk prediction together with increasingly sensitive prostate cancer screening tools is positioned to help reduce prostate cancer–related mortality and morbidity.

Implementation of Germline Genetic Testing

Recommendations for germline genetic testing have recently expanded across the prostate cancer continuum. Testing is now standard practice for all patients with metastatic prostate cancer plus a significant fraction of patients with localized disease (eg, those with high-risk features and/or family history). An important challenge in prostate cancer management is determining how to optimally integrate cancer genetics care, which has been reviewed in a previous ASCO Education session.[32-34] However, broader implementation challenges exist, and consensus recommendations have been made to guide further development.[35] Increasing demand for genetic counseling and testing—coupled to existing accessibility barriers (eg, geographic constraints on in-person services)—has led to bottlenecks in testing, treatment decision making, and familial risk planning. Deficiencies in timely and accessible genetic testing have incentivized a number of experimental practical alternatives to traditional testing models. Efforts to broaden access and alleviate overburdened genetic specialists include the use of online patient video education, as well as reallocating responsibilities of consenting, testing, and/or counseling to oncology professionals (ie, "mainstreaming").[36] These and other novel germline genetic testing paradigms are being investigated prospectively (eg, GENTLeMEN,[37] ProGen,[38] and TARGET studies[39]). Nevertheless at present, collaboration with genetic experts remains crucial when a cancer risk gene is discovered, ensuring that patients and their families receive appropriate education[35] and access to relevant cancer prevention and screening services.

WHAT PROVIDERS NEED TO KNOW ABOUT PROSTATE CANCER RNA EXPRESSION AND HOW IT INFLUENCES MANAGEMENT DECISIONS

The D'Amico/NCCN Risk groups remain the dominant strategy to risk-stratify clinically localized prostate cancer. However, over the past several years, information about prostate cancer RNA expression has substantially augmented our ability to predict patient outcomes and has become an important tool in decision making for many patients with prostate cancer.

Most published literature focuses on the Decipher Genomic Classifier (GC). The Decipher GC uses the Affymetrix Human Exome 1.0st array and is based on a locked model of 22 genes, including genes relevant to cell proliferation, cell motility, cell differentiation, androgen receptor signaling, and immune modulation. This model was originally

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developed to determine the risk of distant metastasis from radical prostatectomy (RP) specimens, and subsequently, a biopsy version of the test has been demonstrated to be prognostic after surveillance, surgery, or radiation.[40] Two other commonly used tests are the Myriad Prolaris test, based on 31 cell-cycle progression (CCP) genes,[41] and the Oncotype DX Genomic Prostate Score (GPS) that evaluates 17 genes including 12 cancer-related genes (androgen signaling, cellular organization, stromal response, and cellular proliferation) and five housekeeping genes.[42] Here, we review the clinical utility of these RNA expression-based GCs in different prostate cancer disease states.

Selecting Patients for Active Surveillance Versus Treatment

Each of the three GCs has shown some utility in identifying low-risk or favorable intermediate-risk patients at risk of progression while on active surveillance or patients who may harbor occult high-grade or stage disease. Therefore, these classifiers are useful for patients who may be borderline between definitive treatment and active surveillance as candidate management options.

Herlemann et al[43] reviewed 220 patients with favorable intermediate-risk prostate cancer who underwent RP and found that the Decipher GC independently predicted adverse pathology (defined as Gleason Grade Group 3-5, pT3b or higher, or N+ disease) with an odds ratio of 1.34 per 0.1 unit increased GC ($P = .002$). Interestingly, patients with GC low or intermediate (ie, <0.6) did not have an increased odds of adverse pathology compared with a population with exclusively very low- or low-risk prostate cancer, suggesting that patients with GC low/intermediate may be reasonable candidates for active surveillance.

Cuzick et al[44] showed in a cohort of 349 patients diagnosed by needle biopsy and managed conservatively that the Prolaris CCP score was the strongest independent predictor of death from prostate cancer (HR per one unit increase, 1.65 [CI, 1.31 to 2.09]; $P = .00003$). The 17-Gene Oncotype DX GPS score was shown to predict adverse pathology and increased risk of biochemical recurrence after RP among men who were initially on active surveillance.[45] Conversely, Lin et al[46] notably evaluated the performance of the GPS score in the Canary Prostate Cancer Active Surveillance Study cohort and did not find a significant independent association of higher GPS score with adverse pathology. In addition, there was no identified association between higher GPS score and subsequent biopsy upgrading in surveilled patients with low-risk prostate cancer who subsequently underwent prostatectomy.

Use of Androgen Deprivation Therapy with Radiation for Intermediate-Risk Prostate Cancer

All three classifiers can potentially help decide if patients with intermediate-risk prostate cancer should receive definitive radiation alone or with androgen deprivation therapy (ADT). Berlin et al[47] found that among a cohort of both favorable and unfavorable intermediate-risk patients managed with radiation alone, the Decipher GC predicted biochemical recurrence and metastasis, whereas the NCCN risk group was not predictive. This suggested that patients with high GC scores may warrant consideration for the addition of ADT to definitive radiation. This approach is being tested prospectively in the NRG-GU-010 trial (ClinicalTrials.gov identifier: NCT05050084) that aims to either intensify or deintensify therapy based on the Decipher GC score.

Tward et al[48] found among 741 patients treated with radiation that the Cell-Cycle Risk score (comprised by combining the Myriad CCP score with the UCSF CAPRA score) identified patients who benefited from ADT (ie, if they scored above the multimodality threshold of 2.112) versus had no benefit from ADT (ie, if they scored below the threshold of 2.112, where the 10-year risk of metastasis was 3.7%, regardless of ADT use). In a small study of 30 patients with Gleason 3 + 4 prostate cancer, GPS was associated with a higher percentage of Gleason pattern 4 at surgery, leading the authors to conclude that GPS may help inform the addition of ADT to radiation.[49]

Prognostication in High-Risk Disease

The role of GCs in changing treatment decisions for high-risk prostate cancer is less firmly established but can still offer prognostic information. A recent example is the Decipher GC was found to be prognostic for outcomes in three RTOG phase III trials.[50] This finding forms the basis for the NRG-GU-009/PREDICT-RT randomized trial that aims to determine whether the Decipher GC can identify patients whose ADT duration can be reduced from 24 to 12 months versus patients who may benefit from up-front treatment intensification with 24 months of ADT plus apalutamide (ClinicalTrials.gov identifier: NCT04513717).

Postprostatectomy Setting: Salvage Radiotherapy Alone Versus Salvage Radiotherapy + ADT

One of the most commonly used classifiers in the postoperative setting is the Decipher GC, which may inform whether to offer ADT with salvage radiation. While gonadotropin-releasing hormone agonists have been shown to improve metastasis-free survival when added to salvage radiation in both the GETUG-16[51] and RADICALS-HD trials,[52] the RTOG 96-01 trial[53] remains particularly influential because it showed that radiotherapy (RT) plus 2 years of ADT in the form of bicalutamide monotherapy 150 mg daily improved overall survival. A post hoc analysis of the RTOG 96-01 trial found that all the survival benefit of ADT was driven by patients with PSA ≥ 0.7, while patients with a PSA < 0.7 did not benefit, causing reluctance among some providers to offer ADT with salvage radiation for patients with PSA < 0.7.[54] However, in a reanalysis of the RTOG 96-01 trial, Feng et al[55] leveraged the

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GC score to provide practical guidance on whether to add ADT to RT for patients with PSA < 0.7. This study showed that among patients with PSA < 0.7, those with a low GC score (<0.45) had worse overall survival with bicalutamide. However, patients with intermediate (≥0.45) or high (>0.6) GC score had better outcomes with bicalutamide, including less distant metastasis, reduced prostate cancer mortality, and better overall survival. Consequently, the Decipher GC score may help identify which patients with PSA < 0.7 (for whom salvage radiation is planned) would benefit from concomitant ADT.

Another GC that has shown promise in the post-prostatectomy setting is the PAM-50 classifier, which was adapted from breast cancer and recreated in a cohort of patients with prostate cancer who had the Decipher GC test. Prostate cancer samples can be classified into luminal and basal subtypes using the same Affymetrix Human Exome 1.0st array as the Decipher GC. Zhao et al[56] found that patients with tumors classified as luminal B benefited more from the addition of postoperative ADT than patients with nonluminal B tumor subtypes. The PAM-50 classifier is being tested prospectively in the NRG-GU-006 randomized trial of salvage radiation plus apalutamide or placebo for patients with rising postoperative PSA (ClinicalTrials.gov identifier: NCT03371719).

Androgen Signaling Inhibitor Benefit in Castrate-Resistant Prostate Cancer

The same PAM-50 classifier may also help prioritize choice of systemic treatment for patients with castration-resistant disease. Feng et al[57] observed that patients with non-metastatic castration-resistant disease and luminal tumor subtype are more likely to benefit from ADT plus apalutamide than ADT alone. In the mCRPC setting, Aggarwal et al[58] demonstrated a link between luminal subtype and biological features suggesting heightened androgen signaling, translating clinically to greater ARPI benefit for patients with luminal tumors versus other subtypes. Ultimately, PAM-50 classification may inform on the degree of tumor androgen reliance and facilitate appropriately tailored treatment.

In summary, RNA expression profiling for genomic classification has enhanced prostate cancer risk stratification in early disease, further broadening the repertoire of genomically informed management strategies across the prostate cancer continuum.

HOW CAN TECHNOLOGY HELP US? NEW AND EMERGING USES FOR ctDNA IN PROSTATE CANCER

As aforementioned, genomic biomarkers are increasingly used for clinical decision making in mCRPC, but challenges of tissue analysis impede integration of biomarkers into routine practice. Routine metastatic tissue biopsy is hampered by financial and health toxicity and high failure rates (16%-40%), especially for bone lesions.[59-61] In addition, archival tissues can be difficult to retrieve, exhausted by previous molecular profiling,[59,62] and may ultimately no longer molecularly reflect contemporaneous mCRPC shaped by often years of previous systemic therapy.[2,4]

Plasma ctDNA is an established minimally invasive source of predictive and prognostic biomarkers, overcoming many of the limitations of tissue-only testing.[63] High concordance of genomic alterations between metastatic tissue and ctDNA[64] plus comparative ease of collection has spurred incorporation of ctDNA profiling into mCRPC clinical trials, including recent pivotal trials of PARPi,[16,19,20,65] PI3K inhibitors,[66,67] and umbrella/platform trials that leverage profiling results for treatment arm assignment.[68-71] Finally, ctDNA testing can democratize access to precision oncology since blood samples can be drawn outside specialized cancer centers and mailed for centralized testing.[72]

Applications for ctDNA testing can be broadly categorized into quantification (ie, detection of ctDNA) or characterization (ie, identifying molecular biomarkers in ctDNA). Detection of ctDNA in mCRPC has prognostic implications across clinical scenarios. For example, high pretreatment ctDNA fraction (ie, the proportion of total cell-free DNA [cfDNA] that is tumor-derived rather than from other sources) is linked to poor treatment response, shorter progression-free survival, and abbreviated overall survival across multiple therapeutic contexts and independent of other established clinical prognostic markers.[73-81] The dynamics of the ctDNA fraction during treatment is a potential surrogate for treatment response, with the magnitude of ctDNA decline (relative to pretreatment levels) associating with time to progression on both taxanes and ARPIs.[74,76] Strikingly, changes in ctDNA fraction may be more informative than on-treatment PSA changes as an early metric of tumor response.

Characterization-based applications include using ctDNA to detect clinically relevant biomarkers, such as truncating defects in *BRCA2* that predict vulnerability to PARPi, as well as mutations in *TP53*, *RB1*, *SPOP*, *PTEN*, and *AR* that may inform prognosis and/or androgen dependency.[78,82] *AR* alterations are an acquired resistance mechanism to AR/androgen-axis drugs with prognostic and potentially predictive relevance but can only be detected in treatment-exposed ctDNA or metastatic tissue (ie, are not present in primary tissue).[1,80,83]

Importantly, ctDNA fraction largely determines which classes of alteration are amenable to de novo detection. Copy number variants (CNVs) require severalfold higher ctDNA fraction compared with mutations and in general detection sensitivity (for all alteration classes) scales with ctDNA fraction.[84] Low ctDNA fraction can therefore lead to

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false-negative results, especially for deletions such as homozygous *BRCA2* or *PTEN* loss. Importantly, some testing platforms do not analyze matched white blood cell controls, potentially resulting in incomplete filtration of clonal hematopoietic variants which can manifest as false-positive ctDNA mutations.[85] It is therefore ideal to perform synchronous tissue and ctDNA testing to mitigate the limitations of each approach.

Beyond Targeted Panel Sequencing: The Promise of Broader DNA Profiling From Liquid Biopsies

Presently, clinical ctDNA tests typically use targeted panel sequencing: profiling of dozens to hundreds of cancer-related genes in parallel. Most ctDNA tests only capture coding exons, although some tests include introns implicated in recurrent oncogenic fusions. Targeted panel sequencing assays have high sensitivity for single-nucleotide variants (SNVs) and small insertions/deletions (InDels), moderate sensitivity for gene-level copy number changes (eg, *PTEN* deletions), and low sensitivity for complex structural rearrangements and large aneuploidies. Cost feasibility forces a practical tradeoff between sequencing depth (ie, redundant read coverage across target regions) and breadth (ie, number of genes or regions examined). However, diminishing sequencing costs are enabling broader sequencing methods such as whole-exome sequencing (WES) and whole-genome sequencing (WGS) to become cost permissive and clinically feasible at scale.

In contrast to targeted panel sequencing, WES enables detection of SNVs, InDels, and gene-level copy number changes across approximately 20,000 genes, while WGS extends detection to noncoding territory (eg, introns, enhancers, intergenic regions, and other types of regions). Growing data indicate that tumor defects in noncoding areas can drive aggressive cancer biology. Notable examples include *AR* enhancer copy gains[86,87] and genomic rearrangements with intronic breakpoints in *RB1*, *PTEN*, *BRCA2*, and *MSH2/6*.[5,7,88-91] Current clinical assays typically cannot detect these biologically relevant truncating rearrangements (due to not profiling introns), but newer iterations of broader tests will enable their detection in future. Finally, a key advantage of WES/WGS is enhanced resolution for whole-genome doubling (WGD). In prostate cancer, WGD is potentially linked to poorer prognosis and can confound accurate discrimination of homozygous from heterozygous deletions (in key genes such as *PTEN* and *BRCA2*).[92,93]

Tumor cell characteristics and clinical phenotypes are shaped by the totality of somatic and germline defects across the genome. Intriguingly, alterations in genes such as *BRCA2* and *MSH2/6* are associated with genome-wide scars whose quantification may be an alternative biomarker measuring the biological consequences of the gene alteration. WES and WGS enable synthesis of second-order information from all mutations, deletions, and structural rearrangements analyzed in aggregate, overcoming many challenges of detecting alterations within individual genes. These challenges include imperfect detection (eg, poor sensitivity for CNVs in low ctDNA fraction), difficulty of predicting alteration pathogenicity and/or likelihood of sensitization to targeted drugs, and inability to characterize nonsequence mechanisms of gene (in)activation (eg, epigenomic alterations).

Higher-order genomic readouts of emerging clinical relevance in mCRPC include tumor mutation burden, microsatellite instability, and CDK12-associated tandem duplications as predictors of immunotherapy response[91,94,95]; indices of overall genomic instability (eg, large-scale transitions, telomeric imbalance, genomic loss of heterozygosity) suggestive of HRR deficiency and PARPi candidacy[5,96-98]; and mutational signatures that reveal mutation etiologies (eg, tobacco exposure).[99] Sophisticated machine learning techniques (eg, gradient tree boosting) can optimally combine many higher-order genomic features for even more accurate identification of patients likely to benefit from targeted therapy.[100-103] These tools promise to help discover new single-gene and combinatorial genomic mediators of HRR/mismatch-repair deficiency, as well as characterize rare HRR gene defects (eg, *ATM*, *BARD1*, *RAD51* family genes) whose biomarker utility is currently uncertain.

Emerging Techniques for Tumor Phenotyping Using ctDNA

DNA alterations are the blueprint for cell phenotype, but regulation of the epigenome, transcriptome, and proteome also affect tumor behavior. New omic techniques are rapidly expanding the phenotype information that can be measured from ctDNA.

Neuroendocrine prostate cancer (NEPC) is a key clinically relevant phenotype in mCRPC but can be difficult to diagnose. Clinical presentation of NEPC can be heterogeneous, and classical NEPC features are often nonspecific (eg, low PSA),[104] metastatic tissue biopsies for definitive histopathological diagnosis are not always feasible and may not generalize to bulk disease, and known genomic correlates of NEPC (eg, *TP53*/*RB1* loss) are also nonspecific[105,106] and technically challenging to detect.[7,88] Treatment-related NEPC transdifferentiation is an increasingly prevalent clinical trajectory in mCRPC, ostensibly because of the growing cumulative exposure to AR-axis drugs across the spectrum of disease (eg, ARPI for castration-sensitive prostate cancer).[107-114] Therefore, there is mounting urgency to develop more accurate tools to detect treatment-induced NEPC and facilitate timely clinical intervention.

Epigenomic markers (eg, 5-methylcytosine and 5-hydroxymethylcytosine) are promising tools for tumor phenotyping.[115] ctDNA methylation assays can augment

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biomarker characterization and classify samples according to global epigenomic features. Methylation assays can distinguish AR-driven mCRPC from NEPC, outperforming traditional DNA-sequencing approaches even in low ctDNA fraction.[116-119] Clinically, ctDNA methylation assays may assess tumor AR dependence, informing timing of treatment change as well as treatment choice (eg, ARPIs versus taxanes or platinum chemotherapy in tumors with low AR signaling). Methylation-based phenotypic subgroups beyond classical NEPC (AR–/neuroendocrine [NE]+)—such as amphicrine (NE+/AR+) and double-negative (NE–/AR–) states[120]—may also be linked to potential therapeutic vulnerabilities (eg, WNT-pathway activation).[106,114,121] Currently, methylation assays are only commercially available for early cancer detection.[122] Standardization and prospective validation are needed to define the role of methylation tests in the management of advanced prostate cancer.

Dying tumor cells release chromatin into the bloodstream as fragmented cfDNA and nucleosomes, which can be analyzed to gain insight into tumor transcriptional activity, gene regulation, and transcription factor binding patterns.[123-129] Fragmentomics is a promising new area that exploits the physical properties of ctDNA to inform tissue of origin and tumor phenotype. In mCRPC, fragmentomic features have been correlated with patient-matched metastatic tissue RNA abundance,[125] as well as AR- and NE-associated transcription factor activity.[123] In a recent article by De Sarkar et al, global fragment features were used to generate a model that classifies prostate cancers along a spectrum of AR- versus NE-driven disease, achieving 90.4% sensitivity (for predicting NEPC) and 97.5% specificity (for predicting AR-driven mCRPC).[128,129] Analogous to methylation-based assays, fragmentomic approaches are being investigated for early cancer detection.[130,131] Chromatin immunoprecipitation and sequencing of cell-free nucleosomes (cfChIP-seq) is another new method that retrieves DNA linked to epigenetically decorated nucleosomes, enabling multiplexed insight into gene regulation and global cell identity.[127] Overall, these experimental techniques are poised to augment the repertoire of ctDNA phenotyping approaches, with methylation techniques most analytically mature for potential clinical use in mCRPC.

Plasma cfDNA includes both DNA from tumor (ctDNA) and from noncancerous normal cells, yet this normal fraction is not currently used for oncology applications. Intriguingly, methylation sequencing and cfChIP-seq can potentially reveal clinically relevant information from normal cfDNA. Normal cfDNA primarily comes from hematopoietic cells, raising the possibility of characterizing immune activity and/or immune-related adverse events.[132] Other cell types can release cfDNA during specific host states, potentially offering measures of organ-specific treatment toxicities (eg, gastrointestinal adverse events) as well as noncancer comorbidities (eg, cardiac dysfunction) that complicate optimal oncological care.[127]

Ultimately, new sequencing and computational techniques that integrate genotype and phenotype are facilitating increasingly multimodal clinical profiling.

CONCLUSIONS

Over the past decade, detailed molecular dissection of thousands of prostate cancer specimens has ushered in a new era of genomics-informed personalized clinical management. DNA biomarkers have become critical tools for informing routine clinical practice, particularly in metastatic disease where FDA-approved PARPi and immune checkpoint inhibitors are available for patients with DNA damage response defects. Genetic and genomic testing is also transforming management for early-stage prostate cancer. Applications include leveraging genetic risk scores for cancer prevention and family risk management and RNA expression tests for navigating options for definitive local therapy and salvage treatment for localized disease. Finally, ctDNA testing has become a recognized minimally invasive tool for biomarker profiling in advanced prostate cancer, and technological advancements for ctDNA tumor phenotyping are continuing to broaden its potential clinical applicability.

A perennial challenge for biomarker-informed care will be balancing clinical pragmatism (eg, dichotomizing patients into easily actionable subgroups) against the risk of oversimplifying complex tumor biology. In the future, multimodal genomic profiling approaches (eg, incorporating DNA, RNA, methylation, and histone markers) will offer increasingly nuanced biological insight, while new machine learning techniques are poised to harmonize this information and streamline clinical decision making. Ongoing education of healthcare practitioners on genomic tools (and their limitations), shifting management practices, and clinical evidence to support decision making will be increasingly critical to ensure caregivers are informed on how to incorporate molecular testing into their daily practice.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc.

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Consulting or Advisory Role: AstraZeneca
Research Funding: ESSA (Inst)

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Consulting or Advisory Role: Bayer, Blue Earth Diagnostics, Boston Scientific, Janssen Oncology, Myovant Sciences
Research Funding: Astellas Pharma, Janssen, Bayer
Patents, Royalties, Other Intellectual Property: Wife has a patent on volatile diagnostics of infections (I)

Heather H. Cheng
Consulting or Advisory Role: AstraZeneca (I)
Research Funding: Sanofi (Inst), Janssen (Inst), Clovis Oncology (Inst), Color Health Foundation (Inst), Medivation/Astellas (Inst), Promontory Therapeutics (Inst)
Patents, Royalties, Other Intellectual Property: UpToDate
Other Relationship: Janssen

No other potential conflicts of interest were reported.

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Prostate. Author manuscript; available in PMC 2023 August 01.

Published in final edited form as:
Prostate. 2022 August ; 82(Suppl 1): S3–S12. doi:10.1002/pros.24340.

Germline Genetics of Prostate Cancer

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Abstract

A number of studies have identified an important fraction (>/~10%) of men with high risk localized prostate cancer and metastatic prostate cancer that carry germline (heritable) pathogenic and likely pathogenic variants (also known as mutations) in DNA repair genes. Moreover, growing evidence suggests that inactivation of specific genes, particularly key genes involved in homologous recombination and mismatch DNA repair, are important in prostate cancer initiation and/or development of metastases. This has led to substantial expansion of the national guidelines for which patients should be offered germline genetic testing. Here, we review key literature on individual genes, with *BRCA2* best understood, and *ATM, CHEK2, BRCA1, HOXB13, MSH2, MSH6, PALB2, TP53* and *NBN* discussed individually. Treatment implications in advanced disease include FDA-approval of rucaparib and olaparib, and pembrolizumab in the metastatic castration resistant setting, and newer clinical studies moving into early disease states and incorporating combination approaches. We review the current germline genetic testing national guidelines, and discuss the importance of cascade genetic testing of relatives, diverse populations and attention to inclusion, as well as prostate cancer screening updates and clinical trial opportunities for men who carry genetic risk factors for prostate cancer.

Keywords

prostate cancer; DNA damage repair; germline mutations; pathogenic variants; *BRCA2* ; *BRCA1* ; *Lynch Syndrome* ; precision oncology

INTRODUCTION:

It has been well established that prostate cancer has a strong genetic association. The discovery of populations with higher prevalence of single high penetrance risk factors such as BRCA2 in specific subgroups such as men with metastatic disease, paired with the increased availability and decreased cost of next generation sequencing have led to the expanded recommendations for germline genetic testing in patients with prostate cancer. These new technologies have led to the discovery of more germline genetic factors implicated in prostate cancer and are now accompanied by new FDA-approved treatment

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Disclosures: HHC receives research funding to her institution from: Astellas, Clovis, Color Genomics, Janssen, Medivation, Phosplatin, and Sanofi and she has been a consultant to AstraZeneca.

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options in the advanced disease setting. This review article will address the landscape of germline genetics of prostate cancer, review current guidelines for testing (including practical considerations), and describe the clinical practice implications of germline DNA repair mutations.

HERITABILITY OF PROSTATE CANCER:

The genetic heritability of prostate cancer has been notably highlighted by two key European studies. The Norwegian Twin Cancer study was published in 2016 and explored prostate cancer risk in 203,000 monozygotic and dizygotic twin pairs. This study suggested that up to 57% of prostate cancer can be attributed to genetic risk factors (1). The Prostate Cancer data Base Sweden (PCBaSE) study showed that the risk of developing prostate cancer was higher in men who had brothers with prostate cancer. In their study, by age 65, men who had brothers with prostate cancer had a risk of 14.9% of also developing prostate cancer, compared to a 4.8% risk of developing prostate cancer for men who did not have a brother with prostate cancer. At age 75, the risk of developing prostate cancer for those with a brother with the disease was 30.3%, compared to 12.9% for those without a brother with prostate cancer. The results were similar if exclusions were made for those with low-risk prostate cancer (2).

Genetic factors may influence not only risk of developing prostate cancer, but also the prognosis of disease that may develop. A separate study conducted in Sweden showed that sons with prostate cancer whose fathers had also had prostate cancer had an overall survival that correlated with their fathers' (3).

DNA REPAIR GENES

Much of the early data exploring the genomic makeup of prostate cancer was obtained from diagnostic prostate biopsies; metastatic prostate cancer tissue was not studied until an international study to characterize the genomic makeup of metastatic biopsies was published in 2015. The review of 150 biopsies from patients with metastatic prostate cancer in this study identified a large number of actionable mutations, including 23% of men whose cancers had evidence of mutations in DNA repair genes including *BRCA1, ATM*, and *BRCA2*. Up to 8% of these DNA repair mutations were germline (4) ; much higher than previously recognized.

In 2016, Pritchard et al studied 692 patients with metastatic castrate resistant prostate cancer who underwent germline genetic testing reported rates of germline DNA repair mutations ranging from 4.6% in localized disease to up 11.8% in metastatic disease (5). Most common genetic germline alterations were in *BRCA2* (5.3%), *CHEK2* (1.9%), *ATM* (1.6%), and BRCA1 (0.9%). Other notable genes were *RAD51D* (0.4%) and *PALB2* (0.4%). Of key importance, the men were not selected for family history of cancer or their age at diagnosis, and the presence of germline genetic mutations in DNA repair were not associated with family history of prostate cancer or age at presentation. In patients whose tumor tissue was also available for sequencing, 67% of tumors had second allele inactivation, suggesting that the germline alterations were contributing to the resulting prostate cancer.

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Other studies have identified similar rates of DNA repair mutations in metastatic prostate cancer patients (6-9). DNA repair mutations have also been seen in metastatic hormone sensitive prostate cancer (9), as well as high-risk localized disease. A recent study conducted by Berchuck et. al found that 9.5% of 201 patients with high-risk localized disease had evidence of DNA repair mutations, most commonly *BRCA2* (3%) and *ATM* (2%) (10). These studies provide justification for expanding the criteria for offering men with high risk localized and those with metastatic prostate cancer opportunities for germline genetic testing.

AGGRESSIVE NATURE OF PROSTATE CANCER WITH DNA REPAIR MUTATIONS

While there have been important advances made in the treatment of metastatic prostate cancers with DNA repair mutations, discussed in further detail later in this issue, it is also important to recognize that prostate cancers with DNA repair mutations (both localized and metastatic) may be associated with a more aggressive phenotype. Several recent studies have highlighted this link between DNA repair mutations and more aggressive disease.

A retrospective study of almost 800 patients with localized prostate cancer analyzed the association of lethal prostate cancer with DNA repair mutations (11). This study included 313 patients with lethal prostate cancer (died of their disease), and 486 patients with low risk localized prostate cancer. Mutations in DNA repair genes including *BRCA1, ATM*, and *BRCA2* were higher in those with lethal prostate cancer, with an incidence of 6.1%, compared with localized disease only, with incidence of 1.4%. In the population with lethal prostate cancer, the incidence of a DNA repair mutation decreased with age; from 10% for those 60 and younger, to 3% for those 75 and over, suggesting that DNA repair mutations lead to an earlier age at death due to prostate cancer.

There has been significant evidence that germline carriers of DNA repair mutations that develop prostate cancer have a higher risk of metastatic progression and subsequent death. Castro et al studied the association of patients with prostate cancer that had germline *BRCA1* and *BRCA2* mutations, and found that patients with these DNA repair alterations were likely to have more aggressive disease. Specifically, this included a Gleason score 8 or above, nodal involvement, and higher T stage. Patients with germline *BRCA1* and *BRCA2* mutation*s* were also more likely to have metastatic disease at diagnosis. Survival related to prostate cancer was longer in patients who were not carriers , at 15.7 years, compared to 8.6 years in patients who were carriers of germline *BRCA1* and *BRCA2* mutation*s*. (12).

Castro et al conducted another study in 2015 that compared rates of metastases in patients with prostate cancer who carried *BRCA1* and *BRCA2* mutations, compared with patients with prostate cancer that did not carry *BRCA1* and *BRCA2* mutations. This study showed that there were lower rates of metastases at 3, 5, and 10 years of treatment in those who were not BRCA carriers (90%, 72%, and 50% in carriers respectively) compared with men who were carriers of *BRCA1* or *BRCA2* mutations (97%, 94%, and 84% respectively), suggesting that germline carriers of *BRCA1* and *BRCA2* mutations have a higher rate of metastatic disease (13). They also found that 3 year, 5 year, and 10 year prostate cancer

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specific survival was significantly worse in carriers of BRCA mutations (96%, 76%, and 61% respectively), when compared to non-carriers (99%, 97%, and 85%).

A prospective cohort study called the PROREPAIR-B study investigated the treatment outcomes of patients with metastatic prostate cancer, and the relationship to germline DNA repair mutations. Sixty-eight out of 419 study participants (16%) had germline DNA repair mutations (14 with *BRCA2*, 8 with *ATM*, 4 with *BRCA1*). There was no statistically significant difference in cause-specific survival between carriers of all combined DNA repair mutations (*BRCA2, ATM, and BRCA1*) and non-carriers, however the cause-specific survival was significantly less in *BRCA2* carriers (17 months vs. 33 months) (6).

Approximately 5% of patients with high-risk localized prostate cancer have germline DNA repair mutations. There is emerging data to suggest that germline DNA repair mutations may be associated with specific histologic features in the localized disease setting, which may offer a potential clinical correlate (10, 14-15). Specifically, patients with germline *BRCA2* mutations are more likely to have intraductal histology, which has been associated with an aggressive clinical course ; higher risk of biochemical recurrence, metastatic disease, and even mortality (16). Aside from intraductal histology, there have been associations with other high-risk pathologic features in patients with localized prostate cancer, such as cribriform pattern 4, lymphovascular invasion, ductal histology, and the presence of Gleason group 5 histology (17-19).

INDIVIDUAL GENES:

DNA repair genes refer to a group of genes that collectively aid in repairing errors in DNA during the replication process. There are variable data for individual genes and an emerging understanding of how they may impact prostate cancer risk and cancer behavior. The data known about individual genes is reviewed below.

BRCA2

The strongest data about the inherited risk of prostate cancer relates to *BRCA2* mutations, largely obtained from cohorts assembled from female relatives with breast and ovarian cancer. The relative risk of developing prostate cancer for germline *BRCA2* mutation carriers by the age of 65 is estimated to be between 2.5 to 8.6 fold when compared with non-carriers (20-22). In another study, the cumulative incidence of being diagnosed with prostate cancer by the age of 65 ranged from 7% to 33% (23).

It has been shown that *BRCA2* mutation carriers have a more aggressive prostate cancer phenotype. Genomic profiles of localized prostate cancer from 14 patients with germline *BRCA2* mutations show a more aggressive phenotype (15). Tumors displayed more genomic instability, with profiles that more closely resemble metastatic prostate cancer than localized prostate cancer. These researchers also discovered genomic and epigenomic dysregulation of the *MED12L/MED12* axis, a pathway often dysregulated in metastatic prostate cancer. The molecular observation that germline *BRCA2* mutations lead to more aggressive disease is also highlighted in several observational studies.

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In an Icelandic study, patients with the founder mutation *BRCA2* 999del5 and prostate cancer were more likely to have a higher-risk disease at a younger age (24). Those patients were also observed to have a shorter median survival time, and an increased risk of prostate-cancer related mortality, when adjusted for age, year of diagnosis, and stage. Yet another study done showed that the risk for developing prostate cancer was three times higher among *BRCA2* carriers, and was also associated with a higher Gleason score (25). This study also showed a higher risk of prostate cancer recurrence and prostate cancer-related death, when compared to non-carriers.

There is also data from the Consortium of Investigators of Modifiers of BRCA1/2 to suggest that carriers of *BRCA2* mutations have an increased risk of developing prostate cancer when compared to *BRCA1* carriers (26).

BRCA1

Germline mutations in *BRCA1* are also associated with higher risks of development of prostate cancer and aggressive nature of disease (12, 25) though the strength of evidence and apparent risk appears to be less than *BRCA2* mutations. In one study, the risk of prostate cancer in carriers of *BRCA1* mutations was estimated to be about 3.75 fold, though not as high as *BRCA2* mutation carriers (27).

ATM

While *ATM* is also a gene involved in DNA repair and is the second most common DNA repair alteration in metastatic prostate cancer after *BRCA2* (5), studies show that it works somewhat differently to *BRCA2*, especially in its response to PARP inhibitors. It is also unclear whether a loss of *ATM* functions to promote initiation of cancer, and/or enhance metastatic potential.

Many of the studies describing germline *ATM* mutations and their pathogenic potential in prostate cancer have been done with other genes of DNA repair, such as *BRCA2*. Much of that data has been presented elsewhere in this article. An Icelandic study published in 2015 studied genetic variants associated with gastric cancer, and identified two loss-of-function variants of *ATM* that were associated with prostate cancer with an OR of 2.18, along with an association with gastric cancer (28).

PALB2

The *PALB2* gene is part of the DNA repair pathway and is commonly associated with DNA repair mutations in breast and ovarian cancer cohorts. In fact, much of the early data linking *PALB2* mutations with prostate cancer comes from data from female relatives with breast and ovarian cancer. However, the exact nature of *PALB2* in the pathogenesis of prostate cancer is unclear. This historic, early data is viewed with caution, as prostate cancer in these studies was often underreported, and there was not a clear distinction between low risk, early-stage prostate cancer, and more advanced, metastatic prostate cancer. Additionally, earlier studies did not show a clear association between germline *PALB2* mutations and hereditary prostate cancer in families with a high rate of prostate cancers before age 55 or multiple affected family members (29-31). However, other, more recent studies have

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suggested the association of germline *PALB2* mutations with aggressive prostate cancer, and some studies have reported resistance of *PALB2*-mutated cancers to PARP inhibitors (32-33)

There is a need to identify more patients with germline *PALB2* mutations, to understand the conferred risk of disease and the biological significance and therapeutic consequences in prostate cancer.

CHEK2

Most of the data that associates germline *CHEK2* mutations with increased prostate cancer risk comes from Poland. Cybulksi and colleagues have led much of this work and have found that there are founder mutations in *CHEK2* including *CHEK2* 1100delC and *CHEK2* IVS2 1 1G>A which are associated with a moderate risk of prostate cancer. These two driver mutations were found in 0.5% of controls, compared with 1.6% of unselected patients with prostate cancer, with an OR of 3.4 (34). Additionally, there is a missense *CHEK2* variant I157T that has been reported in association with prostate cancer (35) and there have been several studies evaluating *CHEK2* c.1100delC separately. A meta-analysis published in 2014 reviewed 12 studies that discussed the specific *CHEK2* c.1100delC variant and its association with prostate cancer risk. Five out of the 12 studies had independent data, which when pooled, showed that *CHEK2* c.1100delC is associated with increased risk of prostate cancer (36). Further, Wu and colleagues showed that *CHEK2* c.1100delC has a higher carrier rate in those with lethal prostate cancer, when compared with lower-risk prostate cancer patients, with an estimated OR of 7.86 in lethal prostate cancer (37).

HOXB13

HOXB13 has been identified as a gene that codes for a transcription factor that is important in prostate development, however the mechanism and pathways that lead to its role in prostate cancer development are not yet identified. There have been several studies that have shown the association of the *HOXB13* G84E variant with prostate cancer, including a European study which showed an increased frequency of the *HOXB13* G84E variant in patients with prostate cancer at 1.4% compared to those without prostate cancer at 0.1% (38). In a separate cohort of 3607 patients with prostate cancer, the *HOXB13* G84E variant was found at a rate of 1.1% (39). The *HOXB13* G84E gene variant does not appear to be independently associated with more aggressive features of prostate cancer (40).

NBN (also called NBS1)

A Polish study showed that the *NBS1* 657del5 founder mutation is associated with increased risk of prostate cancer. They studied the prevalence of this mutation in 56 familial cases of prostate cancer, and compared this to 305 nonfamilial cases of prostate cancer, along with 1500 control cases. They found that the *NSB1* 657del5 founder mutation was present in 9% of patients with familial prostate cancer, 2.2% of patients with nonfamilial prostate cancer, and 0.6% in non-cancer controls. This study also analyzed somatic alterations of *NBS1* to assess for loss of heterozygosity, with 8 samples from carriers of the founder *NBS1* germline mutation. 7/8 samples from founder mutation carriers were found to have second allele inactivation, compared with 1/9 tumors from non-carriers, suggesting that heterozygous carriers of the *NBS1* founder mutation have an increased risk of prostate cancer (41).

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The same authors also conducted a separate study to explore lethality of *NSB1* founder mutation status among patients with prostate cancer. They found that overall mortality as well as 5-year survival was worse for patients with prostate cancer with the *NBS1* 657del5 founder mutation, with a HR for overall mortality at 1.85 and 5 year survival of 49% in those with the founder mutation, compared with 72% for mutation negative cases (42)

Lynch Syndrome Genes

Historically, Lynch syndrome has primarily been associated with increased risk for colorectal and endometrial cancer, however there is mounting evidence that prostate cancer risk may also be increased in associations with mutations in germline Lynch Syndrome genes. These genes are primarily DNA mismatch repair genes including *MSH2, MSH6, MLH1*, and *PMS2*. The Prospective Lynch Syndrome Database reported data on 6350 men with Lynch Syndrome mutations, and found that 1808 of these men prospectively developed prostate cancer. In this population, *MSH2* carriers were noted to have the highest rate of prostate cancer. By the age of 75, men with *MSH2* mutations had a cumulative incidence of 23.8%, compared to 13.8% for *MLH1*, 8.9% for *MSH6*, and 4.6% for *PMS2* (43).

The IMPACT study is an ongoing prospective study that assessed PSA screening in patients aged 40 to 69 with known mutations in *MLH1, MSH2, or MSH6*, and matched them with age-matched controls without mutations in Lynch syndrome genes. They found that in their total population, 1.9% of patients developed prostate cancer. The incidence of prostate cancer was higher among carriers of pathogenic variants of *MSH2* and *MSH6*, but there was no prostate cancer detected in carriers of *MLH1*. The incidence of clinically significant prostate cancer was higher in carriers of *MSH2* and *MSH6*, when compared to noncarrier controls. This finding has important screening implications, and suggests that germline carriers of *MHS2* and *MSH6* mutations should undergo targeted PSA screening (44).

TP53

Germline *TP53* mutations are well known for their association with Li Fraumeni Syndrome, an autosomal dominant condition that predisposes affected individuals to multiple cancers early in life, most commonly breast cancers and sarcomas. A recent study conducted by Maxwell et al describes the relevant association of germline *TP53* mutations and prostate cancer (45). In the cohort of 163 men with Li Fraumeni Syndrome (with a germline *TP53* mutation) studied in this group, 31 were identified to have prostate cancer. Among 117 men with Li Fraumeni Syndrome who did not have prostate cancer at the time of testing, 6 were diagnosed with prostate cancer at a median timeframe of 3 years. In the cohort of prostate cancer patients without known Li Fraumeni Syndrome, 38 of 6850 patients were found to have a germline *TP53* mutation at the time of genetic testing—a relative risk 9 times higher when compared to population controls. The data also indicate that germline *TP53* mutations conferred a more aggressive phenotype of prostate cancer, with 44% of patients having a Gleason score of 8 or above, and 29% with aggressive disease at diagnosis. These findings support inclusion of *TP53* testing for patients with prostate cancer who meet criteria for germline genetic testing, and also support prostate cancer screening of patients with known Li Fraumeni Syndrome.

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POLYGENIC RISK SCORES:

Due to the well-documented increased risks and aggressive nature of prostate cancer with germline DNA repair mutations, there have been attempts to quantify that risk using polygenic risk scoring. There have been several studies that have used susceptibility variants derived from prior studies of *BRCA1* and *BRCA2* mutated breast cancers. A study by Lecarpentier et al demonstrated that by age 80, prostate cancer risk at the 5th and 95th percentile of the polygenic risk score does very greatly—from 7% to 26% for *BRCA1* mutation carriers and from 19% to 61% for *BRCA2* mutation carriers (46). A recent study by Barnes et al used a population based polygenic risk score based approach to determine risk, and found that polygenic risk score for prostate cancer based on a population was associated with higher rates of prostate cancer for *BRCA1* carriers and *BRCA2* carriers. For *BRCA2* carriers by age 85, the 5th and 95th percentile prostate cancer risks were reported as 34.1% to 87.6%, respectively (47).

There has also been recent evidence to suggest that more rare variants of DNA repair mutations such as *HOXB13* also contribute to polygenic risk score assessment, and should be considered in further studies. In a recent study conducted by Darst et al, polygenic risk score assessment for carriers of *HOXB13, BRCA2, ATM*, and *CHEK2* showed that by the age of 85y, the absolute risk of prostate cancer among carriers of the above genes in combination ranged from 9% in the lower polygenic risk score percentile, to 56% in the highest risk score percentile (48).

STANDARD OF CARE CLINICAL GENETIC TESTING GUIDELINES:

Based on the above data, the National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer recommend germline genetic testing for the following groups of patients with prostate cancer (version 1.2022):

NCCN guidelines recommend offering germling testing to these subsets of patients (NCCN guidelines):

1. Patients with node-positive, high-risk, or very high-risk localized prostate cancer
2. Patients with metastatic prostate cancer
3. Patients that meet family history criteria
    - **a.** Family history of high-risk germline genetic mutations, such as BRCA1/2 and Lynch Syndrome
    - **b.** Ashkenazi Jewish ancestry
    - **c.** Personal history of breast cancer
    - **d.** At least one or more first degree, second degree, or third degree relative with breast cancer at age of 50 or less, male breast cancer, ovarian cancer, exocrine pancreatic cancer, or metastatic/regional high-risk, or very high-risk prostate cancer at any age.

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e. One or more first degree relative with prostate cancer at age 60 or less (except for localized, grade group 1).

f. Two or more first, second, or third degree relatives with breast or prostate cancer (except for localized, grade group 1) at any age

g. Three or more first or second degree relatives with Lynch Syndrome related cancers especially diagnosed at age 50 or less; cancers of the biliary tract, endometrium, stomach, ovary, exocrine pancreas, upper tract urothelial, small bowel, colorectal, or glioblastoma.

NCCN guidelines recommend considering germline testing to these subsets of patients:

1. Intermediate risk prostate cancer and intraductal/cribriform histology
2. Personal history of exocrine pancreatic, colorectal, gastric, melanoma, pancreatic, upper tract urothelial, glioblastoma, biliary tract, or small intestinal cancers

The NCCN guidelines recommend that if done, testing includes genes associated with Lynch Syndrome (MSH1, MSH6, MLH1, and PMS2), and homologous recombination repair genes (BRCA 1 and 2, ATM, PALB2, and CHEK2). The NCCN does state that other genes can be tested based on family history or clinical suspicion. Most commercially available genetic testing vendors including Color and Invitae offer much larger panel sizes, that could be more appropriate for metastatic prostate cancer and those considering clinical trial participation.

The optimal delivery method of germline testing is currently unclear. Traditionally, patients have been referred to a genetic counselor to receive education and undergo a pre-test risk assessment prior to undergoing testing. The counselor usually meets with the patient a second time after germline genetic testing results return, to discuss the implications of the results, possibly including cascade genetic testing. Nuances of this testing and proposed new methods to advance testing are presented below.

NOVEL GENETIC TESTING IMPLEMENTATION APPROACHES:

The traditional model has worked well for some time, however given the expanded recommendations for germline testing for prostate cancer and for other malignancies, workforce and resource limitations are being called into question. There have been several recent attempts to standardize provider-led germline testing initiatives. A recent prospective study conducted at multiple cancer centers provided training in germline testing and in patient counseling for cancer providers. Patients who accepted germline testing received pre-test counseling by their oncologist, then underwent testing. If a germline mutation was discovered on their testing, they were then referred to a genetic counselor to discuss further recommendations. The majority of patients (95%) in this study accepted germline testing when offered by their oncologist (49). Another study at the VA evaluated provider-led initiation of germline testing; in this study, 80% of participants accepted germline testing, and were provided with a phone-based counseling visit with a genetic counselor if the test was positive for a germline genetic mutation (50). These results suggest that provider-led germline genetic testing could work to improve access to genetic testing, while

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being mindful of resource limitations. Several ongoing studies are exploring innovative ways to incorporate germline genetic tsting in the face of these limitations, including the GENTLEMEN study (NCT03503097), TARGET study (NCT04447703), and PROMISE study (NCT04995198).

With the increased acceptance of and expanded guidelines for germline genetic testing, there are important unanswered questions that remain. One of these questions is regarding optimal prostate cancer screening for men at risk for prostate cancer by virtue of being a germline carrier of a known prostate cancer risk gene; detailed screening guidelines for individuals carrying germline mutations (pathogenic variants) in prostate cancer risk genes are beginning to emerge. The ongoing IMPACT study preliminarily supports screening men aged 40-69 with BRCA1 and BRCA2 mutations using yearly PSA testing (44, 51-52). As discussed earlier in this review, the IMPACT study's cohort of *MLH1, MSH2*, and *MSH6* carriers show an increased risk of prostate cancer in the *MSH2* and *MSH6* mutation carriers, supporting early screening for this group as well.

The NCCN currently supports referral to a cancer genetics professional for those who carry a germline high-risk pathogenic variant, to engage in shared decision making regarding their individual screening recommendations. They suggest that PSA screening begin at the age of 40, with an annual PSA and DRE, with possible prostate biopsy if PSA is above the median age-matched range (53). The Philadelphia Prostate Cancer Consensus Conference, last convened in 2019, recommends starting screening for prostate cancer at the age of 40, or 10 years prior to the first affected relative's development of prostate cancer, for known carriers *of BRCA2* mutations, with consideration of a similar screening pattern for carriers of *ATM, BRCA1, HOXB13*, and mismatch repair genes (54). However, further research will be important to further refine cancer risk estimates and develop more comprehensive early detection strategies, ideally developing and validating new diagnostic methods. There is ongoing research in this field, to hopefully further refine screening practices for high-risk groups. The NCI is currently conducting a study of men who do not have prostate cancer but are known to have high risk genetic changes including germline DNA repair mutations, to assess their risk for developing prostate cancer. This study incudes close follow up with screening modalities such as PSA testing, physical exam, and prostate MRI (NCT03805919). The PATROL study is ongoing at the University of Washington, and is collecting blood and urine samples every 6-12 months for patients with germline DNA repair mutations for early detection of prostate cancer (NCT04472338). The results of these studies will further inform screening guidelines for these high-risk populations.

As the recommendations for germline testing in prostate cancer incorporate more groups, it is important to ensure that equitable access to genetic testing exists for all patients. There is significant data in the breast cancer population to suggest that disparities in genetic testing for women of color do exist (55-56), raising the possibility of disparities in genetic testing in men with prostate cancer given the shared genetic factors that may contribute to cancer development and pathogenesis. Several studies have highlighted the racial and ethnic disparities that exist in germline genetic testing, specifically in the prostate cancer population.

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A study of 867 patients with metastatic prostate cancer evaluated the rates of pathogenic variants, likely pathogenic variants, and VUS in cancer genes among patients that identified as Caucasian and African American. They showed that the pathogenic and likely pathogenic variants of known cancer genes did not vary by race, however the rates of VUS were higher in the African American group (57).

This effect has also been shown in studies involving larger databases from a commercial provider of germline testing, Color Genomics™. One study using genetic testing from Color analyzed 1351 men with prostate cancer at any stage who underwent germline testing; 78% of these men identified as Caucasian, 11% as Ashkenazi Jewish, 3% as African American/Canadian, 2% as Hispanic, 2% as Asian/Pacific Islander, and 4% as other. The rates of pathogenic variants, likely pathogenic variants, and VUS were compared by race. There were higher rates of VUS in the African American/Canadian, Hispanic, and Asian/Pacific Islander population (58). Another analysis using data from Color Genomics, this time using publicly available, de-idenfied data from 50,000 individuals within the Color Genomics database, was conducted in 2019. This analysis revealed that among individuals who had no personal history of cancer, most identified as European. The pathogenic variant, likely pathogenic variant, and VUS rate was also compared in this study, and found that among the hereditary breast and ovarian cancer syndrome, Lynch syndrome genes, and the “other cancer gene” groups, the rate of VUS was higher in the non-European groups (which included African American, Hispanic, and Asian & Pacific Islander populations) (59).

These studies highlight the disparities in genetic testing that already exist in prostate cancer; in particular with the demonstrated higher rates of VUS, raising the question of inadequate representation among these groups in these larger databases. In order to identify more pathogenic variants among these groups and provide better-informed screening recommendations, improved representation in these larger databases will be imperative. The reasons for these disparities in genetic testing are multifactorial and involve systematic, educational, and workforce issues, well-highlighted in this recent review (60).

IMPORTANCE OF CASCADE GENETIC TESTING:

An important concept within the field of genetic testing is cascade testing, or testing family members of an individual who has tested positive for a pathogenic germline variant that may be an inherited cancer risk for family members. With the widespread use of germline genetic testing in prostate cancer, it is becoming more common for an individual with prostate cancer to be the proband in that family. It is important to identify all possibly affected family members and refer them for genetic counseling and testing, to inform their own cancer risks and screening initiation. For example, this could include opportunities for early detection and risk reduction for women found to have germline mutations (pathogenic variants) in cancer predisposition genes such as BRCA1 and BRCA2 through cascade testing, and may prove to be life-saving.

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CLINICAL PRACTICE IMPLICATIONS:

Germline genetic testing may lead to the identification of a germline mutation that may have treatment implications. There has been mounting evidence suggesting the sensitivity of homologous recombination-deficient prostate cancers to platinum chemotherapy (60-62).

The results of the TOPARP-A trial (63) introduced evidence of the efficacy of PARP inhibitors in patients with metastatic prostate cancer who harbored mutations in DNA repair genes in a limited sample of patients. Since then, the FDA has approved two PARP inhibitors for use in patients with metastatic prostate cancer with DNA repair mutations. Rucaparib was studied in the phase II TRITON study (64), and showed a 51% radiographic response rate in patients with metastatic castrate resistant prostate cancer (mCRPC) and *BRCA1* and *BRCA2* alterations. Notably, the response rate for patients with DNA repair alterations aside from *BRCA1* and *BRCA2* had a much lower response rate at only 13%, and thus are not included in rucaparib's label (64-65). Olaparib was evaluated by the phase III ProFOUND study, and enrolled patients with DNA repair alterations and prostate cancer who had progressed on at least one line of AR-targeted therapy, and treated them with another AR-targeted agent or Olaparib. Olaparib was shown to have a higher progression free survival at 5.8 months vs. 3.5 months, and is approved for patients with metastatic castrate resistant prostate cancer and a mutation in *BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D*, and *RAD54L* (66).

Immunotherapy may also be considered in patients with mCRPC. A phase II KEYNOTE-199 prospectively evaluated pembrolizumab in mCRPC (not selected for biomarkers), and showed a 5% radiographic response rate with a 16.8 month median duration of response, suggesting a durable response (67). Another retrospective study showed that 53% of patients with mCRPC and mismatch repair deficiency or microsatellite instability had a 50% decrease in their PSA (68).

Notably, there is not consistent evidence to suggest that patients with DNA repair alterations do not also have a good response to conventional therapies that are not biomarker-selected (6-8,69-70). Treatments such as abiraterone, enzalutamide, and taxanes are similarly effective in carriers of *BRCA2* mutations and non-carriers, as shown by the PROREPAIR-B study (6), however, more research is needed for this. Registry studies such as the ongoing PROMISE study (NCT04995198) are vital to continue expanding this knowledge.

CONCLUSIONS:

Germline genetic testing has become more widespread in prostate cancer, due to studies reporting the clinically significant prevalence of germline DNA repair alterations. These studies have led to the incorporation of germline genetic testing into prostate cancer guidelines. Information about germline genetics can have impacts on treatments available for patients with prostate cancer, and inform screening and testing for their family members. Ongoing research in this field will lead to continued advancement in how we treat patients with prostate cancer and their families.

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Acknowledgements:

The authors are grateful for support from NIH PNW Prostate SPORE CA097186, NIH T32 CA009515, and NIH CCSG CA015704; CDMRP W81XWH-17-2-0043, the Institute for Prostate Cancer Research, the Prostate Cancer Foundation, and Advancing Cancer Treatment.

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Quality of Life Research (2023) 32:3209–3221
https://doi.org/10.1007/s11136-023-03468-0

Quality of life in the year after new diagnosis with advanced prostate cancer for Black and White individuals living in the US

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Accepted: 20 June 2023 / Published online: 6 July 2023
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Abstract

Purpose To assess differences in baseline and longitudinal quality of life among Black and White individuals in the US with advanced prostate cancer.

Methods Secondary analysis of data from the International Registry for Men with Advanced Prostate Cancer (IRONMAN) including US participants newly diagnosed with advanced prostate cancer and identifying their race as Black or White from 2017 to 2023. Participants completed the EORTC QLQ-C30 Quality of Life (QoL) Survey at study enrollment and every 3 months thereafter for up to 1 year of follow-up reporting 15 scale scores ranging from 0 to 100 (higher functioning and lower symptom scores represent better quality of life). Linear mixed effects models with race and month of questionnaire completion were fit for each scale, and model coefficients were used to assess differences in baseline and longitudinal QoL by race.

Results Eight hundred and seventy-nine participants were included (20% identifying as Black) at 38 US sites. Compared to White participants at baseline, Black participants had worse constipation (mean 6.3 percentage points higher; 95% CI 2.9–9.8), financial insecurity (5.7 (1.4–10.0)), and pain (5.1 (0.9–9.3)). QoL decreased over time similarly by race; most notably, role functioning decreased by 0.7 percentage points (95% CI −0.8, −0.5) per month.

Conclusion There are notable differences in quality of life at new diagnosis of advanced prostate cancer for Black and White individuals, and quality of life declines similarly in the first year for both groups. Interventions that address specific aspects of quality of life in these patients could meaningfully improve the overall survivorship experience.

Keywords Prostate cancer · Epidemiology · Racial disparities · Quality of life

Introduction

In the US, Black individuals have a 1.7 times higher incidence and 2.1 times higher mortality from prostate cancer compared to White individuals [1]. Patients with advanced disease experience the highest prostate cancer-associated morbidity and mortality, and Black individuals have the highest incidence of advanced disease resulting from cultural factors (e.g., mistrust of the medical system and more stigma around prostate cancer) and economic factors (e.g., poorer access to care and increased financial burden of treatment) driven by institutional racism [2, 3]. There are two major categories of advanced prostate cancer: metastatic hormone-sensitive (mHSPC) and castration-resistant prostate cancer (CRPC), both representing incurable states of disease [4].

Quality of life (QoL) is a multidimensional construct that comprises several aspects of the human experience including health and psychological status, independence, social relationships, environment, and personal beliefs. Integration of patient-reported outcome measures of QoL into routine oncology care represents a potential point for intervention to improve survivorship in prostate cancer populations. In a randomized trial of individuals with metastatic solid tumors, the group assigned to complete electronic patient-reported

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symptom measures with notifications sent to the care team for severe/worsening symptoms had a median overall survival time that was 20% longer than the control group [5]. Further, a 10-point increase in global QoL (on a scale of 0 to 100) on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was associated with a 17% lower risk of death in a population of 1,097 prostate cancer patients with primarily localized disease [6].

Several population-based studies of racial disparities in QoL in individuals with localized prostate cancer have found poorer QoL in Black patients compared to White patients [7–10]. For example, in 1178 patients newly diagnosed with prostate cancer in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), Black patients had poorer QoL at baseline and slower improvement over time compared to White patients for numerous QoL scales from pain to mental health and physical functioning [7]. Importantly, these studies all focused on individuals with localized disease, neglecting to include those with advanced prostate cancer who face the most severe QoL burdens due to progressed disease and aggressive therapies.

Studies of QoL in advanced prostate cancer suffer from a lack of racial diversity, primarily because most previous studies have focused on the association between a specific disease-directed therapy and QoL in overwhelmingly White randomized controlled trial (RCT) populations [11–14]. Black individuals are underrepresented in RCT populations due to factors such as fewer clinical trials being offered at institutions where they receive care and bias in health professionals in recommending trial enrollment; as such, investigation of racial disparities in QoL is typically not possible in this setting [3].

Observational studies represent a promising means to investigate QoL independent of a specific disease-directed therapy; however, recent observational studies of QoL in populations with advanced prostate cancer have also only focused on White individuals [15, 16]. For example, a study of 280 White patients with advanced prostate cancer across seven countries in 2007 found a steady decline in QoL over the first year after study enrollment [15]. As Black individuals are the population that is most affected by advanced prostate cancer, there is a need to extend this work into understanding QoL into this population. Identifying specific unmet QoL needs in Black individuals with advanced prostate cancer would meaningfully improve the survivorship experience for this population and also has the potential to decrease racial disparities in overall survival with prostate cancer through intervention on specific QoL detriments.

This study used patient-reported measures to examine racial differences in QoL among individuals newly diagnosed with mHSPC or CRPC in the International Registry for Men with Advanced Prostate Cancer (IRONMAN). We assessed differences in baseline and longitudinal QoL at 3-month intervals over the first year after new diagnosis with mHSPC or CRPC using the EORTC QLQ-C30 questionnaire. We described overall group differences in trajectories of functional status and symptom domains of QoL among IRONMAN participants identifying as Black or White in the US.

Patients and methods

Study participants

Study participants included individuals enrolled in the IRONMAN registry (NCT 03151629) between July 21, 2017 and January 23, 2023. Participants are recruited through IRONMAN-affiliated clinicians at approximately 100 study sites in 16 countries, and detailed data are collected at study enrollment (corresponding to those newly diagnosed with mHSPC or CRPC with no more than 90 days of systemic therapy prior to enrollment for patients with CRPC and no more than 90 days of active therapy for patients with mHSPC) and throughout a follow-up period of at least 5 years [17]. Study sites span academic, private practice, and government health centers and are primarily located in urban centers in regions with high prostate cancer mortality. All study participants gave written informed consent prior to study enrollment and were able to withdraw from the study at any time. Because race has different social and historical contexts with different classifications in different global regions, this analysis focuses specifically on participants enrolled in the US (38 study sites located in 21 states).

Outcome measure: Quality of life (EORTC QLQ-C30 version 3)

QoL was measured with the EORTC QLQ-C30 over a period of up to 12 months, with assessments performed at study enrollment and 3, 6, 9, and 12 months afterward. Surveys were self-administered using a web-based platform (TrueNth) or paper questionnaires [18]. The EORTC QLQ-C30 survey consists of 2 questions on global health status (1–7 Likert scale, “very poor” to “excellent”), 15 questions on functional status (1–4 Likert scale, “not at all” to “very much”), and 13 questions on symptom status (1–4 Likert scale, “not at all” to “very much”). The 30 questions are combined and linearly transformed to 15 scale scores with a range of 0–100. The instrument covers five functional scales (physical, role, emotional, cognitive, and social) with higher scale scores representing better functioning in the domain. In addition, nine symptom scales were assessed (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss,

constipation, diarrhea, and financial difficulties) with higher scale scores representing more severe symptoms.

The EORTC QLQ-C30 questionnaire has shown high construct validity and good reliability in a population of cancer patients and a racially diverse population over the age of 50 years with similar factor structures by race [19, 20]. The EORTC recommends using a minimally important difference (MID) of 5–10 points for interpreting both group differences in QLQ-C30 scale scores as well as changes in scores over time [21]; a study of EORTC outcomes in clinical trials of disease-directed therapies validated this estimate in a population of patients with prostate cancer [22]. Prior to February 20, 2020, IRONMAN participants could complete the questionnaire two weeks before or after the target date; this was subsequently adjusted to be ± three months of the target date to improve study feasibility.

Demographic and clinical characteristics

Demographic information (age, highest level of education, employment status, marital status, military status, race, ethnicity) was collected through a patient-reported questionnaire at study enrollment. Clinical variables (disease state at enrollment, Gleason score, prostate-specific antigen (PSA) level, treatment at baseline, metastatic status at baseline, and type of health center) were abstracted from patient medical records and entered by study sites.

Race was self-reported by participants at study enrollment, allowing multiple selection from the following categories: White/Caucasian, African/African American/Black/Black British/Caribbean, Asian/Asian American/Asian British, Native Hawaiian or Other Pacific Islander, American Indian/Alaska Native, Middle Eastern, and other. Ethnicity was self-reported by participants choosing between "Hispanic/Latino" and "not Hispanic/Latino" categories. This study focuses specifically on individuals self-identifying their race as only Black or White regardless of their ethnicity.

Age at study enrollment (years) was included as a continuous variable. Disease state at enrollment was categorized as mHSPC (de novo metastatic disease at diagnosis or progressed to metastasis after localized prostate cancer diagnosis) and m0 or m1 CRPC (progression of disease while on androgen deprivation therapy or with castrate level of testosterone as determined by the investigator).

Statistical analysis

We summarized demographic and clinical participant characteristics, stratified by self-reported race. We calculated the 15 EORTC scale scores described above for each individual at each time point if the questionnaire and all required questions for each scale were complete [23]. Missing individual covariates and EORTC scale scores on completed questionnaires were imputed using multiple imputation by chained equations (MICE) [24] with the data in wide format. Scale scores in which the entire questionnaire was missing were temporarily given a value of − 250 as a numerical, proxy missing indicator to ensure that these scores would not be imputed. MICE was conducted using classification and regression trees with 10 iterations for each of 10 imputations and with the scale scores constrained between 0 and 100 (inclusive of the bounds). Subsequently, scale scores for missing questionnaires were re-marked as missing. Sensitivity analyses were conducted with different values for the missing indicator.

Longitudinal missingness in questionnaires was assessed, and an in-depth description of missing data exploration is included in the Supplementary Methods. As no clear patterns of reasons for missing whole questionnaires arose from these analyses, we fit linear mixed effects models for each of the fifteen scale scores with timepoints clustered within participant who were then clustered within study site. Initial models included only race, month of follow-up questionnaire time point (continuous), and their interaction, assuming a linear relationship between the outcome scale and time. As we were interested in overall differences by self-reported race, adjusted models additionally controlled for time-invariant variables (age at study enrollment and disease state at enrollment). We did not control for variables that may mediate the association between self-reported race and QoL (e.g., employment, marital status, etc.) in the statistical models [25]. Baseline differences and differences in longitudinal trajectories in each scale by race were estimated and pooled using Rubin's Rules [26]. A sensitivity analysis excluding individuals who were censored due to being off-study was conducted. Figures depicting these trajectories by race using model coefficients were created to visualize trends. The longitudinal analyses were additionally stratified by disease state at enrollment to determine differences for participants with mHSPC and CRPC.

Additional methods information can be found in the Supplementary Methods. All analyses were completed using R version 4.1.0 with statistical significance assessed at the 0.05 level.

Patient involvement

A Black advanced prostate cancer survivor and long-time patient of one of the IRONMAN lead investigators with decades of experience as an advocate in his community was involved in setting the research question, study design, interpretation of the research findings, and review of the manuscript. With the goal of increasing the accessibility of this manuscript to patients and individuals outside of

academia, we have included a *glossary of technical terms* in the supplementary material.

Results

Participant characteristics

This study included 879 participants from IRONMAN self-identifying as White ($N = 704$, 80%) or Black ($N = 175$, 20%) and receiving care at 38 study sites across the US (Fig. 1, Supplementary Table S1). IRONMAN participants enrolled outside of the US ($N = 1979$), missing data on disease state ($N = 7$), and missing race data or identifying with a race that was not Black or White ($N = 227$) were excluded from the analysis to specifically focus on QoL disparities within the US context of race. Demographic and clinical characteristics for the sample, stratified by self-reported race, are shown in Table 1. For the entire cohort, the mean age at enrollment was 69.1 years with a standard deviation of 8.9 years, and most of the participants (65.2%) had mHSPC compared to CRPC (34.8%).

Differences by self-reported race were noted across many of the demographic and clinical characteristics (Table 1). Black participants were diagnosed with advanced prostate cancer at a younger age, reported lower education, were less likely to be married, were more likely to be disabled, had higher first on-study PSA levels, and had a shorter time on study on average compared to White participants. The most commonly received therapies at any point in the first year on study were androgen deprivation therapy (ADT) (88.9%), androgen receptor signaling inhibitors (ARSIs) (61.7%), and chemotherapy (17.5%) (Supplementary Table S2).

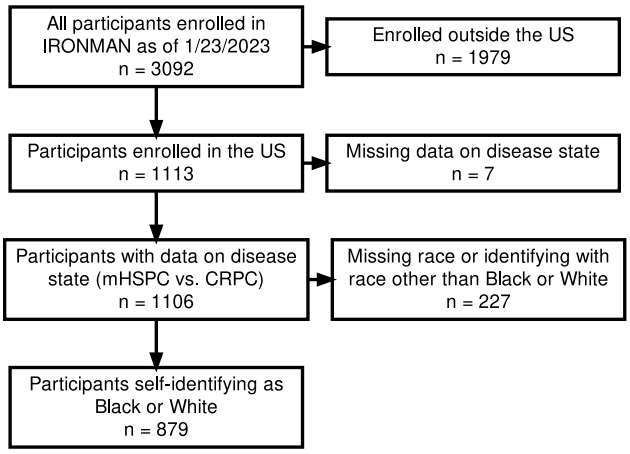

Fig. 1 Selection of study population for analysis of patient-reported outcome measures (IRONMAN, 2017–2023)

Overview of missing data

The proportion of participants completing questionnaires, missing questionnaires, or being off-study is represented in Fig. 2A. Eighty-seven percent of participants completed the baseline questionnaire, declining to 74% completion by individuals on study at month 12.

The longitudinal missing data patterns for full questionnaires are depicted in Fig. 2B. Thirty-nine percent of participants completed questionnaires at all five timepoints. The remainder of study participants exhibited 30 distinct missing non-monotone data patterns. Participants who completed the baseline questionnaire were older, had lower education, were more likely to be retired, and had lower first on-study PSA compared to those who did not complete the baseline questionnaire (Supplementary Table S3). Among participants who were on study at month 12 and reached that timepoint, participants who completed the month 12 questionnaire had higher education, were more likely to be retired, and had lower first on-study PSA compared to those who did not complete the month 12 questionnaire (Supplementary Table S4).

Baseline differences in QoL by race

Baseline results from the longitudinal analyses are shown in Table 2. Overall, participants tended to have high functioning and low symptom burden across each of the scales. White participants had mean functioning scale scores ranging from 80.4 (95% CI 77.7, 83.2) for role functioning to 84.2 (95% CI 82.3, 86.2) for cognitive functioning (on a scale of 0–100; higher score is indicative of higher QoL) at the baseline questionnaire. Symptom burden for White participants was generally low, and the most disruptive symptoms for White participants were sleep problems with a mean scale score of 30.3 (95% CI 27.6, 33.0) and fatigue with a mean scale score of 30.1 (95% CI 27.7, 32.6) (on a scale of 0–100; higher score is indicative of worse QoL).

Compared to White participants, Black participants reported several differences in QoL domains at baseline. Black participants had better emotional functioning (comprising questions about anxious and depressive symptoms) at baseline (increase of mean 4.4 percentage points, 95% CI 1.4, 7.5) compared to White participants. However, Black participants reported worse pain (5.1 point increase, 95% CI 0.9, 9.3) and financial insecurity (7.0 point increase, 95% CI 2.7, 11.4) compared to White participants. Scale scores varied substantially more between participants than between study sites.

Table 1 Cohort demographic and clinical characteristics by self-reported race ($N=879$), 2017–2023

	White ($N=704$)	Black ($N=175$)
Age at study entry, years		
Mean (SD)	69.5 (9.0)	67.2 (8.7)
Hispanic/Latino		
No	657 (97%)	156 (96%)
Yes	22 (3%)	6 (4%)
Missing	$n=25$	$n=13$
Disease state at enrollment		
CRPC	241 (34%)	65 (37%)
mHSPC	463 (66%)	110 (63%)
Highest education level at baseline		
Less than college	29 (14%)	18 (43%)
Some college or bachelor's degree	72 (35%)	13 (31%)
Vocational school/program	2 (1%)	1 (2%)
Graduate degree	101 (49%)	9 (21%)
Other	3 (1%)	1 (2%)
Missing	$n=497$	$n=133$
Marital status at baseline		
Married	545 (78%)	88 (51%)
In a civil partnership	20 (3%)	2 (1%)
Widowed	29 (4%)	12 (7%)
Divorced/separated	76 (11%)	43 (25%)
Never married	28 (4%)	26 (15%)
Missing	$n=6$	$n=4$
Employment status at baseline		
Retired	408 (58%)	82 (48%)
Working full-time	200 (29%)	45 (26%)
Working part-time	58 (8%)	11 (6%)
Unemployed	12 (2%)	16 (9%)
Disabled	22 (3%)	17 (10%)
Missing	$n=4$	$n=4$
Member of national military at baseline		
Yes, currently or previously	182 (33%)	37 (28%)
No, I have never served in the national military	364 (67%)	97 (72%)
Missing	$n=158$	$n=41$
Prostatectomy or biopsy Gleason score		
6 or less	26 (5%)	3 (2%)
7	163 (28%)	45 (34%)
8	106 (18%)	20 (15%)
9–10	278 (49%)	63 (48%)
Missing	$n=131$	$n=44$
First on-study PSA (ng/mL)		
Mean (SD)	88.6 (484.8)	156.9 (396.3)
Missing	$n=33$	$n=8$
Metastases at baseline		
No	65 (9%)	12 (7%)
Yes	639 (91%)	163 (93%)
Type of health center		
Clinic	30 (4%)	7 (4%)
Hospital	125 (18%)	21 (12%)
NCI-designated	535 (76%)	131 (75%)
VA	14 (2%)	16 (9%)
Time on study (months)		
Mean (SD)	28.9 (17.4)	24.8 (17.2)

mHSPC metastatic hormone-sensitive prostate cancer, *CRPC* castration-resistant prostate cancer, *PSA* prostate-specific antigen

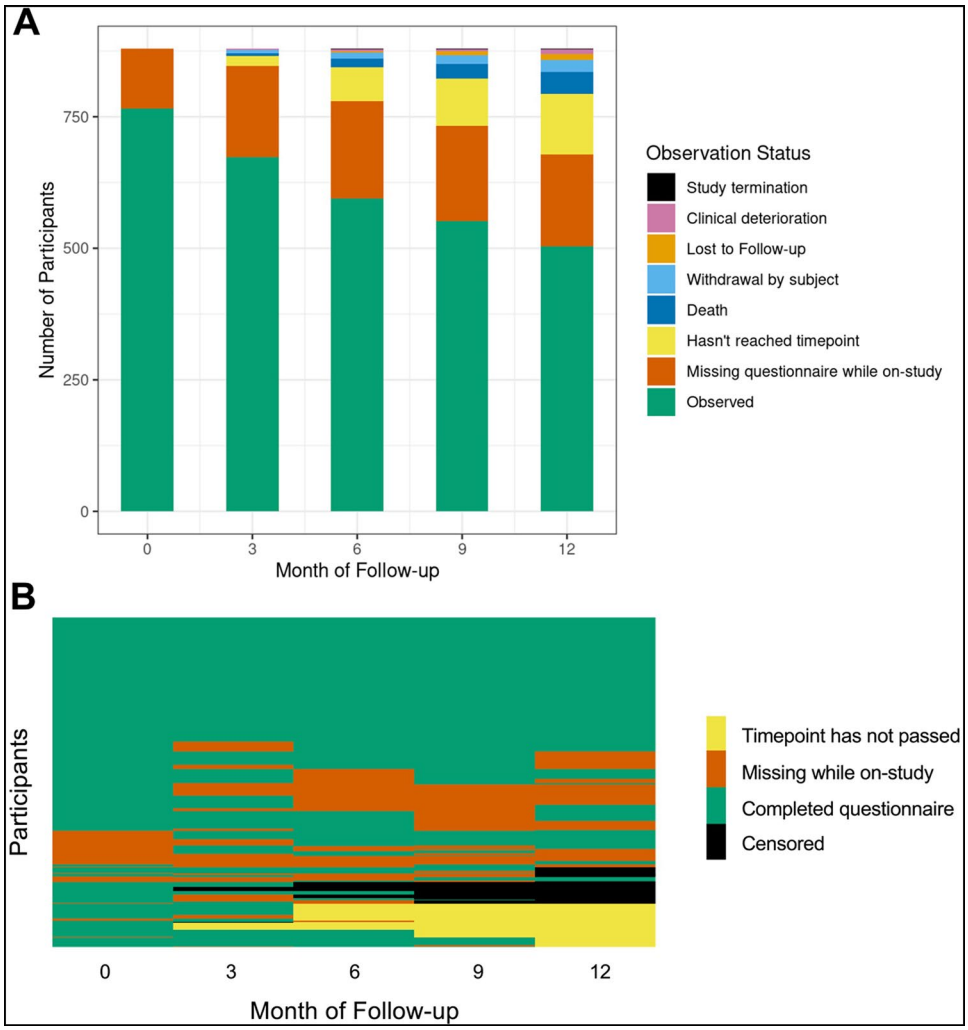

Fig. 2 Overview of longitudinal missing data of cohort in first year of enrollment. **A** Proportion of questionnaire completeness and reasons for incompleteness at each timepoint. **B**: Longitudinal completion of questionnaires for each participant ($N = 897$)

Longitudinal differences in QoL by race

Trajectory results from the longitudinal analyses are provided in Table 3, with a graphical representation provided in Fig. 3. For the majority of scales, White participants showed a decline in QoL over time. Role functioning (the ability to accomplish daily activities) declined most sharply of the functioning scales, with scores for White participants losing 0.7 percentage points on average per month (95% CI − 0.8, − 0.5). Fatigue worsened most sharply of the symptom scales, with scores for White participants gaining 0.6 percentage points on average per month (95% CI 0.5, 0.7).

Black and White participants had similar trajectories in QoL over their first year after enrollment. In a few scales, Black participants had slower decline or faster improvement compared White participants. Most notably, reported financial security for Black participants improved by an additional 0.6 percentage points per month compared to White participants (95% CI − 0.8, − 0.4). The results for both baseline and longitudinal differences in the scale scores were robust to sensitivity analyses with different values for the missing indicator in the MICE procedure (Supplementary Table S5) as well as when individuals who were off-study at any point in the first year were excluded (Supplementary Table S6). When stratified by disease state at study enrollment, results were largely the same across participants with mHSPC and CRPC (Supplementary Tables S7 and S8).

Discussion

In a nationwide sample of 879 individuals with advanced prostate cancer in the US participating in the IRONMAN registry, we found that our study population had better functioning and fewer symptoms at study enrollment compared to the EORTC recurrent/metastatic prostate cancer reference population across all but two scales (diarrhea and financial insecurity) [27]. For example, compared to our study population, the EORTC reference population had poorer global QoL (mean 62.1) and role functioning (mean 67.0) and

Table 2 EORTC QLQ-C30 quality of life scale scores at study enrollment for White and Black participants ($N=879$)

	Score for White participants	Difference for Black participants		Standard deviation of participant random effect	Standard deviation of site random effect
		Mean (95% CI), $N=175$[a]			
	Mean (95% CI), $N=704$	Unadjusted	Adjusted		
Global Quality of Life (QL)[1]	70.9 (68.8, 73.0)	− 0.6 (− 4.0, 2.9)	− 0.7 (− 4.2, 2.8)	15.4	3.3
Functioning Scales[1]					
Physical (PF)	84.1 (81.6, 86.6)	− 1.0 (− 4.3, 2.3)	− 2.0 (− 5.2, 1.2)	15.0	4.9
Emotional (EF)	81.3 (79.3, 83.1)	**4.4 (1.4, 7.5)**	**5.0 (2.0, 8.0)**	13.6	3.0
Social (SF)	80.5 (78.1, 83.0)	0.7 (− 3.1, 4.6)	0.9 (− 3.0, 4.7)	16.3	4.6
Role (RF)	80.4 (77.7, 83.2)	− 0.2 (− 4.6, 4.2)	− 0.5 (− 4.9, 3.9)	18.7	5.0
Cognitive (CF)	84.2 (82.3, 86.2)	0.5 (− 2.5, 3.6)	0.4 (− 2.6, 3.5)	13.8	3.5
Symptom Scales[2]					
Fatigue (FA)	30.1 (27.7, 32.6)	− 1.8 (− 5.7, 2.0)	− 1.8 (− 5.7, 2.1)	17.3	4.5
Nausea/vomiting (NV)	4.1 (3.3, 4.9)	**2.8 (1.0, 4.6)**	**2.4 (0.6, 4.1)**	7.1	0.2
Pain (PA)	19.0 (16.4, 21.6)	**5.1 (0.9, 9.3)**	**4.5 (0.3, 8.6)**	18.3	4.9
Dyspnea (DY)	13.8 (11.7, 15.9)	0.6 (− 3.2, 4.4)	1.2 (− 2.7, 5.0)	17.4	2.9
Sleep (SL)	30.3 (27.6, 33.0)	**− 7.3 (− 11.9, − 2.7)**	**− 7.9 (− 12.5, − 3.3)**	20.0	3.7
Appetite (AP)	10.7 (8.8, 12.6)	2.3 (− 1.1, 5.7)	2.2 (− 1.2, 5.6)	13.9	2.8
Constipation (CO)	12.3 (10.6, 14.0)	**6.0 (2.5, 9.5)**	**6.3 (2.9, 9.8)**	14.5	1.4
Diarrhea (DI)	10.3 (8.5, 12.1)	− 1.4 (− 4.4, 1.6)	− 1.7 (− 4.7, 1.3)	11.4	3.1
Financial insecurity (FI)	16.4 (13.8, 19.0)	**7.0 (2.7, 11.4)**	**5.7 (1.4, 10.0)**	20.2	4.2

Bolded represents statistical significance at the 0.05 level

Unadjusted model includes race as the only covariate. Adjusted model additionally includes age and disease state (mHSPC or CRPC) at study enrollment

All scale scores are rated on a scale of 0–100; [1]a higher score is indicative of higher quality of life for the global and functioning scales, [2]while a lower score is indicative of a higher quality of life for the symptom scales

[a]Interpretation: mean change in EORTC scale score at enrollment for Black participants compared to White participants. For the global and functioning scales, a positive number represents higher quality of life for Black participants compared to White participants. For the symptom scales, a positive number represents lower quality of life for Black participants compared to White participants

worse pain (mean 38.6) and constipation (mean 27.1). These differences are likely due to the EORTC reference population being more diverse and representative of all individuals with advanced prostate cancer (rather than only those receiving care at highly resourced IRONMAN study sites); additionally, the EORTC population only includes individuals who have not yet begun treatment for their prostate cancer, potentially resulting in lower QoL due to higher disease burden at the time of questionnaire completion.

At study enrollment, Black and White participants reported a number of differences in QoL, and the majority of statistically significant differences that we found by race at baseline also reach the 5-point minimally important difference recommended by the EORTC; thus, our findings represent clinically meaningful racial differences as well. Some previous studies in populations with localized prostate cancer suggested that Black individuals have poorer QoL in all domains at baseline compared to White individuals [9, 28], while others reported similar QoL across domains by race [29, 30] or higher QoL in Black individuals [31–33]. Our study suggests that, at the time of new diagnosis with advanced prostate cancer, Black individuals have either similar or worse QoL compared to White individuals. One exception to this is that Black participants reported better baseline emotional functioning than White participants in our study. A 2014 study of 50,856 individuals with prostate cancer in the SEER-Medicare database similarly found that Black individuals had a lower risk of clinically diagnosed mental health disorders compared to White individuals [32]. These findings could be a result of increased stigma around mental health disorders in Black communities leading to underreporting of true symptoms in our study population [34]. Assuming true symptoms were reported, one of many possible explanations for higher emotional functioning in Black participants is higher levels of spirituality leading to better QoL. Numerous studies have shown that spirituality and religiosity are positively associated with well-being in prostate cancer populations often due to increased

Table 3 Longitudinal changes in EORTC QLQ-C30 scale per month for White and Black participants during the first month after study enrollment ($N = 879$)

	Change per month for White participants[a]		Additional change for Black participants[b]	
	Mean (95% CI), $N = 704$		Mean (95% CI), $N = 175$	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Global Quality of Life (QL)[1]	**− 0.4 (− 0.5, − 0.2)**	**− 0.4 (− 0.5, − 0.2)**	0.1 (− 0.2, 0.4)	− 0.1 (− 0.2, 0.1)
Functioning Scales[1]				
Physical (PF)	**− 0.6 (− 0.7, − 0.5)**	**− 0.6 (− 0.7, − 0.5)**	0.1 (− 0.1, 0.4)	**− 0.4 (− 0.5, − 0.3)**
Emotional (EF)	− 0.1 (− 0.2, 0)	− 0.1 (− 0.2, 0)	0.1 (− 0.2, 0.4)	**0.3 (0.2, 0.4)**
Social (SF)	**− 0.3 (− 0.4, − 0.1)**	**− 0.3 (− 0.4, − 0.1)**	0.1 (− 0.3, 0.5)	0.1 (− 0.1, 0.2)
Role (RF)	**− 0.7 (− 0.8, − 0.5)**	**− 0.6 (− 0.8, − 0.5)**	0.3 (− 0.1, 0.7)	− 0.1 (− 0.3, 0)
Cognitive (CF)	**− 0.3 (− 0.5, − 0.2)**	**− 0.3 (− 0.5, − 0.2)**	0.3 (0, 0.7)	0 (− 0.1, 0.1)
Symptom Scales[2]				
Fatigue (FA)	**0.6 (0.5, 0.7)**	**0.6 (0.5, 0.7)**	**− 0.5 (− 0.9, − 0.2)**	0 (− 0.1, 0.2)
Nausea/vomiting (NV)	0 (− 0.1, 0.1)	0 (− 0.1, 0.1)	− 0.1 (− 0.3, 0.1)	**− 0.2 (− 0.2, − 0.1)**
Pain (PA)	**0.4 (0.2, 0.6)**	**0.4 (0.2, 0.6)**	− 0.2 (− 0.6, 0.2)	**− 0.3 (− 0.4, − 0.1)**
Dyspnea (DY)	**0.6 (0.4, 0.7)**	**0.6 (0.4, 0.7)**	− 0.1 (− 0.4, 0.3)	0.2 (0, 0.3)
Sleep (SL)	0.1 (− 0.1, 0.3)	0.1 (− 0.1, 0.3)	0.2 (− 0.3, 0.6)	**− 0.3 (− 0.5, − 0.2)**
Appetite (AP)	0.1 (− 0.1, 0.2)	0 (− 0.1, 0.2)	0 (− 0.4, 0.4)	0 (− 0.1, 0.1)
Constipation (CO)	**0.2 (0.1, 0.4)**	**0.2 (0.1, 0.4)**	− 0.3 (− 0.7, 0.1)	0.1 (0, 0.2)
Diarrhea (DI)	0.1 (0, 0.2)	0.1 (− 0.1, 0.2)	− 0.1 (− 0.5, 0.2)	− 0.1 (− 0.2, 0)
Financial insecurity (FI)	− 0.1 (− 0.3, 0.1)	− 0.1 (− 0.3, 0)	− 0.2 (− 0.6, 0.2)	**− 0.6 (− 0.8, − 0.4)**

Bolded represents statistical significance at the 0.05 level

Unadjusted model includes race as the only covariate. Adjusted model additionally includes age and disease state (mHSPC or CRPC) at study enrollment

All scale scores are rated on a scale of 0–100; [1]a higher score is indicative of higher quality of life for the global and functioning scales, [2]while a lower score is indicative of a higher quality of life for the symptom scales

[a]Interpretation: the mean change in EORTC scale score per month for White participants. For the global and functioning scales, a positive number represents an increase in quality of life over time. For the symptom scales, a positive number represents a decrease in quality of life over time

[b]Interpretation: the mean additional change in EORTC scale score per month for Black participants compared to White participants. Adding this number to the change in score per month for White participants gives the change in score per month for Black participants

hopefulness and positivity [35], and this is particularly important for Black populations where spirituality tends to be an integral part of daily life [36]. Health professionals should be supportive of the role that spirituality can play to support overall QoL in Black populations.

Longitudinally, QoL generally declined for both Black and White participants in our study during their first year after enrollment in IRONMAN. A previous study of White individuals with advanced prostate cancer found declines in QoL corresponding to between 3 and 17 points on the EORTC scales over the first 9 months after enrollment [15]. We observed declines in the QoL scales by three to seven points in our study population over the first year, indicating that, while both populations experienced declines in QoL over time, the IRONMAN population exhibited a less steep decline in QoL compared to this previous study. Again, this is likely due to the IRONMAN population most commonly receiving care at highly resourced centers that can provide additional supports for patients when needed. Regardless, a monthly change of approximately 0.4 percentage points per month in our study correlates to the clinically meaningful change of 5 percentage points in a year [22], demonstrating that the majority of statistically significant changes that we find in QoL over time are also clinically meaningful for the participant and their cancer care.

Many factors can mediate the association between race and QoL in patients with prostate cancer and are worth investigating in future studies as potential points of intervention. One such potential mediator is therapy received, especially because Black individuals with advanced prostate cancer are less likely to receive aggressive treatments compared to White individuals [37]. The majority of participants in our study population received ADT and/or ARSIs in their first year on study. Multiple randomized controlled trials in advanced prostate cancer populations have shown changes in QoL after treatment with various combinations of ADT and ARSIs with and without other treatment options including chemotherapy and radiotherapy for advanced prostate cancer

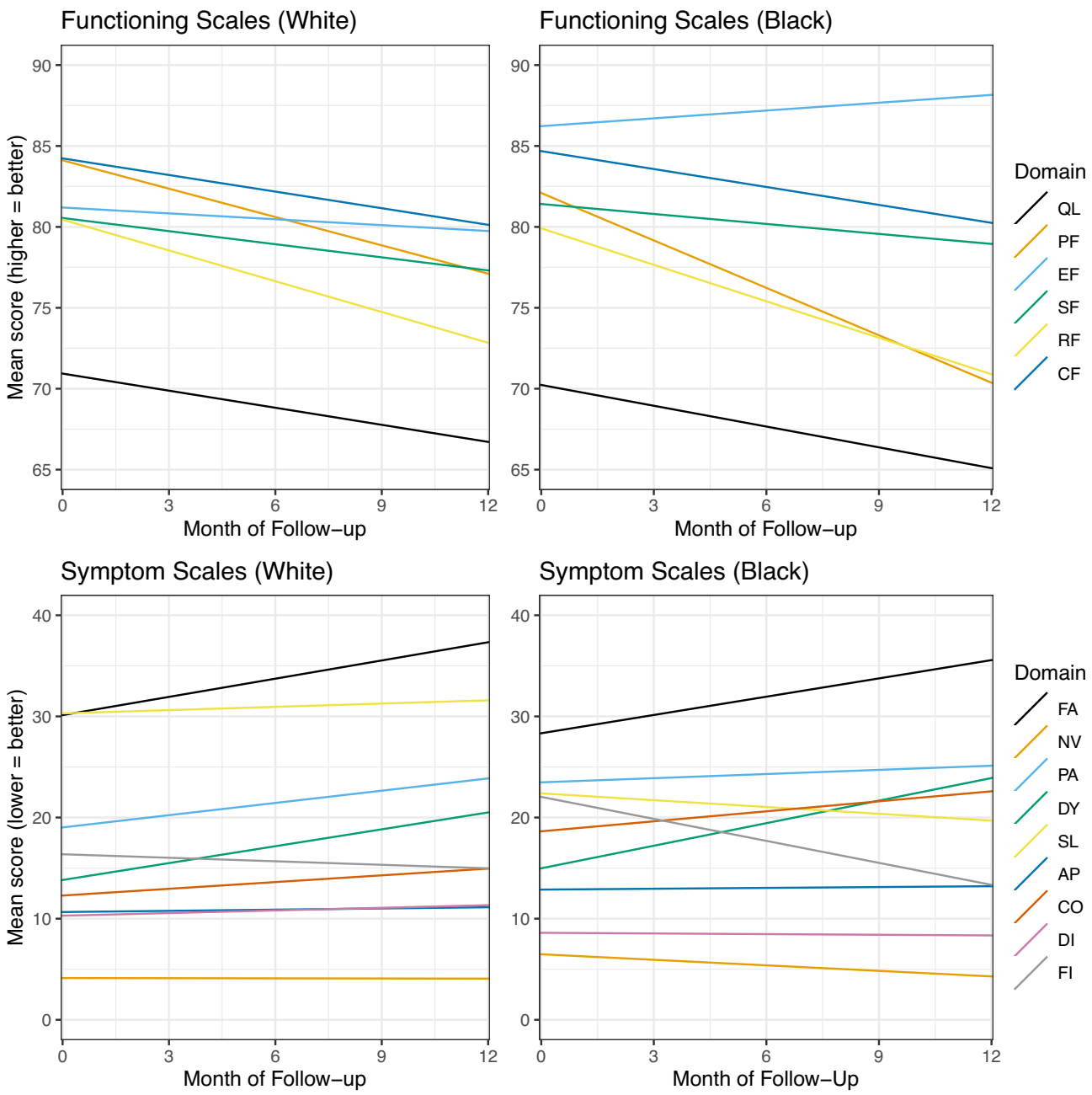

Fig. 3 Longitudinal trajectories in EORTC QLQ-C30 scale scores. **A** Trajectories of functioning scales for White participants. **B** Trajectories of functioning scales for Black participants. **C**: Trajectories of symptom scales for White participants. **D** Trajectories of symptom scales for Black participants. QL = global quality of life, PF = physical functioning, EF = emotional functioning, SF = social functioning, RF = role functioning, CF = cognitive function, FA = fatigue, NV = nausea/vomiting, PA = pain, DY = dyspnea, SL = sleep, AP = appetite, CO = constipation, DI = diarrhea, FI = financial insecurity

[38–41]. These therapies have the ability to improve QoL by decreasing disease burden; however, these therapies are also known to have side effect profiles that can worsen QoL including increased risk of inflammatory rheumatic diseases and back pain [42, 43]. Health professionals should monitor treatment side effects and adjust regimens accordingly to ensure that QoL is negatively impacted as little as possible.

Other potential mediators are social factors that differ by race such as access to social determinants of health resources that support a nutritious diet, physical activity and dietary supplements, quiet living spaces to support high

quality sleep, and access to healthcare resources to decrease treatment side effects, among others [44]. Health institutions should strive to support their patients' socioeconomic needs outside the hospital as much as possible as these are fundamental for improving QoL and overall health. Our study lays the foundation for future studies to investigate the mechanisms underlying differences in QoL seen here and determine the impact of specific interventions on QoL and overall survival.

There are several potential limitations of this study. First, this study focuses specifically on participants self-identifying their race as either Black or White; it is important to expand this research among more diverse populations. Second, the EORTC QLQ-C30 questionnaire has not specifically been validated in this study population; however, the majority of scales have shown high reliability in a racially diverse population over the age of 50 years with similar factor structures in Black and White individuals that reflect our study population [45, 46]. Finally, these results may not be generalizable to individuals who choose not to participate in IRONMAN or individuals receiving care at other health centers within or outside of the US. Centers participating in IRONMAN tend to be highly resourced and located in urban environments; individuals living in more rural areas of the US or receiving care at urban centers with less clinical trial infrastructure could have different distributions and trajectories of QoL.

Our study expands QoL research into a more racially diverse population of individuals diagnosed with advanced prostate cancer. We found that Black participants tended to report poorer QoL at diagnosis compared to White participants, and QoL decreased similarly over time for both groups. We identified clinically meaningful increased pain, constipation, and financial insecurity for Black participants; health professionals shouldask about and address these symptoms as needed with clinical treatments and support navigating healthcare costs to improve QoL for this population. As QoL decreased over the first year on study for both Black and White participants, there is a need for health professionals to monitor QoL longitudinally and adjust support as needed to improve survivorship. Our study additionally highlights opportunities for deeper investigation into QoL interventions to improve the prostate cancer survivorship experience and potentially improve overall survival for this patient population, particularly for Black individuals who face the greatest burden of advanced prostate cancer.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11136-023-03468-0.

Acknowledgements The authors would like to thank the participants enrolled in the IRONMAN registry, without whom this research would not be possible. We would also like to thank the IRONMAN investigators and study teams at the 38 sites included in this study for their efforts to enroll and support the IRONMAN participants.

Funding E.M. Rencsok was supported by the National Cancer Institute [F30CA264965] and the National Institute of General Medical Sciences [T32GM007753, T32GM144273]; L.A. Mucci is a Prostate Cancer Foundation Young Investigator; D.J. George and L.A. Mucci are recipients of the Prostate Cancer Foundation Challenge Award; the International Registry for Men with Advanced Prostate Cancer (IRONMAN, NCT 03151629) is funded by Amgen, AstraZeneca, Astellas, Bayer, Janssen, Merck, and Sanofi. This project is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of General Medical Sciences or the National Institutes of Health.

Data availability Raw data was provided by the Prostate Cancer Clinical Trials Consortium (PCCTC), and investigators are not approved to share raw data with others directly. Researchers interested in working with the IRONMAN data can submit a study proposal to PCCTC to obtain access.

Declarations

Competing interest AM consults for Astellas, AstraZeneca, AAA, Bayer, Dendreon, Exelixis, Janssen, Pfizer, Myovant, Novartis, Myriad Genetics, Lantheus, Telix, Sanofi and receives research funding from Astellas, Bayer, Pfizer, Myovant, Sanofi, SeaGen. PB consults for Astellas, AVEO Oncology, Bayer, BMS, Dendreon, Eisai, Exelixis, Janssen, EMD Serono, Guardant Health, Pfizer, Seattle Genetics; receives research support from AstraZeneca, AVEO Oncology, BlueEarth Diagnostics, Merck, Natera, Caris Life Sciences; and is part of the speaker's bureau for Bayer, Caris Life Sciences, Pfizer, Myovant, Natera. HHC receives institutional research support from Astellas, Clovis Oncology, Color Genomics, Janssen, Medivation, Promontory Therapeutics, Sanofi; consults for AstraZeneca; and receives royalties from UpToDate. RD consults for Astellas, Aveo, Bayer, Exelixis, Gilead, Hinova, Janssen, Merck, Pfizer, Sanofi Genzyme, Tavanta. EH consults for Astellas Pharma, Bayer, Janssen Research & Development LLC, Sanofi; receives paid travel from Astellas Pharma, Caris Life Sciences, Sanofi, Seattle Genetics; receives research funding from Astellas Pharma, Arvinas, AstraZeneca, BioXcel Therapeutics, Bristol-Myers Squibb, Calibr, Calithera Biosciences Inc, Caris Life Sciences, Corcept Therapeutics, Corvis Pharmaceuticals, Daiichi Sankyo Inc, Eisai Inc, Exelixis, Five Prime Therapeutics, Fortis Therapeutics, GlaxoSmithKline, Gilead Sciences Inc, Harpoon Therapeutics, Hoffman-La Roche, Infinity Pharmaceuticals, iTeos Therapeutics, Janssen Research & Development LLC, Merck Sharp & Dohme Merck, Mirati Therapeutics, Modra Pharmaceuticals, Oncolys BioPharma, Peloton Therapeutics Inc, Pfizer, Pharmacyclics LLC, POINT Biopharma, Seattle Genetics; and receives honoraria from Bayer, Sanofi, and Seattle Genetics. RRM consults for Aveo, AstraZeneca, Bayer, BMS, Calithera, Caris, Dendreon, Exelixis, JNJ, Lilly, Myovant, Merck, Novartis, Pfizer, Sanofi, Sorrento Therapeutics, Telix, Tempus; receives research funding from Bayer, Tempus, AstraZeneca, Oncternal Therapeutics. DR receives institutional research support from Janssen, Bayer, AstraZeneca, Genentech, BMS/Celgene, Taiho, Promontory; serves on the board for Janssen, AstraZeneca, Bayer, Myovant, Genentech, Promontory, BMS/Celgene. ST receives institutional research support from Sanofi, Medivation, Astellas, Janssen, Amgen, Progenics, Dendreon, Lilly, Genentech, Newlink, BMS, Inovio, AstraZeneca, Immunomedics, Aveo, Rexahn, Atlab, Boehringer Ingelheim, Millennium, Bayer, Merck, Abbvie, Karyopharm, Endocyte, Clovis, Seattle Genetics, Novartis, Gilead, POINT Biopharma, Ambrx; consults for Sanofi, Medivation/Astellas, Dendreon, Janssen, Genentech, Bayer, Endocyte, Eisai, Immunomedics, Karyopharm, Abbvie, Tolmar, Seattle Genetics,

Amgen, Clovis, QED, Pfizer, AAA/Novartis, Clarity, Genomic Health, POINT Biopharma, Blue Earth, AIkido Pharma, Telix Pharma, Convergent Therapeutics, EMD Serono, Myovant, Merck, Atlab Pharma, Phosplatin Therapeutics, Amgen, Ambrx; has a patent on biomarkers for sacituzumab govitecan therapy (Immunomedics / Gilead / Weill Cornell). YW receives institutional research support from Arvinas, Clovis Oncology; consults for Janssen. PWK has investment interest in Convergent Therapeutics, Context Therapeutics LLC, ESSA Pharma; serves on the board for Convergent Therapeutics, Context Therapeutics, ESSA Pharma; consults for ImmunisAI, PrognomIQ. LAM serves on the board of Convergent Therapeutics; consults for Bayer; receives institutional research support from Janssen, AstraZeneca. All other authors report no conflicts of interest.

Ethical approval The original project underwent ethics review and was approved by the Institutional Review Board of the Harvard T. H. Chan School of Public Health. Informed consent was obtained from all participants in the IRONMAN Registry and included consent to access their personal demographic and health information in addition to use of their de-identified data for analyses using IRONMAN Registry data. The authors received access to de-identified IRONMAN registry data for the analyses presented here through an arrangement between the Harvard T. H. Chan School of Public Health and the Prostate Cancer Clinical Trials Consortium (the Clinical and Data Coordination Center for the IRONMAN Registry).

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Check for updates

Received: 16 July 2022 | Accepted: 14 October 2022

DOI: 10.1002/pros.24454

ORIGINAL ARTICLE

The Prostate WILEY

Differential responses to taxanes and PARP inhibitors in *ATM*- versus *BRCA2*-mutated metastatic castrate-resistant prostate cancer

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Abstract

Background: PARP (poly(ADP-ribose) polymerase) inhibitors (PARPi) are now standard of care in metastatic castrate-resistant prostate cancer (mCRPC) patients with select mutations in DNA damage repair (DDR) pathways, but patients with *ATM*- and *BRCA2* mutations may respond differently to PARPi. We hypothesized that differences may also exist in response to taxanes, which may inform treatment sequencing decisions.

Methods: mCRPC patients ($N = 158$) with deleterious *ATM* or *BRCA2* mutations who received taxanes, PARPi, or both were retrospectively identified from 11 US academic

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Funding information
National Cancer Institute,
Grant/Award Numbers: P30-CA-015704, P50-CA-097186, T32-CA-009515, T32-CA-236621

centers. Demographic, treatment, and survival data were collected. Kaplan–Meier analyses were performed and Cox hazard ratios (HR) were calculated for progression-free survival (PFS) as well as overall survival (OS), from time of first taxane or PARPi therapy.

Results: Fifty-eight patients with *ATM* mutations and 100 with *BRCA2* mutations were identified. Fourty-four (76%) patients with *ATM* mutations received taxane only or taxane before PARPi, while 14 (24%) received PARPi only or PARPi before taxane. Patients with *ATM* mutations had longer PFS when taxane was given first versus PARPi given first (HR: 0.74 [95% confidence interval [CI]: 0.37–1.50]; $p = 0.40$). Similarly, OS was longer in patients with *ATM* mutations who received taxane first (HR: 0.56 [CI: 0.20–1.54]; $p = 0.26$). Among patients with *BRCA2* mutations, 51 (51%) received taxane first and 49 (49%) received PARPi first. In contrast, patients with *BRCA2* mutations had longer PFS when PARPi was given first versus taxane given first (HR: 0.85 [CI: 0.54–1.35]; $p = 0.49$). Similarly, OS was longer in patients with *BRCA2* mutations who received PARPi first (HR: 0.75 [CI: 0.41–1.37]; $p = 0.35$).

Conclusions: Our retrospective data suggest differential response between *ATM* and *BRCA2* mutated prostate cancers in terms of response to PARPi and to taxane chemotherapy. When considering the sequence of PARPi versus taxane chemotherapy for mCRPC with DDR mutations, *ATM*, and *BRCA2* mutation status may be helpful in guiding choice of initial therapy.

KEYWORDS
ATM, *BRCA2*, DNA repair, mCRPC, overall survival, progression-free survival

1 | INTRODUCTION

Germline and somatic mutations in DNA damage repair (DDR) pathway genes are emerging therapeutic targets in advanced prostate cancer.[1–5] In particular, optimizing treatment for patients with mutations in the DDR genes (especially *BRCA1*, *BRCA2*, and *ATM*) is a key area of research, as these mutations portend aggressive clinical courses.[6–11] Poly(ADP-ribose) polymerase (PARP) inhibitors have revolutionized cancer therapy for patients with *BRCA2* mutations[5,12–15]; however, the utility of PARP inhibitors in patients with *ATM* mutations is less clear. Further, optimal sequencing of PARP inhibitors relative to taxane chemotherapy is undefined.

ATM is mutated in approximately 5% of all cancers, in malignancies as diverse as mantle cell lymphoma to lung cancer.[16] Early gene panel assays that identified *ATM* as a successful treatment target for PARP inhibitors required a complete loss of function in the gene.[17] In the real world, the mutational landscape of *ATM* is vast and the clinical phenotype of many of these mutations are yet unknown.[16]

Treatment outcomes in metastatic castration-resistant prostate cancer (mCRPC) patients with *ATM* mutations is an area of active investigation. In the TOPARP-B trial, complete loss of the *ATM* protein by immunohistochemistry was associated with notable improved clinical response to olaparib, but the overall response of patients with *ATM* mutations to olaparib remained significantly lower than those observed in patients with *BRCA* mutations.[18] A large multicenter retrospective analysis of mCRPC patients with *BRCA2* and ATM mutations revealed that patients with *ATM* mutations had longer time to next treatment with first-line enzalutamide, similar times with taxanes, and shorter times with PARP inhibitors compared to patients with *BRCA* mutations, respectively.[19] Cell culture studies have demonstrated limited PARP inhibitor response, even when the prostate cancer cells are fully *ATM*-deficient.[20] This limited response parallels outcomes in patients with only *ATM* mutations in PROFOUND[21] (olaparib) and TRITON2[22] (rucaparib).

As there remains ambiguity regarding optimal treatment, we investigated the optimal sequencing of PARP inhibitors relative to conventional chemotherapy (taxanes) in *ATM*-mutated mCRPC via a large multicenter retrospective review. In light of the limited response to PARP inhibitors reported in previous studies, we hypothesized that using taxanes first (before PARP inhibition) may yield better survival than using PARP inhibitors first in mCRPC patients with *ATM* mutations, and vice versa in patients with *BRCA2* mutations. We assembled a retrospective cohort of 158 mCRPC

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patients with *ATM* or *BRCA2* mutations to answer this question. For perspective, we analyzed 58 patients with *ATM* mutations, relative to the number of patients with *ATM* mutations in the prospective trials PROFOUND (86), TRITON2 (49), and TOPARP-B (21).

2 | METHODS

2.1 | Study population

A retrospective chart review of mCRPC patients across 11 academic centers in the United States was conducted from June to August 2021. Patients were included if any deleterious somatic or germline *ATM* or *BRCA2* mutation was detected on available clinical-grade genetic sequencing performed by individual study sites. Deleterious mutations were defined as genetic changes that led to predicted protein truncation or loss (frameshift, nonsense or splicing mutations, or homozygous deletions) or missense mutations that were classified as deleterious by the sequencing platform used. Patients were excluded from final analysis if they harbored a mutation in both *BRCA2* and *ATM*. In addition to the presence of a deleterious *ATM or BRCA2* mutation, patient must have also received a taxane (docetaxel or cabazitaxel) and/or a PARP inhibitor (any type) for the diagnosis of castration-resistant prostate cancer. Prior therapy with abiraterone and/or enzalutamide was permitted. Patients were additionally excluded from final analysis if they received ≤21 days of therapy.

2.2 | Study outcomes

Demographic, staging, treatment, and genomic characteristics were collected from all patients. This included age, Gleason sum, histology, presence of M1 disease at initial diagnosis, site of metastases, prior enzalutamide and abiraterone exposure, duration of taxane and PARP inhibitor therapy, progression (prostate-specific antigen [PSA] or radiologic/clinical), and vital status. Genomic data included mutation mechanism, mutation origin (germline or somatic), and zygosity status (monoallelic vs. biallelic). The presence of concurrent genomic alterations in *BRCA1*, *CDK12*, *CHD1*, *FOXA1*, *FOXO1*, *MED12*, *MYC*, *PIK3CA*, *PTEN*, *RB1*, *SPOP*, and *TP53* were also collected. Statistical analysis between cooccurrence of *BRCA2*, *ATM*, *PTEN*, *RB1*, and *TP53* alterations was performed.

The primary study outcome was progression-free survival (PFS) on first taxane or PARP inhibitor therapy. This PFS outcome was a composite outcome combining both PSA progression and investigator-assessed radiographic or clinical progression. Disease progression was defined as PSA progression (≥25% increase in PSA from baseline or nadir) or investigator-assessed radiographic or clinical progression. In patients with both PSA progression and investigator-assessed radiographic/clinical progression, the earlier date was denoted as the date of disease progression. The secondary study outcome was overall survival (OS), from the time of first taxane or PARP inhibitor therapy until death from any cause.

2.3 | Statistical analysis

Univariate analyses were performed for demographic, staging, treatment, and genomic characteristics using Pearson's χ^2 or Fisher's exact tests and Wilcoxon rank-sum test for categorical and continuous variables, respectively. Kaplan–Meier survival analysis was performed for the primary and secondary time-to-event outcomes. Multivariable Cox proportional-hazards modeling with backward stepwise selection was employed to assess the contribution of possible confounders on the primary and secondary outcomes. All analyses were performed using SAS version 9.4.

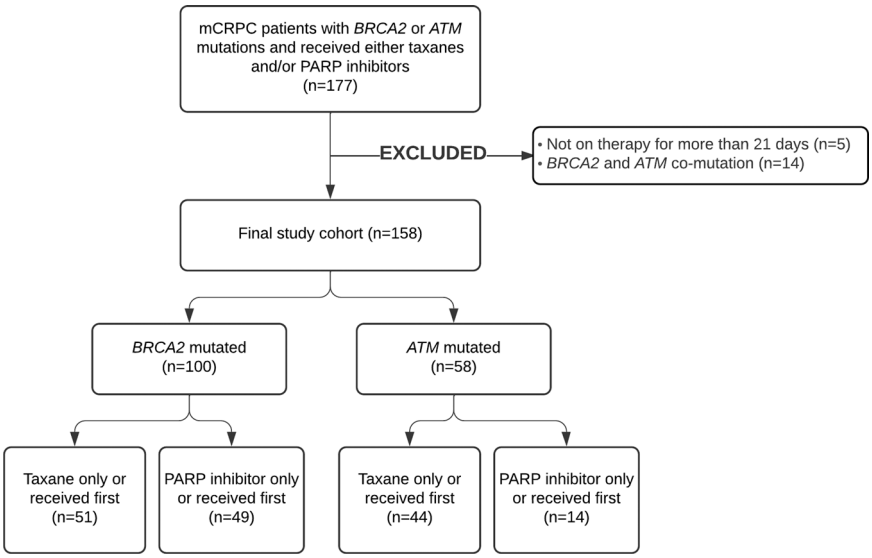

FIGURE 1 Patient selection schematic. mCRPC, metastatic castrate-resistant prostate cancer; PARP, poly(ADP-ribose) polymerase.

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TABLE 1 Demographic, staging, and treatment characteristics of study population

Characteristic	Overall	*BRCA2*-mutated patients	*ATM*-mutated patients	*p* Value
N	158	100	58	
Median age at first taxane or PARP inhibitor therapy, years (interquartile range)	72 (62–72)	66 (60–71)	69 (63–74)	<0.01
Gleason sum at diagnosis (%)				0.34
8–10	107 (75%)	69 (78%)	38 (70%)	
6–7	36 (25%)	20 (22%)	16 (30%)	
Unknown	15	11	4	
M1 disease at initial diagnosis (%)				0.37
Yes	70 (44%)	47 (47%)	23 (40%)	
No	88 (56%)	53 (53%)	35 (60%)	
Presence of bone metastases				0.04
Yes	132 (84%)	79 (79%)	53 (91%)	
No	26 (16%)	21 (21%)	5 (9%)	
Presence of nodal metastases				0.25
Yes	99 (63%)	66 (66%)	33 (57%)	
No	59 (37%)	34 (34%)	25 (43%)	
Presence of liver metastases				0.32
Yes	35 (22%)	25 (25%)	10 (17%)	
No	123 (78%)	75 (75%)	48 (83%)	
Presence of lung metastases				0.43
Yes	35 (22%)	20 (20%)	15 (26%)	
No	123 (78%)	80 (80%)	43 (74%)	
Prior enzalutamide therapy				0.68
Yes	96 (61%)	62 (62%)	34 (59%)	
No	62 (39%)	39 (38%)	24 (41%)	
Prior abiraterone therapy				0.61
Yes	126 (80%)	81 (81%)	45 (78%)	
No	32 (20%)	19 (19%)	13 (22%)	
Taxane and PARP inhibitor treatment pattern				<0.001
Taxane only	51 (32%)	21 (21%)	30 (52%)	
PARP inhibitor only	38 (24%)	29 (29%)	9 (16%)	
Taxane first, then PARP inhibitor	44 (28%)	30 (30%)	14 (24%)	
PARP inhibitor first, then taxane	25 (16%)	20 (20%)	5 (9%)	

Abbreviation: PARP, poly(ADP-ribose) polymerase.

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Institutional review board approval was obtained at the local level at each participating site.

3 | RESULTS

3.1 | Study population

The patient selection schema is shown in Figure 1. The final patient population comprised 158 patients, with 100 (63%) and 58 (37%) patients having deleterious *BRCA2* and *ATM* mutations, respectively. Among patients with *BRCA2* mutations, 51 (51%) received a taxane only or taxane before PARP inhibitor treatment, while 49 (49%) received a PARP inhibitor only or PARP inhibitor before taxane treatment. Among patients with *ATM* mutations, 44 (76%) received a taxane only or taxane before a PARP inhibitor, while 14 (24%) received a PARP inhibitor only or PARP inhibitor before a taxane.

3.2 | Patient characteristics

Patient demographic, staging, and treatment data are shown in Table 1. The median age of all patients at the time of first taxane or PARP inhibitor treatment was 67 years (interquartile range 62–72 years). There was a significant difference in age at receipt of first taxane or PARP inhibitor therapy between the patients with *BRCA2* and *ATM* mutations (median age 66 years for the *BRCA2*-mutated group and 69 years for the *ATM*-mutated group, $p < 0.01$). There was also a significant difference between bone metastases, present in 79% and 91% of patients with *BRCA2* and *ATM* mutations, respectively ($p = 0.04$). There were no significant differences between the *BRCA2*-mutated and *ATM*-mutated groups with respect to Gleason sum at diagnosis, M1 disease at diagnosis, presence of metastases (nodal, liver, or lung), prior enzalutamide therapy, or prior abiraterone therapy. Among patients with *BRCA2* mutations, 21 (21%) received a taxane only, 29 (29%) received a PARP inhibitor only, 30 (30%) received a taxane first then a PARP inhibitor, and 20 (20%) received a PARP inhibitor first then a taxane. Among patients with *ATM* mutations, 30 (52%) received a taxane only, 9 (16%) received a PARP inhibitor only, 14 (24%) received a taxane first then a PARP inhibitor, and 5 (9%) received a PARP inhibitor first then a taxane. This overall treatment pattern is significantly different between patients with *BRCA2* and *ATM* mutations ($p < 0.001$).

Mutation characteristics are shown in Table 2. Tissue samples were obtained from primary tumor (41%), metastatic tissue (36%), circulating tumor DNA (10%), or in some cases by germline-only testing (13%). The mechanisms of *BRCA2* mutation included homozygous deletions (55%), frameshift mutations (31%), missense mutations (6%), and nonsense mutations (8%); while the mechanisms for *ATM* mutations included deletions (28%), frameshift mutations (28%), missense mutations (22%), nonsense mutations (17%), and splice site mutations (5%). In the overall patient population, 50 (32%) had germline mutations, and 105 (68%) had somatic mutations. A total of 31 (20%) of patients had confirmed biallelic mutations. There was a significant difference in concurrent *RB1* alteration between *BRCA2*-mutated and *ATM*-mutated patients (35% vs. 17%, $p = 0.04$); there were no differences in cooccurrence in *TP53* and *PTEN* alterations between the two cohorts.

TABLE 2 Baseline mutation characteristics of study population

Characteristic	Overall	*BRCA2*-mutated patients	*ATM*-mutated patients	*p* Value
N	158	100	58	
Sample source				0.21
Primary tissue	60 (41%)	42 (46%)	18 (33%)	
Metastatic tissue	52 (36%)	30 (33%)	22 (41%)	
Circulating tumor DNA	14 (10%)	6 (7%)	8 (15%)	
Germline-only testing	19 (13%)	13 (14%)	6 (11%)	
Unknown	13	9	4	
Mechanism of mutation				<0.001
Homozygous deletion	69 (45%)	53 (55%)	16 (28%)	
Frameshift	46 (30%)	30 (31%)	16 (28%)	
Missense	19 (12%)	6 (6%)	13 (22%)	
Nonsense	18 (12%)	8 (8%)	10 (17%)	
Splicing	3 (2%)	0 (0%)	3 (5%)	
Unknown	3	3	0	
Origin of mutation				0.09
Germline	50 (32%)	36 (37%)	14 (24%)	
Somatic	105 (68%)	61 (63%)	44 (76%)	
Unknown	3	3	0	
Allelic status of mutation				0.49
Bialleic	31 (20%)	21 (22%)	10 (17%)	
Monoalleic or unconfirmed	123 (80%)	75 (78%)	48 (83%)	
Unknown	4	4	0	
TP53 comutation (missing data = 35)				0.70
No	80 (65%)	49 (64%)	31 (67%)	
Yes	43 (35%)	28 (36%)	15 (33%)	
PTEN comutation (missing data = 35)				0.85
No	76 (62%)	47 (61%)	29 (63%)	
Yes	47 (38%)	30 (39%)	17 (37%)	
RB1 comutation (missing data = 35)				0.04
No	88 (72%)	50 (65%)	38 (83%)	
Yes	35 (28%)	27 (35%)	8 (17%)	

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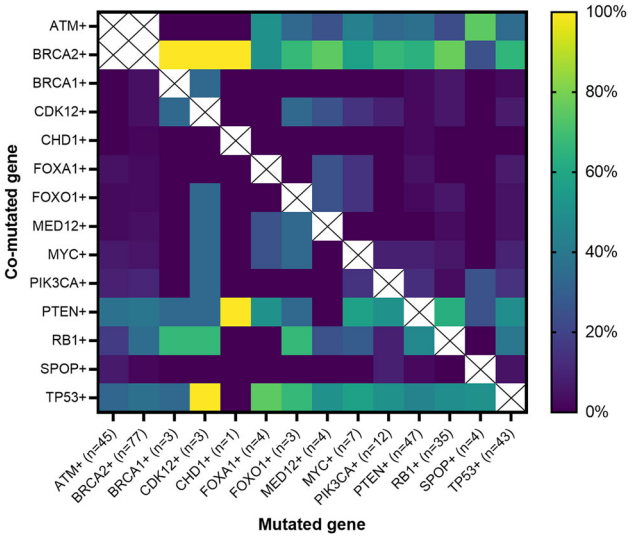

FIGURE 2 Heatmap of cooccurring alterations. The *X*-axis indicates the primary mutated gene (*n* indicates the number of patients), and the *Y*-axis indicates the second comutated gene. The colored squares demonstrate the percentage of patients with a genetic mutation shown in the *X*-axis, who also have a concurrent mutation denoted by the *Y*-axis. Patients with both *BRCA2* and *ATM* mutations were specifically excluded. [Color figure can be viewed at wileyonlinelibrary.com]

The pattern of cooccurring mutations in 14 preselected prostate cancer-relevant genes is shown in Figure 2. Statistical analyses between the most commonly expressed genes other than *ATM* and *BRCA2* (*PTEN*, *RB1*, *and TP53*) demonstrate significant coalteration of *RB1* in *PTEN* mutated patients (47% vs. 17% in *PTEN* nonmutated patients, $p < 0.001$).

3.3 | Study outcomes

The primary outcome of PFS on first taxane or PARP inhibitor therapy by *ATM* or *BRCA2* mutation status is shown in Figure 3. Patients with *ATM* mutations who received a taxane first had numerically longer median PFS compared to those who received a PARP inhibitor first (6.2 vs. 3.3 months, hazard ratio [HR] with 95% confidence interval [CI] 0.74 [0.37–1.50]; $p = 0.40$). In contrast, patients with *BRCA2* mutations who received a PARP inhibitor first had numerically longer median PFS compared to those who received a taxane first (11.2 vs. 7.2 months, HR: 0.85 (0.54–1.35); $p = 0.49$). These differences were not statistically significant.

The secondary outcome of OS from the time of first taxane or PARP inhibitor therapy to death, by *ATM* or *BRCA2* mutation status, is shown in Figure 4. Patients with *ATM* mutations who received taxanes first had numerically longer median OS compared to those who received PARP inhibitors first (38.1 vs. 33.0 months, HR: 0.56 (0.20–1.54); $p = 0.26$). In contrast, patients with *BRCA2* mutations who received PARP inhibitors first had numerically longer median OS compared to those who received taxanes first (36.6 vs. 32.8 months, HR: 0.75 (0.41–1.37); $p = 0.35$). Again, these differences did not reach statistical significance.

Multivariable Cox proportional-hazards modeling using backward stepwise selection to evaluate the impact of possible factors, including choice of first therapy (taxane vs. PARP inhibitor), age, Gleason score, presence of M1 disease at initiation diagnosis, presence of metastases (nodal, liver, or lung), and prior enzalutamide or abiraterone exposure on patients with *ATM* or *BRCA2* mutations did not demonstrate a significant association of any factor with PFS or OS in our model.

4 | DISCUSSION

In our multicenter retrospective chart review investigating the optimal sequencing of PARP inhibitors and taxanes in mCRPC patients with *ATM* or *BRCA2* mutations, we found that patients with *ATM* mutations demonstrated a trend toward longer PFS and OS when taxane was given first rather than PARP inhibitors. The reverse was true for patients with *BRCA2* mutations: that PARP inhibitors demonstrated numerically longer PFS and OS when given first over taxanes. However, none of these survival analyses were statistically significant.

The following factors may have contributed to the observed PFS and OS results. First, previous studies[17,18] have demonstrated that complete loss of *ATM* is associated with improved response to PARP inhibitors. As 28% of patients with *ATM* mutations in our cohort had homozygous deletions in *ATM*, these patients may have demonstrated a better response to PARP inhibitors compared to other *ATM*-mutated patients. It is important to note, however, that other types of *ATM*-mutations observed in our cohort may have also led to a loss-of-function phenotype, increasing the number of patients in this group. Second, there may have been other unmeasured differences in baseline demographics, clinical characteristics, or previous prostate cancer therapy between the cohorts that affected survival. However, our baseline demographics and clinical characteristics are similar to *ATM* and *BRCA2* patient cohorts in other mCRPC studies.[19,23] Third, our cohorts may not have contained sufficient patient numbers to detect a significant difference in outcomes given the unknown relative hazard of PARP inhibitor and taxane therapy in patients with *ATM* or *BRCA2* mutations, and thus our analysis was likely underpowered to interrogate differential treatment sequences.

Although the PFS and OS differences did not reach statistical significance, our study provides insight into the current treatment landscape of mCRPC patients with *ATM* or *BRCA2* mutations. First, the observed numeric advantage in PFS and OS of upfront taxanes compared to upfront PARP inhibitors in *ATM*-mutated mCRPC should be confirmed in larger datasets and prospective studies, such as TRITON3. Since mCRPC patients with *ATM* mutations also appear to be less sensitive to platinum chemotherapy,[19,24] ascertaining an efficacious treatment agent in this population is especially important. Second, 49% of patients with *BRCA2* mutations in our cohort received PARP inhibitors as the first line of mCRPC therapy, compared to only 25% of patients with *ATM* mutations, showing the increasing uptake of upfront PARP inhibitor therapy in mCRPC patients with *BRCA2* mutations.

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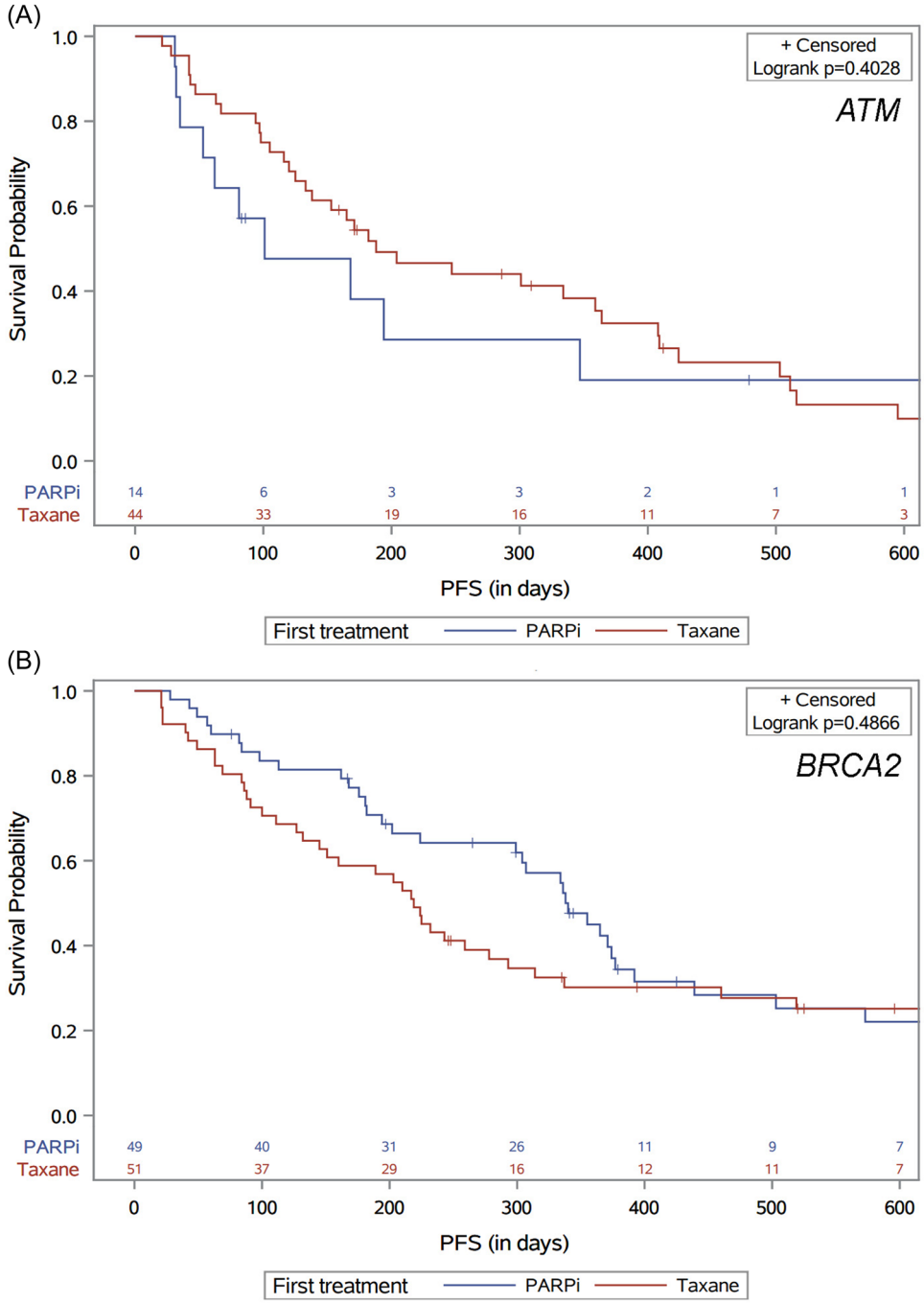

FIGURE 3 Progression-free survival (PFS) by first taxane or PARP inhibitor therapy, in (A) patients with *ATM* mutations and (B) patients with *BRCA2* mutations.PARP, poly(ADP-ribose) polymerase. [Color figure can be viewed at wileyonlinelibrary.com]

There were several limitations to our study, including the retrospective nature and the possible heterogenous phenotypes in our *ATM*-mutated cohort. Second, composite PFS was defined as the earliest of three possible indicators of disease progression (biochemical progression, radiological progression, investigator-determined clinical progression) in this study which may have affected the PFS analysis. Although using a defined biochemical progression would be preferable, limitations in retrospective clinical data across multiple institutions made standardizing this data challenging. Third, retrospective sequencing studies in the metastatic population require controlling for previous treatment courses that may have affected tumor biology at the time of receipt of the treatments of interest. To address this, we did account for prior abiraterone and enzalutamide use in our analysis. Despite these limitations, we were able to collate the largest retrospective *ATM*- and *BRCA2*-mutated mCRPC cohort in the literature to our knowledge that contains detailed diagnostic and treatment data with respect to sequencing of taxane and PARP inhibitor agents in these patients.[19,23]

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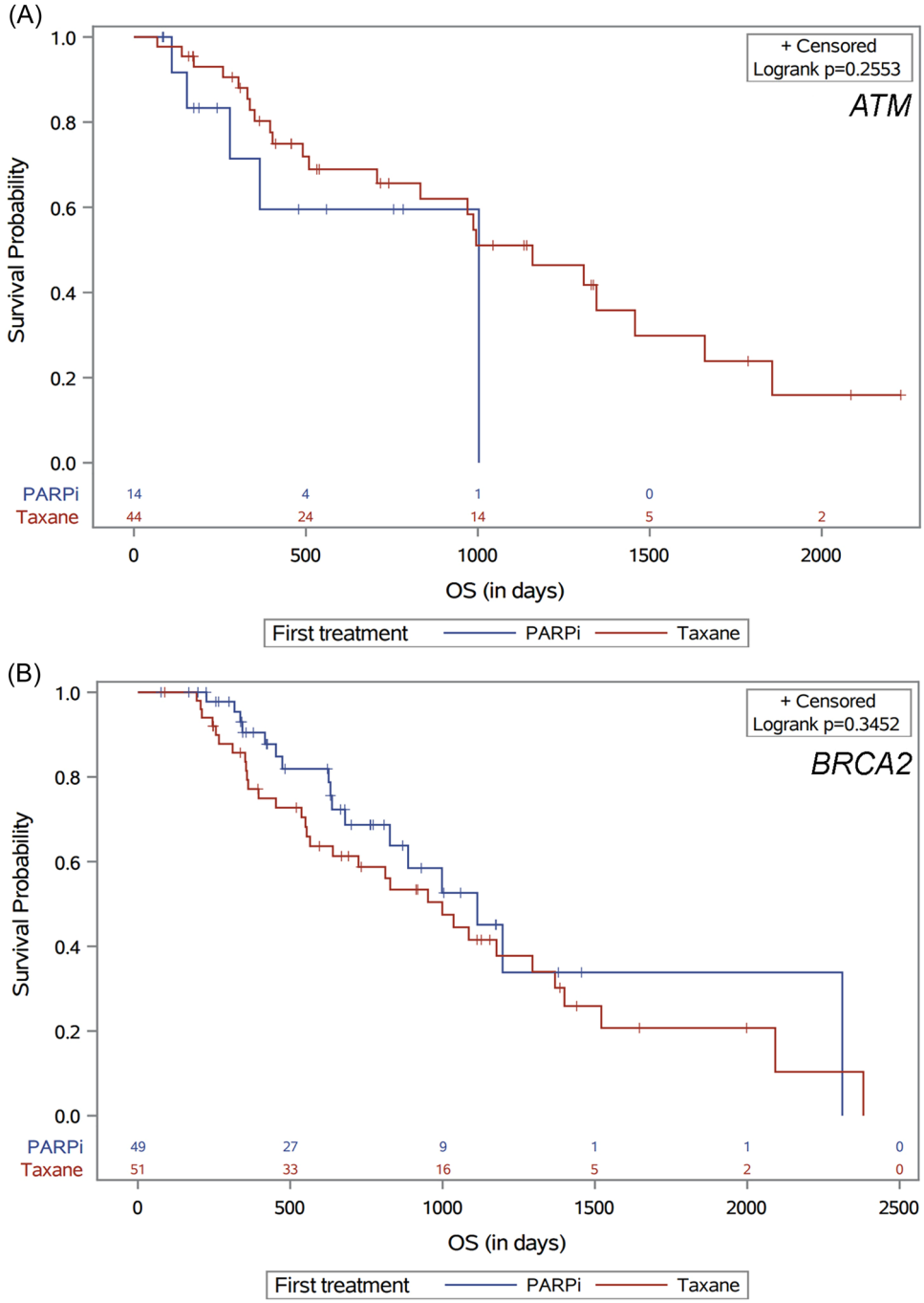

FIGURE 4 Overall survival (OS) by first taxane or PARP inhibitor therapy, in (A) patients with *ATM* mutations and (B) patients with *BRCA2* mutations.PARP, poly(ADP-ribose) polymerase. [Color figure can be viewed at wileyonlinelibrary.com]

5 | CONCLUSION

Our retrospective multicenter analysis of mCRPC patients with *ATM* or *BRCA2* mutations demonstrates a numerically increased PFS and OS when taxanes are given upfront in patients with *ATM* mutations, and vice versa with PARP inhibitors in patients with *BRCA2* mutations. These differences in clinical outcomes, while not statistically significant, support increasing genomic profiling uptake and the use of tailored optimal sequencing of therapies for mCRPC patients with specific classes of DDR mutations. We hope that these hypothesis-generating results inspire additional clinical consortia to confirm or refute these findings in larger genetically-defined mCRPC populations.

ACKNOWLEDGMENTS

This study was funded by National Cancer Institute T32-CA-236621 (to Christopher Su) and PNW SPORE:P50 CA097186, CCSG:P30 CA015704 & T32CA009515 (to Alexandra Sokolova).

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CONFLICTS OF INTEREST

Emily Nizialek: Consulting or Advisory Role: AstraZeneca. Jacob E. Berchuck: Honoraria: Digital Science Press. Consulting or Advisory Role: Genome Medical, VetOncoDx. Equity: Genome Medical, VetOncoDx, Cityblock Health (spouse). Employment: Cityblock Health (spouse). Travel, Accommodations, Expenses: Digital Science Press. Patents: Institutional patent filed on methods to detect neuroendocrine prostate cancer through tissue-informed cell-free DNA methylation analysis. Pedro C. Barata: Consultant (Institutional): Astellas; Eisai; AVEO Oncology, Janssen, EMD Serono; Dendreon; Pfizer, Seattle Genetics, BMS, Bayer, Guardant Health. Contracted Research (Institutional): AstraZeneca, Merck, AVEO Oncology. Research Grant (Institutional): Blue Earth Diagnostics. Speaker's Bureau (Institutional): Bayer, Caris, Myovant. Rahul R. Aggarwal: Honoraria: Clovis Oncology. Consulting or Advisory Role: Advanced Accelerator Applications; Alessa Therapeutics; Alessa Therapeutics; Amgen; AstraZeneca; Axiom Biotechnologies; Clovis Oncology; Dendreon; Jubilant Pharmaceuticals; Merck; Pfizer. Research Funding: Abbvie (Inst); Amgen (Inst); AstraZeneca (Inst); BioXCel therapeutics (Inst); Cancer Targeted Technology (Inst); Janssen (Inst); Merck (Inst); Novartis (Inst); Xynomic Pharma (Inst); Zenith Epigenetics (Inst). Rana R. McKay: Consulting or Advisory Role: Aveo, Astellas, Medivation, AstraZeneca, Bayer, Bristol Myers Squibb, Calithera Biosciences, Caris, Dendreon, Exelixis, Janssen, Merck, Myovant, Novartis, Pfizer, Sanofi, Sorrento Therapeutics, Tempus, and Vividion Therapeutics. R. R. M. receives research funding from Tempus, Bayer. Neerja Agarwal: Consulting or Advisory Role: Astellas, Astra Zeneca, Aveo, Bayer, Bristol Myers Squibb, Calithera, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Foundation Medicine, Genentech, Gilead, Janssen, Merck, MEI Pharma, Nektar, Novartis, Pfizer, Pharmacyclics, and Seattle Genetics. Funding to Institution: Astellas, Astra Zeneca, Bavarian Nordic, Bayer, Bristol Myers Squibb, Calithera, Celldex, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Gilead, Glaxo Smith Kline, Immunomedics, Janssen, Medivation, Merck, Nektar, New Link Genetics, Novartis, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Seattle Genetics, Takeda, and Tracon. Alan H. Bryce: Funding to Institution: Janssen, AstraZeneca, Gilead. Consulting: Merck, Bayer. Honoraria: Elsevier, Fallon Medica, Horizon CME, PRIME Education, MJH Life Sciences. Patents: Therapeutic Targeting of Cancer Patients wiht NRG1 Rearrangements 15/735,289. Oliver Sartor: Consulting: Advanced Accelerator Applications (AAA), Astellas, AstraZeneca, Bayer, Blue Earth Diagnostics, Inc., Bavarian Nordic, Bristol Myers Squibb, Clarity Pharmaceuticals, Clovis, Constellation, Dendreon, EMD Serono, Fusion, Isotopen Technologien Meunchen, Janssen, Myovant, Myriad, Noria Therapeutics, Inc., Novartis, Noxopharm, Progenics, POINT Biopharma, Pfizer, Sanofi, Tenebio, Telix, Theragnostics. Grant/Research Support: Advanced Accelerator Applications, Amgen, AstraZeneca, Bayer, Constellation, Endocyte, Invitae, Janssen, Lantheus, Merck, Progenics, Tenebio. Heather H. Cheng: Research Funds to Institution: Clovis Oncology, Color Genomics, Janssen, Medivation, Phosplatin, Sanofi; Consultant: AstraZeneca; Royalties: UpToDate. Nabil Adra: Consulting or Advisory Role: Astellas Pharma; Aveo; Bristol Myers Squibb Foundation; Bristol Myers Squibb Foundation; Exelixis; Merck; Sanofi. Research Funding: Exelixis (Inst); Genentech (Inst); Merck (Inst). Cora N. Sternberg: Funding, consultancy, advisory: Astellas Pharma/AstraZeneca/Bayer/Genzyme/Gilead/Medscape/Janssen; Merck/MSD/Pfizer/Roche/Impact Pharma/BMS/Sanofi-Genzyme/UroToday/CCO Clinical, GLC; NCI. Mary-Ellen Taplin: Consulting or Advisory Role: Janssen, Arcus Bioscience, Roviant, Arvinas, Blue Earth, Clovis, AstraZeneca, Epizyme, Research To Practice, Pfizer, UpToDate. Ajjai S. Alva: Consulting or Advisory Role: AstraZeneca; BMS; Merck; Pfizer. Research Funding: Arcus Biosciences (Inst); Astellas Pharma (Inst); AstraZeneca (Inst); Bayer (Inst); Bristol-Myers Squibb (Inst); Celgene (Inst); Genentech (Inst); Harpoon Therapeutics (Inst); Janssen (Inst); Merck Sharp & Dohme (Inst); Mirati Therapeutics (Inst); Progenics (Inst); Progenics (Inst); Prometheus (Inst); Roche (Inst). Travel, Accommodations, Expenses: BMS; Merck. Emmanuel S. Antonarakis: Consulting or Advisory Role: Janssen, Astellas, Sanofi, Dendreon, Bayer, BMS, Amgen, ESSA, Constellation, Blue Earth, Exact Sciences, Invitae, Curium, Pfizer, Merck, AstraZeneca, Clovis, Eli Lilly. Grant/Research Support: Janssen, J&J, Sanofi, BMS, Pfizer, AstraZeneca, Novartis, Curium, Constellation, ESSA, Celgene, Merck, Bayer, Clovis. Inventions/patents: Coinventor of AR-V7 technology licensed to Qiagen. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Deidentified data that support the findings of this study may be available upon reasonable request from the corresponding author. The data set is not publicly available due to privacy concerns related to protected health information.

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How to cite this article: Su CT, Nizialek E, Berchuck JE, et al. Differential responses to taxanes and PARP inhibitors in *ATM*- versus *BRCA2*-mutated metastatic castrate-resistant prostate cancer. *The Prostate*. 2023;83:227-236. doi:10.1002/pros.24454

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CANCER GENETICS

Internet-Based Germline Genetic Testing for Men With Metastatic Prostate Cancer

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abstract

PURPOSE Germline mutations in DNA repair genes are present in approximately 10% of men with metastatic prostate cancer (mPC), and guidelines recommend genetic germline testing. Notable barriers exist, including access to genetic counseling, insurance coverage, and out-of-pocket costs. The GENTIeMEN study was designed to determine the feasibility of an Internet-based, patient-driven germline genetic testing approach for men with mPC.

PATIENTS AND METHODS In this prospective cohort study, men with mPC provided informed consent via an Internet-based platform and completed a questionnaire including demographics and family cancer history. Supporting medical data were also collected. Genetic testing was performed using the Color Genomics 30-gene targeted panel of cancer predisposition genes on a mailed saliva sample. Men whose test results identified a germline pathogenic or likely pathogenic variant received results by phone or telehealth genetic counseling; other participants received results by email with an option for phone-based or telehealth genetic counseling.

RESULTS As of August 18, 2021, 816 eligible men were consented, of whom 68% (551) completed genetic testing, and 8.7% (48 of 551) were found to carry a pathogenic or likely pathogenic variant in a germline DNA repair gene: *CHEK2* (17), *BRCA2* (15), *ATM* (6), *NBN1* (3), *BRCA1* (2), *PALB2* (2), *PMS2* (2), and *MSH6* (1). Participants were more likely to complete the testing process if they were non-Hispanic White, married, highly educated, or from a higher-income bracket.

CONCLUSION Here, we show the feasibility of delivering germline (inherited) genetic testing by a voluntary, patient-driven, Internet-based platform to men with mPC. Preliminary results show rates of germline DNA repair mutations, consistent with other cohorts. Although feasible for some, reduced steps for participation, more dedicated diverse outreach and participant support, and identification and addressing of additional barriers is needed to ensure equitable access and optimization.

JCO Precis Oncol 7:e2200104. © 2023 by American Society of Clinical Oncology

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INTRODUCTION

Germline DNA repair gene mutations are present in approximately 10% of patients with metastatic prostate cancer (mPC).[1,2] Identification of germline DNA repair gene mutations has two important implications for patients with mPC: potential prostate cancer treatment planning and potential family cancer risk. Specifically, olaparib and rucaparib are oral poly adenosine diphosphate-ribose polymerase inhibitors, now approved by the Food and Drug Administration for men with metastatic castration-resistant prostate cancer in association with germline and/or somatic *BRCA1* and *BRCA2* mutations (rucaparib)[1] and *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L* (olaparib).[2] Finally, immune checkpoint inhibitor pembrolizumab is Food and Drug Administration–approved for patients with mPC whose tumors have evidence of high microsatellite instability, mismatch repair deficiency, or tumor mutational burden ≥ 10 mut/Mb.[1-3] The potential family implications are also critically important, with opportunities for genetic testing of relatives and, if relatives carry the same germline genetic variants, options for modified cancer screening and cancer risk reduction. The National Comprehensive Cancer Network (NCCN) guidelines both for Prostate Cancer and for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic recommend offering germline testing to all men with mPC.[4,5] Despite the importance of identifying patients with prostate cancer and germline DNA repair gene mutations, there are important barriers, including limited access to genetics services, insurance coverage, and high out-of-pocket costs.[6,7] At the time of

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on November 18, 2022 and published at ascopubs.org/journal/po on January 9, 2023: DOI https://doi.org/10.1200/PO.22.00104

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CONTEXT

Key Objective

The GENTleMEN study was designed to determine the feasibility of an Internet-based, patient-driven germline genetic testing approach for men with metastatic prostate cancer.

Knowledge Generated

Preliminary data demonstrate the feasibility of Internet-based, patient-driven, genetic testing with 68% test completion. We found that 8.7% of those completing testing carried pathogenic or likely pathogenic variant in germline DNA repair genes, in the range of other published cohorts. Participants were more likely to complete testing if they were non-Hispanic White, married, highly educated, or from a higher-income bracket.

Relevance

Internet-based, patient-driven genetic testing is a feasible delivery mechanism for a subset of patients. However, our data indicate that further efforts to optimize clinical implementation for a wider cross-section of men with metastatic prostate cancer will be needed, and may include reducing steps for participation, improving educational outreach and further exploring and addressing barriers.

study inception, the NCCN guidelines criteria did not yet include consideration for germline genetic testing (2017) or the subsequent recommendation for offering germline genetic testing to all patients with mPC (2019). The overarching goal for the study was in recognition that first, the standard of care was likely to change and second that there was a need and opportunity to consider novel genetic education and testing delivery methods because of the substantial expansion of the number of patients needing genetic counseling and limited genetic counselors. To address these challenges, we conducted the Genetic Testing for Men with Metastatic Prostate Cancer (GENTleMEN) research study to determine whether an Internet-based, patient-driven, cost-free genetic testing program would be feasible for interested patients and could provide clinical genetic testing for patients with mPC by removing barriers of access and cost.

PATIENTS AND METHODS

Design, Setting, and Participants

This prospective, nonpilot feasibility cohort study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Consortium. Informed consent was provided in accordance with the precepts established by the Declaration of Helsinki via a study-specific, Health Insurance Portability and Accountability Act-compliant web application.[8]

The study opened on September 16, 2016, with the goal of testing up to 2,000 participants. This initial analysis includes participants consenting and completing surveys through August 18, 2021. Approximately two additional months were allowed for the maturation of data, including return of saliva samples, and results reporting. Patients were recruited through a variety of mechanisms: their medical provider, patient support group, prostate cancer newsletters, or social media. Enrollment is patient-driven, which we define as the self-directed patient-participant visits Gentlemen Study website[9] (currently on pause, please contact corresponding author for information) or calls the study telephone line. or calls the study telephone line. Research coordinators are available for assistance by phone or email, although participants need to initiate a request for help by phone and/or email, and the study team is not able to actively reach out to participants who do not make requests for help.

The website provides background information about the study and potential risks and benefits of germline genetic testing before informed consent and participant survey. The website was not designed to be interactive with the participant. Additional optional educational materials and videos are available to participants after test kit activation and provide additional review of the rationale and potential benefits for testing (potential treatment options and family implications), genetic discrimination risks, and Genetic Information Nondiscrimination Act laws. Although the additional materials can be viewed as many times as needed, they are not required for study participation. All study materials are in English and tailored to an 8th grade reading level. An email and telephone number for additional support is provided. Self-directed electronic informed consent is provided via a Health Insurance Portability and Accountability Act-compliant Redcap platform.[9] The study flow diagram is shown in Figure 1.

Inclusion criteria include individuals age older than 18 years who have documented mPC (as defined by one of the following: radiographic evidence of distant prostate cancer involvement, serum prostate-specific antigen > 100 ng/mL, and/or pathology report indicating prostate cancer); willingness to undergo germline genetic testing; willingness to provide basic demographic information and family cancer history; willingness to complete patient survey at enrollment and at 6-month follow-up; willingness and ability to provide a saliva sample; residing in the United States with a US mailing address; and having a personal email address. Study materials are only available in English, and therefore study participants need to be able to read and write in

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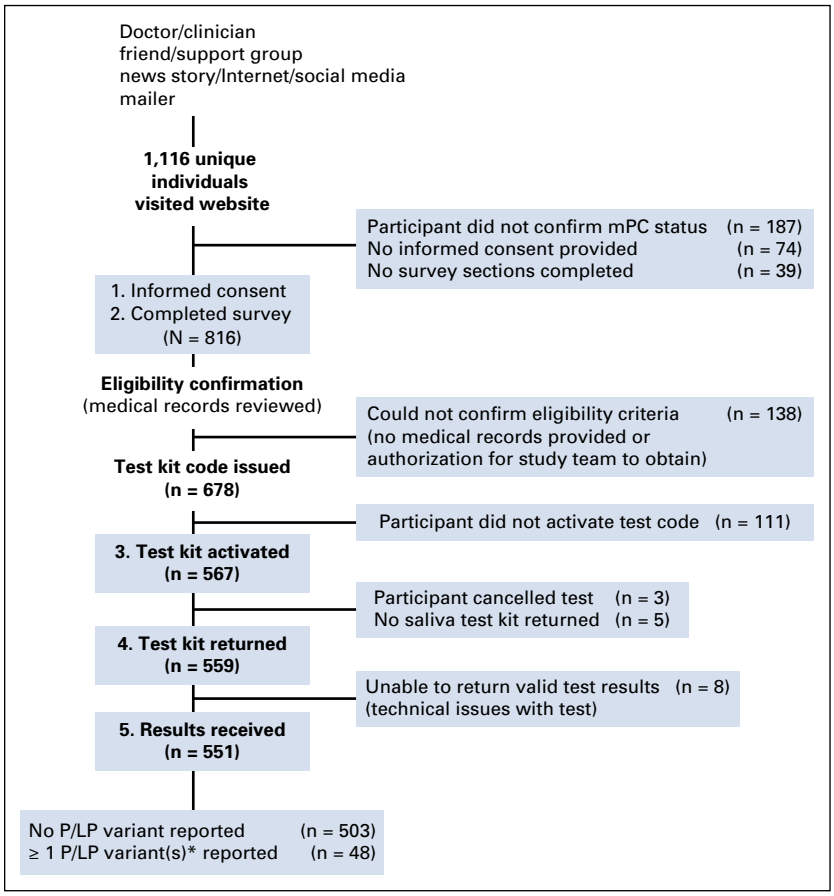

FIG 1. Study flow diagram. Numbered, bolded boxes contain active steps that participant must complete to proceed with study. *Four genes not specifically associated with prostate cancer risk were excluded: *APC*, *CDKN2A*, *MITF*, *and MUTYH*. mPC, metastatic prostate cancer; P/LP, pathogenic or likely pathogenic.

English to enroll. Exclusion criteria include inability or unwillingness to provide necessary information for eligibility, self-reported history of bone marrow transplant, or hematologic malignancy (because of inability to ensure a valid test result under these conditions).

Survey Instruments

After providing informed consent, participants were directed to complete a survey that included demographics, family cancer history, and six validated instruments: GAD7,[10] PHQ9,[11] Cancer Distress, Risk Perception, Decision Conflict, and Knowledge of and Concern with Genetic Testing.[12,13] Supporting medical records were collected by the research team (with permission from participants) or uploaded directly by participants.

Two versions of the survey were used. Version 2 (V2) had the order of questions rearranged for earlier screening of ineligible individuals. There were 1,423 survey entries in total (V1, n = 23 and V2, n = 1,400). Although eligibility for study required a willingness to complete patient survey at enrollment and at 6-month follow-up, completion of all survey questions was not required. We included participants who returned survey responses to at least one of the six validated instruments.

After filtering out spam and duplicate records, we identified 1,116 unique visitors to the website, of whom 816 participants provided consent and completed the minimum survey response (defined as having completed at least one of six validated survey instruments), had medical records available and reviewed, and were confirmed to be eligible.

After eligibility confirmation, participants were issued a test kit promotional code to receive a test kit. Participants used the promotional code to create an account on the Color Health website[14] and to activate their testing kit. After code activation, participants were mailed a saliva collection kit with instructions on sample collection. A study-specific email and phone line are available for questions and/or technical assistance.

Germline Genetic Testing

Germline genetic testing costs were covered by institutional research study funds and by foundational grants. Genetic testing was performed on the saliva sample via the clinical Color Genomics targeted panel of 30 cancer predisposition genes: *APC*, *ATM*, *BAP1*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A(p14ARF)*, *CDKN2A (p16INK4a)*, *CHEK2*, *EPCAM*, *GREM1*, *MITF*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *POLD1*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, *SMAD4*, *STK11*, and *TP53*.

Statistical Analysis

Patient demographics, decisions to participate, and univariate associations with advancement through stages to

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complete genetic testing were evaluated using Kruskal-Wallis or Fisher's exact tests. Post hoc multivariate logistic regression examined odds of completing genetic testing for non-Hispanic White participants (*v* combined Asian and Asian American, African American and Black, Hispanic, Latino and Spanish origin, and mixed and/or other participants) after adjusting for age at diagnosis, marital status, number of biological children, highest education, employment, and income level. All calculations were performed using R version 3.6.3.[15] A P value $< .05$ was considered statistically significant.

RESULTS

Between September 16, 2016, and August 18, 2021, 816 participants were enrolled and included in this analysis. The demographics of the study participants are summarized in Table 1. Eighty-three percent (678 of 816) of participants completed the minimum survey requirements, were confirmed to be eligible after medical records review, and were issued a test kit promotion code. The remaining 16.9% (138 of 816) of participants either did not upload their medical records or did not authorize the study team to do so on their behalf so that eligibility could not be confirmed. Among the 99.4% (811 of 816) of participants for whom the time to complete survey was available, the median time spent for survey completion was 56 minutes. Of the participants who were issued a test kit promotion code, 84% (567 of 678) activated the testing account, of whom 97% (551 of 567) completed the testing process and received results (Fig 1).

Pathogenic or likely pathogenic variant (P/LPV) in genes previously associated with mPC were identified in 8.7% (48 of 551) of participants who completed testing (Fig 2). Among the 503 participants with no P/LPV in genes not currently associated with prostate cancer, 2% (10 of 503) had P/LPV in genes associated with risk of other non-prostate cancers; 18% (92 of 503) were found to have no P/LPV, but at least one variant of unknown significance (VUS). Two percent (10 of 503) had a P/LPV in a gene not currently associated with prostate cancer and at least one VUS (Appendix Table A1 and Table A2). All participants found to have any P/LPV were required to receive their results through a phone or telehealth genetic counseling visit. Among the 493 men without P/LPV in any of the genes tested, 4% (20 of 493) requested follow-up post-test phone genetic counseling in addition to the results letter, of whom 25% (5 of 20) had a reported VUS.

Advancement through the stages of complete testing was associated with race and ethnicity (both $P < .001$), age at diagnosis ($P = .02$), marital status ($P = .03$), number of biological children ($P = .006$), education ($P < .001$), employment status ($P < .001$), and annual household income ($P = .01$). Most participants completing testing self-identified as non-Hispanic White, married, and reported higher education and annual household income > $75,000 US dollars (Table 1). In multivariate analysis, the odds of completing testing for non-Hispanic White participants was 1.15 times (95% CI, 1.04 to 1.26; $P = .005$) the odds for other participants. Despite a smaller proportion of Asian and Asian American, African American and Black, Hispanic, Latino and Spanish origin, and mixed or other participants, the dropoff rate at each step was similar across all of these groups (Appendix Fig A1).

DISCUSSION

Germline genetic testing is increasingly relevant to the care of men with mPC and their families, as reflected in various guidelines, including the NCCN Prostate Cancer as well as Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic guidelines.[16,17] When the GENTleMEN study was conceptualized and initiated, there was a limited role for germline genetic testing in prostate cancer which was largely reserved for those with a very strong family history of cancer rather than for patients with a personal history of mPC. Thus, the initial study priority in 2016 was to investigate feasibility of a new method (patient-driven, Internet-based) of germline genetic test delivery. In this preliminary report, we observed that the participant follow-through from eligibility verification and test code issuance through completion of genetic testing was approximately two-thirds, demonstrating feasibility of this approach. Moreover, as the COVID-19 pandemic unfolded, participants were able to continue to enroll and proceed through the steps of the study remotely.

The two-thirds completion rate may result from a variety of factors. For example, reliance on patient-driven actions and timing may be suboptimal. Patients may be initiating systemic therapies such as androgen deprivation therapy, oral androgen receptor signaling inhibitors (eg, abiraterone or enzalutamide) and/or docetaxel chemotherapy, and overwhelmed by competing priorities and the participant time burden. The median time to complete survey instruments was unexpectedly long at nearly an hour, and some participants may have simply given up because of time burden. It may also be that in some cases an incomplete understanding of importance of genetic testing or confusion about study process and/or hesitancy or personal decision not to proceed with genetic testing may also have been barriers. Because of the self-driven, multifactorial nature of recruitment for GENTleMEN, we are not able to determine reasons participants do not follow-through if they do not wish to share the feedback.

We believe that removing insurance/cost and access considerations may have helped individuals who were motivated get testing. The baseline knowledge about cancer genetics and validated distress measures will be reported separately and may reveal unique aspects of communication and decision making around genetics in individuals with mPC who opted to participate. We found

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TABLE 1. Sociodemographic Characteristics of Study Participants and Association with Stage of Completing Genetic Testing

Characteristic	Did Not Meet All Criteria (N = 138)	Did Not Activate Code (N = 111)	Activated Code (N = 567)	*P*
Age at time of completing survey, median (IQR), years	71 (64, 77)	71 (66, 77)	70 (65, 75)	.2
Age at diagnosis of prostate cancer, median (IQR), years	62 (57, 68)	67 (61, 72)	64 (59, 69)	.019
Number of biological children, median (range)	2 (0, 7)	2 (0, 8)	2 (0, 10)	.006
Race, No. (%)				< .001
Asian, Asian American[a]	6 (4.3%)	2 (1.8%)	20 (3.5%)	
Black, African American	3 (2.2%)	7 (6.3%)	15 (2.6%)	
Mixed/other[b]	7 (5.1%)	10 (9.0%)	19 (3.4%)	
White, Caucasian	101 (73%)	92 (83%)	507 (89%)	
Unknown[c]	21 (15%)	0 (0%)	6 (1.1%)	
Hispanic, Latino, or Spanish origin, No. (%)				< .001
No	110 (80%)	102 (92%)	542 (96%)	
Yes[d]	6 (4.3%)	5 (4.5%)	14 (2.5%)	
Unknown	22 (16%)	4 (3.6%)	11 (1.9%)	
Marital status, No. (%)				.031
Married	88 (64%)	74 (67%)	413 (73%)	
Divorced	10 (7.2%)	15 (14%)	40 (7.1%)	
Widowed	4 (2.9%)	4 (3.6%)	27 (4.8%)	
Never married	5 (3.6%)	2 (1.8%)	21 (3.7%)	
Separated	0 (0%)	1 (0.9%)	5 (0.9%)	
Unknown[e]	31 (22%)	15 (14%)	61 (11%)	
Education, No. (%)				< .001
No school or kindergarten only	0 (0%)	0 (0%)	0 (0%)	
Grades 1 through 8 (elementary/middle)	1 (0.7%)	1 (0.9%)	2 (0.4%)	
Grades 9 through 11 (some high school)	2 (1.4%)	2 (1.8%)	11 (1.9%)	
Grade 12 or General Educational Development (high school graduate)	11 (8.0%)	25 (23%)	62 (11%)	
College 1-3 years (some college)	31 (22%)	39 (35%)	141 (25%)	
College 4 years or more (college graduate)	28 (20%)	21 (19%)	129 (23%)	
Postgraduate, professional, or advanced degree	46 (33%)	23 (21%)	209 (37%)	
Unknown	19 (14%)	0 (0%)	13 (2.3%)	
Employment, No. (%)				< .001
Retired[f]	76 (55%)	76 (68%)	385 (68%)	
Employed[g]	31 (22%)	28 (25%)	138 (24%)	
Unable to work[h]	7 (5.1%)	2 (1.8%)	17 (3.0%)	
Out of work for 1 year or more[i]	2 (1.4%)	3 (2.7%)	14 (2.5%)	
Out of work for < 1 year[j]	3 (2.2%)	1 (0.9%)	7 (1.2%)	
Unknown	19 (14%)	1 (0.9%)	6 (1.1%)	

(Continued on following page)

that the participants in GENTIeMEN who completed testing were largely non-Hispanic White, married, highly educated, and from a higher-income bracket. These demographic characteristics may associate with early adoption of new methods along with greater comfort and trust with the Internet and electronic media applications. It may also be the case that these men were more likely to hear about the study because of their medical providers and/or participation in patient support groups may have had further encouragement by married partners to follow-through, and the time and means to complete the survey and testing process. We plan to

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TABLE 1. Sociodemographic Characteristics of Study Participants and Association with Stage of Completing Genetic Testing (Continued)

Characteristic	Did Not Meet All Criteria (N = 138)	Did Not Activate Code (N = 111)	Activated Code (N = 567)	*P*
Annual household income in US dollars, No. (%)				.010
Less than $10,000	5 (3.6%)	5 (4.5%)	14 (2.5%)	
Less than $15,000 ($10,000 to less than $15,000)	2 (1.4%)	2 (1.8%)	11 (1.9%)	
Less than $20,000 ($15,000 to less than $20,000)	2 (1.4%)	3 (2.7%)	12 (2.1%)	
Less than $25,000 ($20,000 to less than $25,000)	3 (2.2%)	4 (3.6%)	16 (2.8%)	
Less than $35,000 ($25,000 to less than $35,000)	10 (7.2%)	13 (12%)	30 (5.3%)	
Less than $50,000 ($35,000 to less than $50,000)	10 (7.2%)	15 (14%)	68 (12%)	
Less than $75,000 ($50,000 to less than $75,000)	22 (16%)	15 (14%)	86 (15%)	
$75,000 or more	56 (41%)	45 (41%)	288 (51%)	
Unknown	28 (20%)	9 (8.1%)	42 (7.4%)	
Source for finding out about study, No. (%)				< .001
Doctor or clinician[k]	70 (51%)	94 (85%)	416 (73%)	
News, Internet, or social media[l]	19 (14%)	3 (2.7%)	28 (4.9%)	
Friend or support group member[m]	11 (8.0%)	3 (2.7%)	22 (3.9%)	
Other[n]	17 (12%)	1 (0.9%)	21 (3.7%)	
Unknown	21 (15%)	10 (9.0%)	80 (14%)	
Helped decide to participate in study, No. (%)				< .001
Doctor or clinician[o]	42 (30%)	66 (59%)	321 (57%)	
Spouse/significant other[p]	33 (24%)	25 (23%)	89 (16%)	
Other[q]	4 (2.9%)	3 (2.7%)	11 (1.9%)	
Unknown	59 (43%)	17 (15%)	146 (26%)	

[a]Includes Pacific Islander.

[b]Includes two or more race categories from the list "Asian, Asian American," "Black, African American," "Native American, American Indian or Alaskan Native," "Pacific Islander," "White, Caucasian," or "other."

[c]Includes race category "Unknown" or two or more race categories one of which was "do not know/not sure" or "Unknown."

[d]Includes "Cuban," "Mexican, Mexican American, Chicano," "Puerto Rican," "Another Hispanic, Latino/a, or Spanish origin," or "Not sure."

[e]Includes "Unmarried couple/domestic partnership" or two or more marital status categories from the list "Married, " "Divorced, " "Widowed, " "Never married," "Separated, "or "Unmarried couple/domestic partnership."

[f]Includes "Employed for wages" or "Self-employed" or both with or without the employment status category "A student."

[g]Includes "Retired" with or without additional employment status categories from the list "Employed for wages," "Out of work for < 1 year," "Out of work for 1 year or more," "Self-employed," or "Unable to work."

[h]Includes the combination "Unable to work" and "Self-employed."

[i]Includes "Out of work for 1 year or more," "A homemaker," or "A student" with or without additional employment status categories from the list "Self-employed" or "Unable to work."

[j]Includes "Out of work for < 1 year" with or without additional employment status categories from the list "Self-employed" or "Unable to work."

[k]Includes "From my doctor or clinician" with or without additional sources from the list "From a friend or support group member," "From a news story, Internet search or social media," "From information sent by mail," or "Other."

[l]Includes "From a news story or social media" with or without the additional source "Other."

[m]Includes "From a friend or support group member."

[n]Includes "From information sent by mail."

[o]Includes "Doctor/nurse/health care provider" with or without additional persons "Spouse/significant other," "Other family member," "Friend/nonrelative," or "Do not know/not sure."

[p]Includes "Spouse/significant other" with or without additional persons "Other family member" or "Friend/nonrelative."

[q]Includes "Friend/nonrelative" or "Other family member."

increase education and outreach to more diverse members of our community to increase awareness of genetic testing and the study. An important limitation is that we are not able to accurately distinguish between participants who changed their mind after consenting and decided not to proceed from those who wished to proceed but ran into technical difficulties and did not reach out for assistance. We acknowledge this will be important to understand further, as the approaches to address each may be different.

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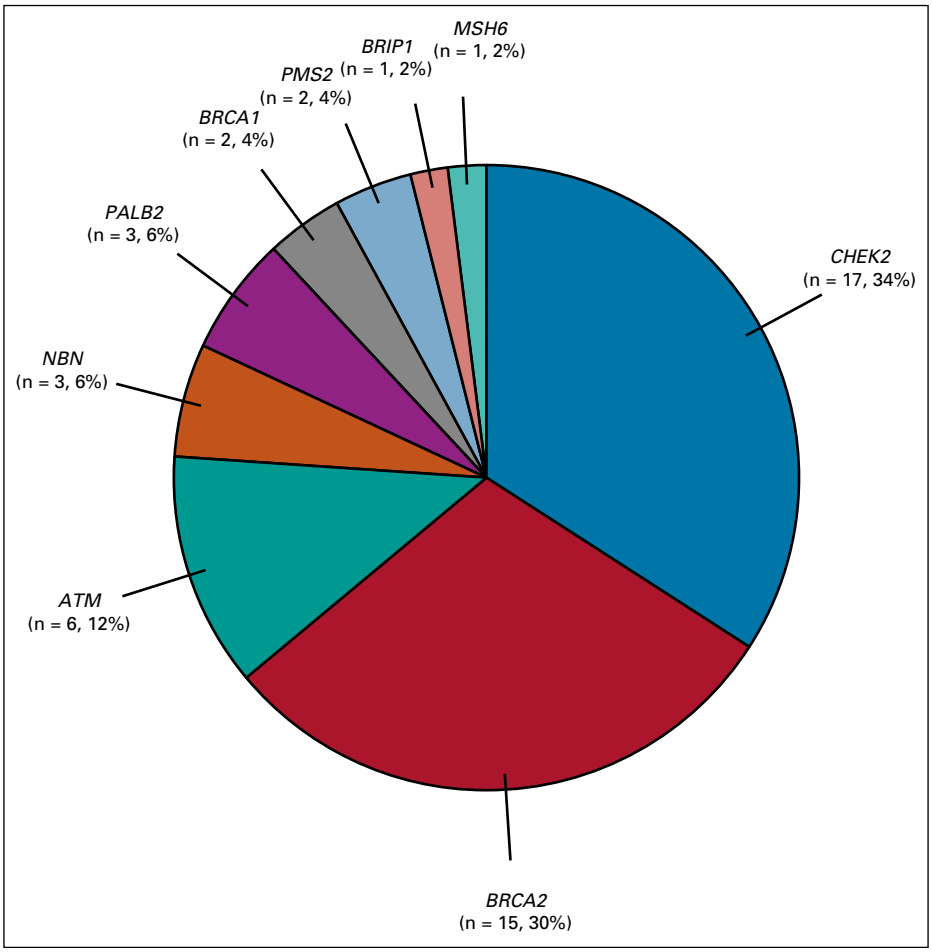

FIG 2. Distribution of genes associated with prostate cancer with pathogenic and likely pathogenic variants. Fifty L/PV found among 48 unique patients who underwent genetic testing: One participant found to have L/PV in *ATM* and *PMS2*, and one participant found to have L/PV in *BRCA1* and *CHEK2*. L/PV, pathogenic and likely pathogenic variants.

The proportion of men with mPC and pathogenic germline mutations in GENTleMEN reported here (approximately 9%) is similar but slightly lower than reported in previous studies (approximately 12%-17%).[18-20] This could potentially be due to differences in patient populations, for example, men with the most striking family histories of cancer may be more likely to be referred to clinical genetics and genetic counseling for testing and/or have undergone cascade genetic testing. Thus, participants of the GENTleMEN study may represent individuals without the most striking family cancer histories. On the other hand, some family cancer history may be a motivating factor for participation and follow through. Preliminary analysis did not suggest family history of prostate cancer to be associated with test completion, but further analysis is planned with study completion.

Although our findings demonstrate the feasibility of an Internet-based approach, they also reveal limitations. Completing study surveys and activating testing kit promotional codes represented barriers for participants with significant dropoff at each of these steps. Following these interim findings, the recruitment strategies and workflow are being altered (Fig 3). As discussed above, the GENTleMEN study was not designed to systematically assess reasons participants did not ultimately follow through, but we acknowledge these reasons are important to understand, especially as NCCN guidelines now recommend offering genetic testing, and we anticipate that genetics care access and insurance coverage will improve. For example, other studies have been reported and/or are also investigating novel education and care delivery methods, including mainstreaming[21] video education in the PROGEN study (NCT03328091),[22] and web-based education in the TARGET study (NCT04447703). These models will help extend and triage genetic counselor services to highest need/impact care points, such as for individuals with pathogenic or likely pathogenic variant, with VUS, and/or in cascade genetic testing. The results from GENTleMEN suggest that a fraction of men with mPC are likely to be able to successfully engage in self-directed, Internet-based genetic testing, similar men in the video-education arm of PROGEN and in the web-based education arm of TARGET.

In 2022, germline genetic testing is now standard of care for many individuals with prostate cancer, so insurance coverage may be less of a barrier than in the past. However, there remains the need to minimize disparities observed in the study to date. We observed similar dropoff across all non-White race and ethnicity groups (Asian and Asian

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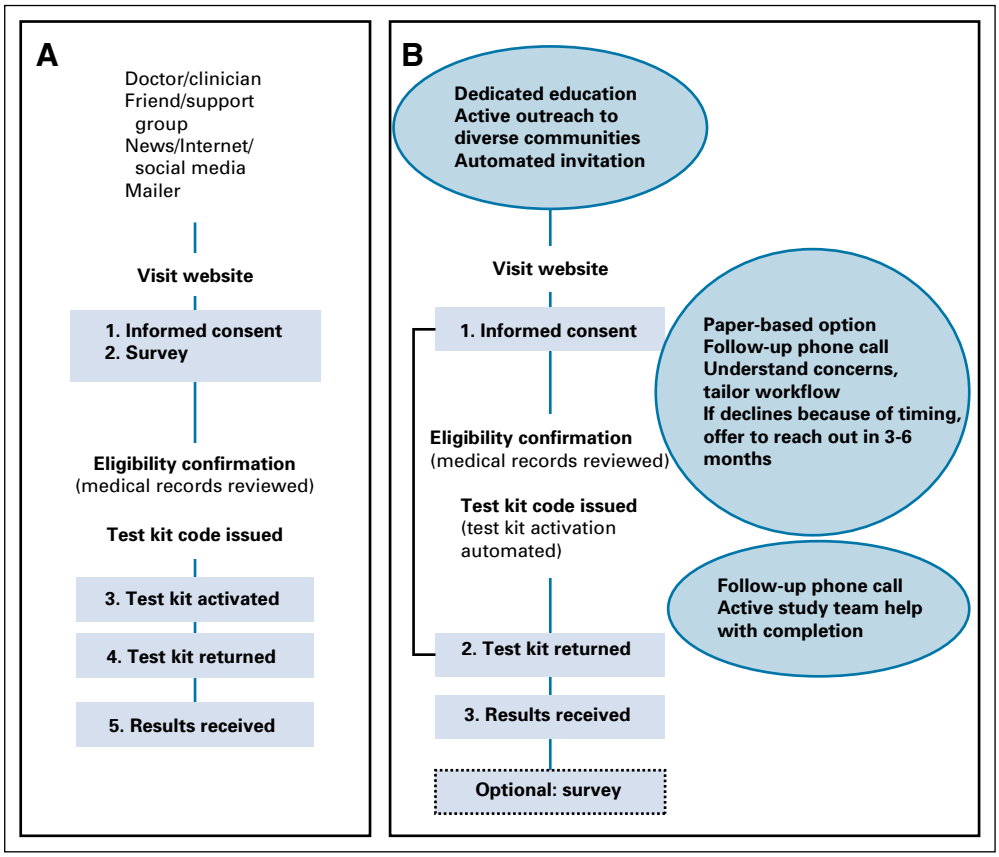

FIG 3. Steps to improve completion, inclusiveness, and diversity. (A) Initial study flow (left) and (B) proposed modifications (right). Numbered boxes are required steps for participants. Compared with (A), (B) illustrates reduced participant-required steps from five to three and changes the order of survey instruments. Circles contain additional proposed modifications to support broadened recruitment and more active participant support.

American, African American and Black, Hispanic, Latino and Spanish origin, and mixed or other participants). This has been previously reported and warrants urgent attention.[23,24] Development of tailored and culturally sensitive and tailored genetic counseling education materials and resources can be codeveloped with appropriate community leader partnerships.

To address some of these issues, we are planning specific modifications to the study flow with dedicated education, active outreach, and engagement within communities that are underrepresented and also plan to minimize or remove study steps that are burdensome to participants (Fig 3). Other steps such as automating and systematizing invitation within a clinic or health care system may also be effective. We plan to offer paper-based survey options, for those more comfortable answering in this format. In addition, more dedicated clinical support resources, through follow-up phone calls, web and in-person options for help (with patient preference and ease of scheduling in mind).

Additional clinical and research efforts are needed to understand and address imbalances that may further exacerbate health disparities. In parallel, we are investigating potential differences observed with recruitment of patients to a germline testing study using cancer registry ascertainment of men with mPC (NCT04254133).[25] In addition, further integration with care navigation where possible will also help reduce disparities and promote equitable access to this important aspect of care. This and other studies will be needed to determine whether a patient-driven, Internet-based approach can be further optimized to be broadly feasible and applicable to all patients or whether they are mainly improving convenience to those most likely to be offered and most likely to be enthusiastic in participating in genetic testing. On a patient level, continued attention and clinical partnership with the oncology and genetics teams, dedicated efforts to ensure patient-tailored education, repeated opportunities to engage, and hybrid workflows with additional education, support, and reminders will likely be needed and may require different approaches for different patient needs. From a systems level, multifaceted approaches with collaborative stakeholder involvement, combined with ongoing research and re-evaluation, will be needed to further optimize genetics care access and delivery for all men with prostate cancer meeting criteria for germline genetic testing.

In conclusion, Internet-based, patient-driven delivery of genetic testing is feasible for some patients, and the proportion of pathogenic or likely pathogenic variant in DNA repair genes associated with prostate cancer is consistent with expected rates. Although our approach addresses some barriers to meeting the needs of expanded genetic testing guidelines (access), remaining barriers exist and need further study and optimization to ensure all men with mPC have access to genetic testing and counseling services.

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SUPPORT

Supported by awards from the Institute for Prostate Cancer Research, Pacific Northwest Prostate Cancer SPORE P50 CA097186, Prostate Cancer Foundation, NIH/NCI Cancer Center Support Grant P30 CA015704, T32CA009515, R50 CA221836, DOD PCRP grants: W81XWH-18-1-0354, W81XWH-21-1-0264, and Institute for Translational Health UL1 TR002319.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Research Funding: Pfizer (Inst), Clovis Oncology (Inst), Bavarian Nordic (Inst), Bristol Myers Squibb (Inst), Debiopharm Group (Inst), Merck (Inst), QED Therapeutics (Inst), GlaxoSmithKline (Inst), Mirati Therapeutics (Inst), EMD Serono (Inst), G1 Therapeutics (Inst), Gilead Sciences (Inst)

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No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

We would like to acknowledge our coauthor, D.B., PhD, who passed before the publication of this work. "Deb" was a highly accomplished researcher and mentor to many. Her career's contributions were focused on biobehavioral determinants of diverse forms of health care delivery and health promotion, including cancer prevention and genomic medicine. Her input was foundational to this project, and its impact represents an important part of her enduring legacy.

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APPENDIX

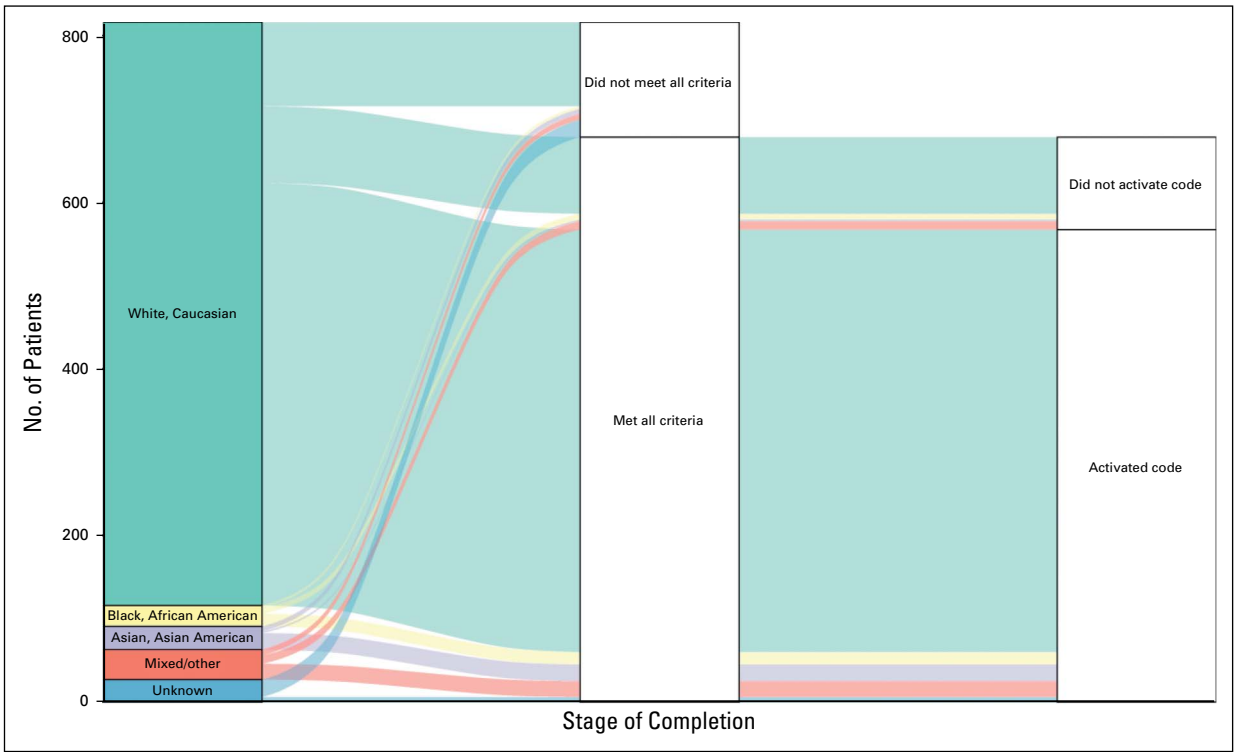

FIG A1. Alluvial plot of stages of completing genetic testing by race category. "Asian, Asian American" includes Pacific Islander; "Mixed/Other" includes two or more race categories from the list "Asian, Asian American," "Black, African American," "Native American, American Indian or Alaskan Native," "Pacific Islander," "White, Caucasian," or "Other"; "Unknown" includes race category "Unknown" or two or more race categories one of which was do not know/not sure or "Unknown."

TABLE A1. Cross-Tabulation of the Number of P/LPV Associated With Prostate Cancer and the Number of VUS Among Participants Who Completed Testing

	No. of VUS		
No. of P/LPV	**0**	**≥ 1**	**Total**
0	411	92	503[a]
≥ 1	38	10	48
Total	449	102	551

Abbreviations: P/LPV, pathogenic or likely pathogenic variant; VUS, variants of unknown significance.

[a]Includes 10 participants with P/LPV in genes not specifically associated with prostate cancer.

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TABLE A2. Pathogenic or Likely Pathogenic Variant(s) in Genes Tested, by Participant

Participant	Gene[a]	Specific Variant	Second Gene (if identified)[a]	Specific Variant
239_2	***ATM***	c.2921+1G>A		
123_2	***ATM***	c.2938del (pTyr980Ilefs*12)	***PMS2***	c.823C>T (p.Gln275*)
352_2	***ATM***	c.3648T>G (p.Tyr1216*)		
30_2	***ATM***	c.4111del (p.Asp1371Ilefs*15)		
49_2	***ATM***	c.5228C>T	*MUTYH*	c.933+3A>G
488_2	***ATM***	c.6403_6404del (p.Leu2135Lysfs*10)		
312_2	***BRCA1***	c.5109T>G (p.Tyr1703*)		
817_2	***BRCA1***	c.68_69del (p.Glu23Valfs*17)	***CHEK2***	c.1100del (p.Thr367Metfs*15)
1083_2	***BRCA2***	c.1273del (p.Gly425Lysfs*5)		
322_2	***BRCA2***	c.1389_1390delAG (p.Val464Glyfs*3)		
459_2	***BRCA2***	c.2845del (p.Tyr949Metfs*11)		
493_2	***BRCA2***	c.2957dup (p.Asn986Lysfs*2)		
78_2	***BRCA2***	c.3103>T (p.Glu1035*)		
18_1	***BRCA2***	c.3244A>T (p.Lys1082*)		
1456_2	***BRCA2***	c.3847_3848del (p.Val1283Lysfs*2)		
614_2	***BRCA2***	c.5158dup (p.Ser1720Phefs*7)		
217_2	***BRCA2***	c.5217_5223delTTTAAGT (p.Tyr1739*)		
552_2	***BRCA2***	c.5946del (p.Ser1982Argfs*22)		
394_2	***BRCA2***	c.5992C>T (p.Gly1998*)		
482_2	***BRCA2***	c.8575C>T (p.Gln2859*)		
1337_2	***BRCA2***	c.9154C>T (p.Arg3052Trp)		
357_2	***BRCA2***	c.9435_9436delGT (p.Ser3147Cysfs*2)		
988_2	***BRCA2***	c.9666delT (p.Cys3222Trpfs*27)		
1034_2	***BRIP1***	c.2492_2492+5del		
277_2	***CHEK2***	c.1100delC (p.Thr367Metfs*15)		
321_2	***CHEK2***	c.1100delC (p.Thr367Metfs*15)		
689_2	***CHEK2***	c.1100delC (p.Thr367Metfs*15)		
1356_2	***CHEK2***	c.1100delC (p.Thr367Metfs*15)		
448_2	***CHEK2***	c.1100delC (p.Thr367Metfs*15)	*MUTYH*	c.1187G>A (p.Gly396Asp)
1363_2	***CHEK2***	c.1187G>A (p.Gly396Asp)	*MUTYH*	c.190G>A (p.Glu64Lys)
88_2	***CHEK2***	c.1283C>T (p.Ser428Phe)		
344_2	***CHEK2***	c.349A>G (p.Arg117Gly)		
74_2	***CHEK2***	c.470T>C (p.Ile157Thr)		
191_2	***CHEK2***	c.470T>C (p.Ile157Thr)		
438_2	***CHEK2***	c.470T>C (p.Ile157Thr)		
474_2	***CHEK2***	c.470T>C (p.Ile157Thr)		
955_2	***CHEK2***	c.470T>C (p.Ile157Thr)		
1126_2	***CHEK2***	c.470T>C (p.Ile157Thr)		
1161_2	***CHEK2***	c.470T>C (p.Ile157Thr)		
1427_2	***CHEK2***	c.470T>C (p.Ile157Thr)		
190_2	***MSH6***	c.3804dup (p.Cys1269Metfs*6)		
278_2	***NBN***	c.657_661delACAAA (p.Lys219Asnfs*16)		
175_2	***NBN***	c.698_701delAACA (p.Lys233Serfs*5)		
469_2	***NBN***	c.698_701delAACA (p.Lys233Serfs*5)		

(Continued on following page)

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TABLE A2. Pathogenic or Likely Pathogenic Variant(s) in Genes Tested, by Participant (Continued)

Participant	Gene[a]	Specific Variant	Second Gene (if identified)[a]	Specific Variant
1290_2	***PALB2***	c.1546delA (p.Arg516fs*45)		
1388_2	***PALB2***	c.3256C>T (p.Arg1086*)		
129_2	***PALB2***	c.697delG (p.Val233Leufs*5)		
918_2	***PMS2***	c.137G>T (p.Ser46Ile)		
296_2	*APC*	c.3920T>A (p.Ile1307Lys)		
916_2	*APC*	c.3920T>A (p.Ile1307Lys)		
1164_2	*APC*	c.3920T>A (p.Ile1307Lys)		
938_2	*CDKN2A*	c.334C>G (p.Arg112Gly)		
903_2	*MITF*	c.952G>A (p.Glu318Lys)		
185_2	*MUTYH*	c.1187G>A (p.Gly396Asp)		
420_2	*MUTYH*	c.1187G>A (p.Gly396Asp)		
1003_2	*MUTYH*	c.1227_1228dup (p.Glu410Glyfs*43)		
873_2	*MUTYH*	c.536A>G (p.Tyr179Cys)		
958_2	*MUTYH*	c.536A>G (p.Tyr179Cys)		

Abbreviation: mPC, metastatic prostate cancer.

[a]Bolded genes are those previously reported in association with mPC (Pritchard et al[10]).

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ARX517, an Anti-Prostate-Specific Membrane Antigen (PSMA) Antibody-Drug Conjugate (ADC), Demonstrates Promising Safety and Efficacy in Heavily Pre-Treated Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC)

1804P

John Shen[1], Russell Pachynski[2], Luke Nordquist[3], Nabil Adra[4], Mehmet Asim Bilen[5], Rahul Aggarwal[6], Zachery Reichert[7], Michael Schweizer[8], Amir Iravani[9], Thuy Lee[10], Quan Hong[10], Colin Hessel[10], Shawn Zhang[10], Sandra Aung[10], Scott Tagawa[11]

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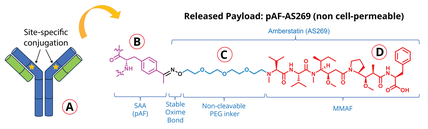
INTRODUCTION

- Previous PSMA-targeted ADCs demonstrated early clinical efficacy, but drug development was discontinued due to intolerable toxicities, resulting from premature release and off-target delivery of the cytotoxic payload.[1-5]
- ARX517 is a novel anti-PSMA ADC designed to overcome the stability and resulting toxicity challenges of other PSMA-targeted ADCs (**Figure 1**). Key differentiating features enabling increased stability include:
  - Unique oxime conjugation chemistry using a genetically encoded and biosynthetically incorporated synthetic amino acid (SAA)
  - Non-cleavable PEG linker
  - Non-cell permeable payload
- APEX-01 is a Phase 1/2 first-in-human trial evaluating ARX517 in patients with mCRPC resistant or refractory to prior therapies (NCT04662580). Safety and efficacy from the initial dose escalation and expansion are reported.

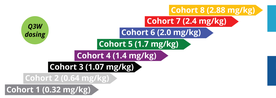
Figure 1. ARX517 structure



ARX517 is comprised of 4 key elements: (**A**) a humanized J591 anti-PSMA antibody; (**B**) a payload covalently conjugated to a SAA, para-acetyl phenylalanine (pAF), genetically encoded and biosynthetically incorporated at amino acid position 114 on the heavy chain of the anti-PSMA antibody; (**C**) a non-cleavable PEG linker; and (**D**) a non cell-permeable cytotoxic payload of a microtubule targeting antineoplastic agent (AS269).

STUDY DESIGN

Figure 2. Phase 1 study design



Phase 1a Dose Escalation, i3+3 Design

Phase 1b Dose Expansion, 20-30 patients per cohort

Eligibility

Must have had at least two FDA-approved therapies for mCRPC with at least one being a 2nd generation ARPI (abiraterone, enzalutamide, darolutamide, apalutamide)

- Documented progression by one or more of the following
  - PD by RECIST v1.1
  - PSA progression
  - Radiographic progression in bone

Objectives

- To determine safety and tolerability
- To determine MTD and/or establish recommended phase 2 dose regimen(s)

Table 1. Demographics

	Total (N=65)
Race, n (%)	
Asian	4 (6)
Black or African American	4 (6)
White	53 (82)
Other	4 (6)
Age (years)	
Median	68.0
Min, Max	50, 100
Baseline Weight (kg)	
Median	86.7
Min, Max	54, 133
Prior Lines of Cancer Therapy	
Median	4.0
Min, Max	1, 13
Prior Taxane, n (%)	
Y	43 (66)
N	22 (34)
Prior IO agent, n (%)	
Y	30 (46)
N	35 (54)
Prior PSMA targeted RLT, n (%)	
Y	11 (17)
N	54 (83)
Number of Prior ARPI treatments	
Median	2.0
Min, Max	1, 5
Prior 2nd generation ARPI, n (%))	
Abiraterone	49 (75)
Enzalutamide	45 (69)
Both Abiraterone and Enzalutamide	31 (48)
Lesion Site, n (%)	
Liver or lung	12 (19)
Lymph node	30 (46)
Bone	52 (80)
Any Measurable Lesions per RECIST, n (%)	
Y	22 (34)
N	43 (66)
Baseline ECOG Performance Status, n (%)	
0	24 (37)
1	38 (59)
2	2 (3)
Missing	1 (2)
Baseline PSA (ug/L)	
Median	47.0
Min, Max	1, 3845
Baseline Alkaline Phosphatase (U/L)	
Median	108.0
Min, Max	30, 848
Baseline LDH (U/L)	
Median	200.0
Min, Max	93, 1492

Table 2. Treatment-Related Safety Summary

	Cohort 1 0.32 mg/kg (n=1)	Cohort 2 0.64 mg/kg (n=3)	Cohort 3 1.07 mg/kg (n=3)	Cohort 4 1.4 mg/kg (n=21)	Cohort 5 1.7 mg/kg (n=5)	Cohort 6 2.0 mg/kg (n=20)	Cohort 7 2.4 mg/kg (n=6)	Cohort 8 2.88 mg/kg (n=6)	All Cohorts (N=65)
n (%)									
All AEs	0	2 (67)	3 (100)	12 (57)	5 (100)	15 (75)	6 (100)	5 (83)	48 (74)
Grade 3 AEs	0	0	0	1 (5)	1 (20)	2 (10)	1 (17)	1 (17)	6 (9)
Grade 4 AEs	0	0	0	0	0	0	0	0	0
SAEs	0	0	0	0	0	0	0	0	0
AEs leading to discontinuation	0	1* (33)	0	0	0	1† (5)	0	0	2 (3)
Deaths (grade 5 AEs)	0	0	0	0	0	0	0	0	0

*Patient at dose 0.64 mg/kg experienced grade 1 platelet count decrease 22 days post C1D1 with no clinical symptoms.
†Patient at dose 2.0 mg/kg experienced grade 2 decreased appetite and dysphagia 7 days post C2D1.

Table 3. Grade 3 Treatment-Related AEs

	Cohort 1 0.32 mg/kg (n=1)	Cohort 2 0.64 mg/kg (n=3)	Cohort 3 1.07 mg/kg (n=3)	Cohort 4 1.4 mg/kg (n=21)	Cohort 5 1.7 mg/kg (n=5)	Cohort 6 2.0 mg/kg (n=20)	Cohort 7 2.4 mg/kg (n=6)	Cohort 8 2.88 mg/kg (n=6)	All Cohorts (N=65)
n (%)									
Lymphocyte count decreased	0	0	0	0	1 (20)	1 (5)	1 (17)	0	3 (5)
Platelet count decreased	0	0	0	0	0	1 (5)	0	1 (17)	2 (3)
Left ventricular dysfunction	0	0	0	1 (5)	0	0	0	0	1 (2)

Note: 6 patients reported Gr3 TRAEs, 3 experienced lymphocyte count decrease and 2 experienced transient platelet count decrease that were not clinically significant. At 1.4 mg/kg dose one patient reported transient, asymptomatic left ventricular dysfunction, patient recovered after IV infusion, this event was deemed not serious.

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Abbreviations: AE, adverse event; **ARPI,** androgen receptor pathway inhibitor; **ctDNA**, circulating tumor DNA; **C1D1,** cycle 1 day 1; **DCR,** disease control rate; **DLT,** dose limiting toxicity; **Gr3,** Grade 3; **IO,** immunotherapy; **LDH,** lactate dehydrogenase; **MTD,** maximum tolerated dose; **ORR,** objective response rate; **PD,** progressive disease; **PEG**, polyethylene glycol; **PSA,** prostate-specific antigen; **PSMA,** prostate-specific membrane antigen; **PSMA-Targeted RLT,** PSMA-targeted radioligand therapy; **SAA,** synthetic amino acid; **SAE,** serious adverse event; **TRAE,** treatment-related adverse event.

The APEX-01 study is sponsored by Ambrx, Inc.

RESULTS

Table 4. Frequent Grade 1/2 Treatment-Related Adverse Events in ≥10% of Patients

	Cohort 1 0.32 mg/kg (n=1)	Cohort 2 0.64 mg/kg (n=3)	Cohort 3 1.07 mg/kg (n=3)	Cohort 4 1.4 mg/kg (n=21)	Cohort 5 1.7 mg/kg (n=5)	Cohort 6 2.0 mg/kg (n=20)	Cohort 7 2.4 mg/kg (n=6)	Cohort 8 2.88 mg/kg (n=6)	All Cohorts (N=65)
Patients with any Grade 1/2 AE	0	2 (67)	3 (100)	12 (57)	5 (100)	15 (75)	6 (100)	5 (83)	48 (74)
Dry mouth	0	0	1 (33)	3 (14)	3 (60)	6 (30)	2 (33)	3 (50)	18 (28)
Dry eye	0	0	1 (33)	1 (5)	0	6 (30)	4 (67)	2 (33)	14 (22)
Fatigue	0	0	3 (100)	1 (5)	1 (20)	5 (25)	2 (33)	1 (17)	13 (20)
Diarrhoea	0	1 (33)	0	3 (14)	1 (20)	3 (15)	2 (33)	0	10 (15)
Decreased appetite	0	0	1 (33)	2 (10)	1 (20.0)	2 (10)	3 (50.0)	0	9 (14)
Nausea	0	1 (33)	1 (33)	0	0	3 (15)	4 (67)	0	9 (14)
Dysgeusia	0	0	0	1 (5)	1 (20)	3 (15)	3 (50)	0	8 (12)
Vomiting	0	1 (33)	1 (33)	0	0	1 (5)	4 (67)	1 (17)	8 (12)
Aspartate amino-transferase increased	0	0	0	0	1 (20)	4 (20)	1 (17)	1 (17)	7 (11)
Platelet count decreased	0	1 (33)	1 (33)	0	0	1 (5)	0	2 (33)	5 (8)

Figure 3. Deep PSA reductions with increasing ARX517 dose

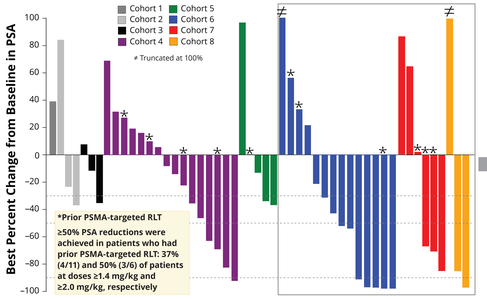
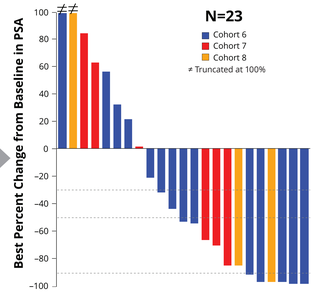


Figure 4. 52% (12/23) of patients experienced a ≥50% PSA reduction at putative therapeutic doses (≥2.0 mg kg)

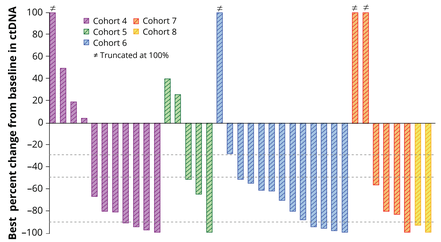


PSA waterfall includes patients with at least two on-treatment PSA assessments or discontinued before the second assessment.
Prior to reaching MTD, two dose cohorts (4 and 6) were expanded based on three criteria 1) PSA decline of ≥50%
2) no treatment-related SAEs 3) target lesion reduction or RECIST v1.1 response.

Table 5. Greater frequency and depth of PSA response at putative therapeutic doses (≥2.0 mg kg)

	C1–3 n=7	C4 n=16	C5 n=5	C6 n=14	C7 n=6	C8 n=3	C6–8 n=23
≥30% PSA	29%	38%	40%	64%	50%	67%	61%
≥50% PSA	0	25%	0	50%	50%	67%	52%
≥90% PSA	0	6%	0	36%	0	33%	26%

Figure 5. Circulating tumor DNA (ctDNA) decline correlates with PSA reduction



On treatment changes in ctDNA have been shown to predict time to progression and survival.[6,7] Serial plasma samples were collected at baseline, C3D1, C4D1 and EOT, best percent change from baseline is shown. ctDNA was measured using GuardantINFINITY test (Guardant Health) with a specificity of 96.9%, a sensitivity of 91.3% and a reported lower limit of detection 0.06%. Samples were processed after passing multiple quality control measurements encompassing DNA yield, GC bias, methylation bias, diversity, and contamination checks. ctDNA changes compared with its baseline level were measured based on aggregated tumor-specific methylation signal scores.

Figure 6. Duration on treatment (Cohorts 4-8)

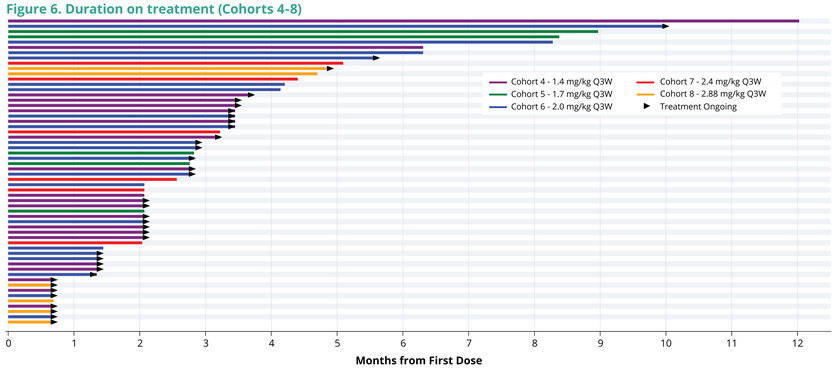
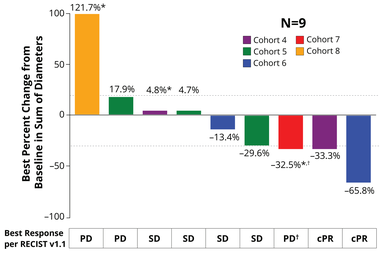


Figure 7. RECIST v1.1 Target lesion reduction was observed in 56% (5/9) of patients (Cohorts 4–8)



Evaluable population includes all patients with measurable target lesion(s) at baseline per RECIST v1.1 who had at least two post baseline tumor assessments or progressed or discontinued treatment prior to the 2nd assessment.
cPR, confirmed partial response per RECIST v1.1
*Patients with lung/liver target lesions
†Patient had PR in target lesions; 1 liver lesion reduced in size from 38 to 14mm and 1 lung lesion from 18 to 9mm, but growth in non-target lesion resulted in PD by RECIST v1.1.

SUMMARY

- **ARX517 was well-tolerated at all doses tested up to 2.88 mg/kg every 3 weeks**
  - No treatment-related SAEs
  - No DLTs
- **At putative therapeutic doses (≥2.0 mg kg)**
  - 52% (12/23) of patients had a ≥50% PSA reduction
  - 86% (18/21) of patients had a reduction in ctDNA
- **Target lesion reduction achieved in 56% (5/9) of patients; 2 had confirmed RECIST v1.1 responses**
- **PSA responses were observed in patients who had prior PSMA-targeted radioligand therapy**

CONCLUSIONS

Without PSMA imaging selection, ARX517 monotherapy achieved favorable safety and demonstrated early efficacy, with deep PSA and ctDNA reductions and confirmed RECIST v1.1 tumor response in patients with mCRPC who progressed on multiple FDA-approved treatments.

Acknowledgements

The authors want to thank all those who participated in this study: The study patients and their families, the investigators, site study coordinators and the sponsor team.

Disclosures

Dr. Shen is an investigator on the APEX-01 study and his institution (UCLA) receives associated research funding.

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On-going and Next Steps

- Expansion of Cohort 8
- Escalate into next higher dose, Cohort 9

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Journal for ImmunoTherapy of Cancer

Re-sensitization to pembrolizumab following PSMA-CD3 T-cell redirection therapy with JNJ-081 in a patient with mismatch repair-deficient metastatic castration-resistant prostate cancer: a case report

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To cite: Reed-Perino DE, Lai M, Yu EY, *et al*. Re-sensitization to pembrolizumab following PSMA-CD3 T-cell redirection therapy with JNJ-081 in a patient with mismatch repair-deficient metastatic castration-resistant prostate cancer: a case report. *Journal for ImmunoTherapy of Cancer* 2023;**11**:e006794. doi:10.1136/jitc-2023-006794

Accepted 03 May 2023

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ABSTRACT

While checkpoint inhibitor therapy has revolutionized the treatment landscape of some solid tumors, it has shown limited efficacy in metastatic castration-resistant prostate cancers (mCRPC). A small (~3–5%) but clinically distinct subset of mCRPC tumors have a DNA mismatch repair deficiency (dMMR) and develop a hypermutation phenotype with elevated tumor mutational burden and high microsatellite instability (MSI-H). Retrospective analyses have shown dMMR/MSI-H status to be a predictive biomarker for response to pembrolizumab in prostate tumors. Here, in this report, we present a case of a patient with mCRPC harboring a somatic dMMR who had progressed on pembrolizumab after an initial response. He enrolled on a clinical trial with JNJ-081, a prostate-specific membrane antigen-CD3 bispecific T-cell engager antibody and experienced a partial response with course complicated by cytokine release syndrome. On progression, he was reinitiated on pembrolizumab and experienced an exceptional second response, with his prostate-specific antigen falling from a high of 20.01 to undetectable after 6 weeks and remaining undetectable for >11 months. To our knowledge, this represents the first reported case of bispecific T-cell engager-mediated re-sensitization to checkpoint inhibitor therapy in any cancer.

INTRODUCTION

Checkpoint inhibitor therapies have revolutionized the treatment of some solid tumors but have not proven to be effective for most men with metastatic castration-resistant prostate cancer (mCRPC). A small (~3–5%) clinically distinct subset of these tumors harbor mutations in mismatch repair (MMR) genes (ie, *MLH1*, *MSH2*, *MSH6* or *PMS2*), which in turn leads to a high tumor mutational burden (TMB) and microsatellite instability (MSI).[1] MMR deficient (dMMR) prostate tumors have aggressive pathologic and clinical features, including high Gleason scores and the presence of de novo metastatic disease at diagnosis.[1] Prospective clinical studies in tumor type-agnostic dMMR/MSI-high (MSI-H) solid tumors showed high response rates and long progression-free survival with the anti-programmed cell death protein-1 (PD-1) monoclonal antibody pembrolizumab. Retrospective analyses showed dMMR/MSI-H status to be a useful predictive biomarker for response to pembrolizumab in the few prostate tumors included in these trials, whereas clinical response in unselected patients with mCRPC is exceedingly low (3–5%).[1]

Secondary resistance mechanisms have hindered realizing the full potential of immunotherapy in mCRPC. Given that a large proportion of tumors lack T-cell infiltration, so called 'cold tumors', significant research has been dedicated to triggering T-cell infiltration into the tumor, creating a 'hot tumor'. One avenue has been through bispecific antibodies comprised of two single-chain variable fragments linked together, one recognizing CD3 on T-cells and the other binding a tumor-associated antigen of interest, stimulating cytolytic T-cell activity independent of T-cell receptor-major histocompatibility complex signaling. Bispecific T-cell engager antibodies have been successful in the treatment of hematologic malignancies. Blinatumomab, a CD19-CD3 bispecific T-cell engager antibody, is now a component of standard-of-care treatment for acute lymphoblastic leukemia. Tebentafusp, a bp100-CD3 bispecific T-cell engager, was recently Food and Drug Administration-approved for the treatment of metastatic uveal melanoma.

We participated in a Phase 1 clinical trial of JNJ-081, a bispecific T-cell engager antibody

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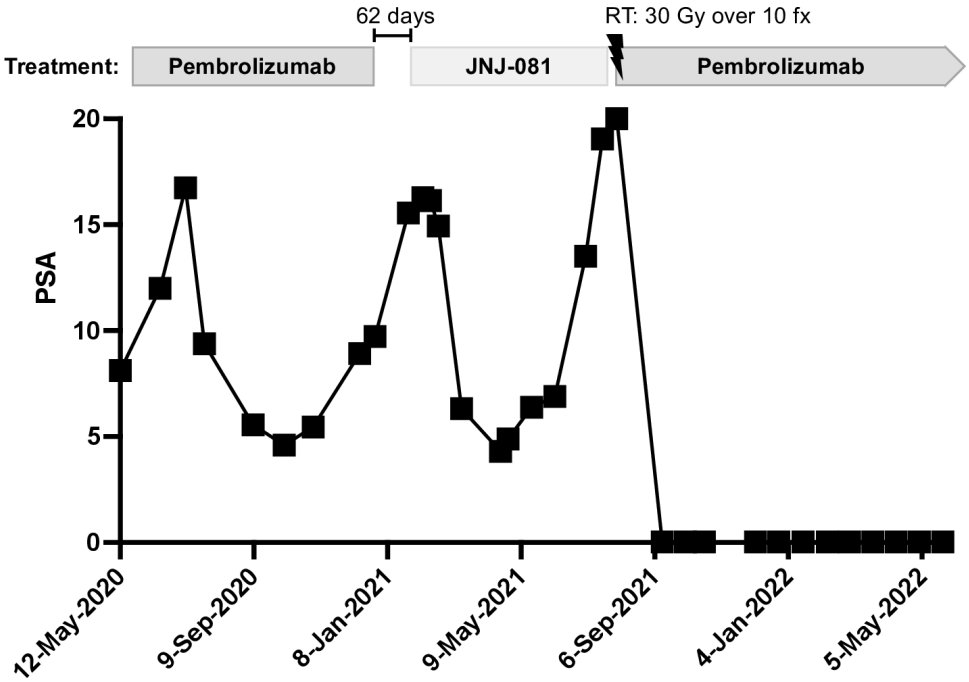

Figure 1 PSA trend through first pembrolizumab course, the JNJ-081 bispecific antibody clinical trial, and second course of pembrolizumab. Radiation treatment is denoted by lightning bolt. PSA levels below the limit of detection (<0.03) for our laboratory are plotted as 0.029. PSA, prostate-specific antigen; RT, radiation treatment.

recognizing CD3 and prostate-specific membrane antigen (PSMA), expressed by the majority of mCRPC.[2] Although transient decreases in prostate-specific antigen (PSA) were seen, most patients treated developed anti-drug antibodies resulting in loss of exposure to the drug and limiting its therapeutic potential. We present the case of a patient with dMMR/MSI-H mCRPC who developed secondary resistance to pembrolizumab and then proceeded to receive JNJ-081. On progression on JNJ-081, he was rechallenged with pembrolizumab and subsequently experienced an ongoing durable response.

CASE

A man >70 years old was diagnosed with Gleason 4+5=9 localized prostate adenocarcinoma in 2013 with a PSA of 2.39 and underwent robotic-assisted radical prostatectomy. He experienced early biochemical recurrence before 12 months and completed salvage radiation therapy without PSA response and 6 months later he began androgen deprivation therapy with leuprolide. His PSA continued to increase, consistent with castration-resistant disease, and enzalutamide was added 9 months later resulting in a durable response with an undetectable PSA for several years. Fluciclovine PET 3 years later for a rising PSA revealed progressive bone and lymph node metastases. He was treated with sipuleucel-T without any PSA response followed by abiraterone and prednisone resulting in a 1-month PSA response.

He underwent biopsy of a left supraclavicular lymph node with pathology consistent with metastatic prostatic adenocarcinoma. Immunohistochemical staining for DNA mismatch repair proteins revealed loss of nuclear MSH6 expression in tumor cells, suggestive of dMMR. Targeted somatic sequencing of his tumor with UW-OncoPlex revealed bi-allelic *MSH6* mutations, a TMB of 21 mutations per megabase and MSI-H. Other findings included an *AR* missense mutation in the ligand binding domain (p.T878A) reported to confer resistance to androgen receptor signaling inhibitors, *CHD1* homozygous copy loss, bi-allelic inactivation of *RB1* and a pathogenic *SPOP* mutation.[3] Germline testing was notably negative. He was initiated on pembrolizumab without baseline imaging, and his PSA declined by 73% reaching a nadir 5 months into treatment before rising again. Pembrolizumab was discontinued after 7 months and he was referred to our cancer center for a second opinion (figure 1).

Restaging scans showed new mediastinal lymph node and bone metastases compared with baseline scans 6 years prior. At that point, he enrolled on a Phase I clinical trial testing the PSMA-CD3 T-cell engager, JNJ-081, and began treatment 62 days after discontinuing pembrolizumab. He received a 10 mcg/kg subcutaneous priming dose on week 1 followed by weekly 55 mcg/kg doses thereafter. His course was complicated by Grade 1 cytokine release syndrome (CRS) following his third dose, managed with antipyretics and intravenous fluids, with a negative infectious work-up. He developed Grade 3 transaminitis, with liver function tests normalizing following a 1 week dose hold. He had an acute increase in inflammatory cytokines following study drug administration, which was marked following the first few doses coinciding with the occurrence of CRS but persisted throughout treatment and progression in the case of interferon-gamma and remained intermittently elevated in the case of tumor

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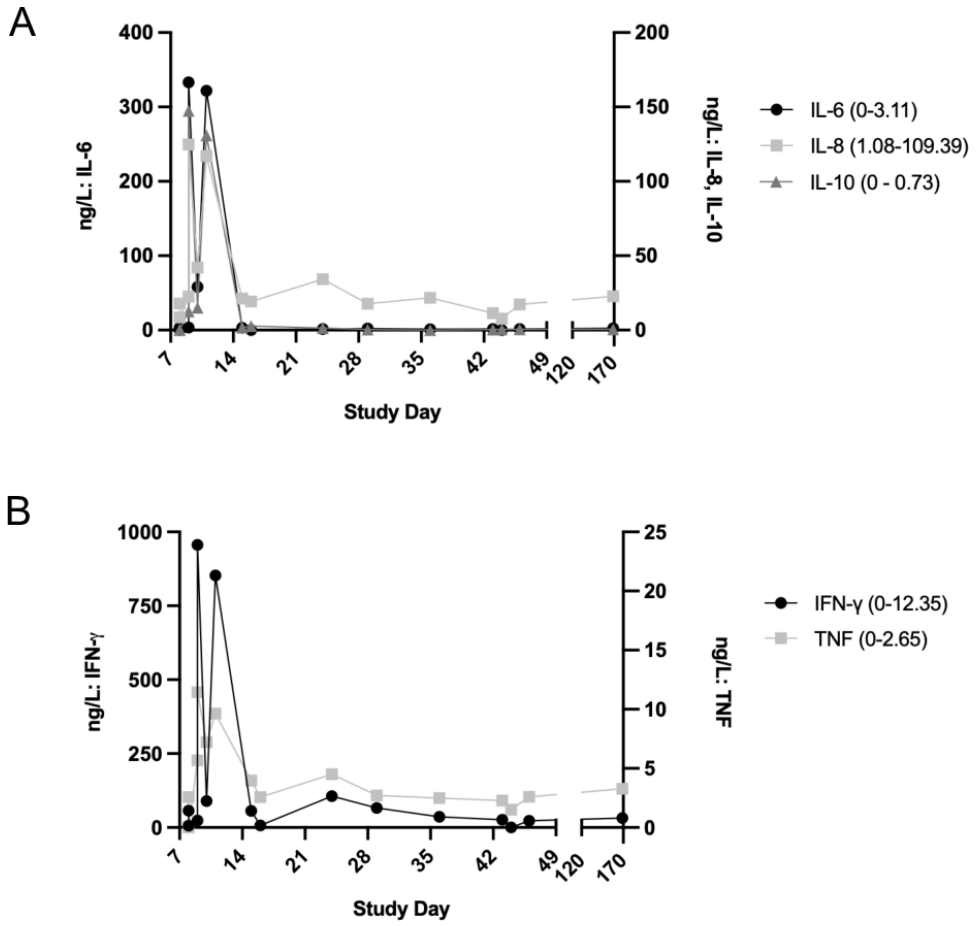

Figure 2 Inflammatory marker trends while on the JNJ-081 bispecific antibody trial. (A) Interleukin-6 (IL-6), interleukin-8 (IL-8) and interleukin-10 (IL-10) levels. (B) Interferon-gamma (IFN-γ) and tumor necrosis factor (TNF) levels. Normal reference ranges for all inflammatory markers are denoted in parentheses following label in legend.

necrosis factor (figure 2A–B). He developed evidence of anti-drug antibody formation on Day 8 of treatment. Baseline PSA of 16.14 declined to a nadir of 4.30 (73% decrease) on Day 84. Best imaging response was assessed as stable disease with a 9.3% decline in lymph node size.

He developed radiographic progression on Day 181 in thoracic and retroperitoneal lymphadenopathy, most notably in a left lower jugular/retrosternal lymph node conglomerate with narrowing of the left internal jugular vein and mass effect on the left brachiocephalic vein. He concurrently developed acute onset dysphonia with clinical concern for compression or involvement of the recurrent laryngeal nerve and was referred for palliative radiation to the affected area. Docetaxel chemotherapy was discussed, however, the patient elected to rechallenge with pembrolizumab, initiated concurrently with radiation. PSA fell from a high of 20.01 to undetectable after 6weeks. More than 11 months later, his PSA remained undetectable at <0.03 (figure 1).

DISCUSSION

Identifying strategies to overcome the resistance to immunotherapy is an active area of research. Reported re-sensitization strategies to immune checkpoint inhibitors include combinations with tyrosine kinase inhibitors and intratumoral chemotherapy.[4 5] Case reports show resistance to blinatumomab through increased expression of the immunoinhibitory protein PD-L1, and re-sensitization with the addition of pembrolizumab.[6 7] To our knowledge, this represents the first possible case of bispecific T-cell engager-mediated re-sensitization to checkpoint inhibitor therapy in any cancer.

Prostate tumors harbor multiple mechanisms of immune suppression and evasion including a hostile tumor microenvironment (TME) comprised of myeloid-derived cells secreting immunosuppressive cytokines, tumor cells overexpressing immunoinhibitory ligands and prostate cell secretion products causing T-cell dysfunction.[8 9] While checkpoint blockade is effective for many dMMR/MSI-H prostate tumors, mechanisms of immunosuppression beyond PD-1 activation likely mediate primary and secondary resistance to pembrolizumab. Bispecific T-cell engagers are resistant to some mechanisms of tumor immune suppression and evasion by bypassing the requirement for a co-stimulatory secondary signal. We hypothesize that the exceptional response to pembrolizumab observed in this case was mediated by recruitment of T-cells to the TME by the bispecific T-cell

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engager JNJ-081, which were subsequently reactivated on pembrolizumab rechallenge. Whether persistent effector T cells in the tumor were required for ongoing response to pembrolizumab rechallenge or whether the initial tumor-killing effect was robust enough to result in a persistently undetectable PSA remains unknown. This patient's partial response, CRS and elevated cytokines following treatment with JNJ-081 are consistent with immune system activation and support this theory. While it is possible the activity of JNJ-081 may have been augmented by prior pembrolizumab, we suspect that the effect of prior anti-PD1 therapy was minor given that 2.8 half-lives had elapsed when he initiated step-up dosing of this T-cell engager.[10] It is also possible that radiation therapy augmented his response to pembrolizumab; however, whether radiation is able to induce a clinically meaningful abscopal effect in prostate cancer remains unclear.

CRS is a well-documented adverse effect from T cell-engaging therapies, and it is not remarkable that our patient experienced CRS. Rather, it is remarkable that he experienced a complete biochemical response to subsequent line immunotherapy. Can a response to T-cell engaging therapies serve as one mechanism for turning a 'cold tumor' into a 'hot tumor', even after progression? Might we be able to hardwire into a tumor a response to the next line of treatment, potentially months before it's needed? Clinical trials combining concurrent administration of bispecific antibodies, including T-cell engagers, with checkpoint inhibitors in solid tumors are ongoing, but our case suggests testing sequential administration of bispecific T-cell engagers followed by immunotherapy may be effective. Sequential treatment strategies are likely to be better tolerated and associated with decreased rates of immune-related adverse effects.

Although our patient was the ideal candidate for pembrolizumab with dMMR/MSI-H and an elevated TMB, he only experienced a 7-month long partial response at first exposure. If treatment with a bispecific T-cell engager short-circuits the immunosuppressive TME in 'cold' tumors like prostate, pancreatic and breast tumors by trafficking in effector T cells, could they be a predesigned method to creating 'hot' tumors? The field of T-cell engaging therapies is growing, and one could imagine adding trispecific antibodies (or multiple bispecific antibodies) to traffic additional immune-supportive cell subsets into the TME or an antibody-drug conjugate carrying a favorable cytokine payload toward the TME. Rational combinations, based on our case, may potentially open an opportunity for further investigation of checkpoint inhibitors on progression.

Acknowledgements The authors would like to thank Sonia Goyal for her assistance with clinical research coordination.

Contributors DER, ML, EYY and MTS analyzed and interpreted data. DER, EYY and MTS contributed to writing the manuscript. DER, EYY and MTS edited the manuscript. All authors reviewed and approved the final version of the manuscript.

Funding Janssen Pharmaceuticals provided funding for the clinical trial.

Competing interests No, there are no competing interests.

Patient consent for publication Not applicable.

Ethics approval Approved by WCG IRB for the The University of Washington/Fred Hutchinson Cancer Center, IRB number is RG1004978. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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J Immunother Cancer: first published as 10.1136/jitc-2023-006794 on 23 May 2023. Downloaded from http://jitc.bmj.com/ on October 13, 2023 at University of Washington. Protected by copyright.

Original Study

Phase 1 Study of Safety and Preliminary Clinical Activity of JNJ-63898081, a PSMA and CD3 Bispecific Antibody, for Metastatic Castration-Resistant Prostate Cancer

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Abstract

PSMA expression is preserved throughout all stages of prostate cancer. In this phase 1 study of JNJ-63898081, a bispecific antibody binding to PSMA-expressing tumor cells and CD3-expressing T cells, patients with metastatic castration-resistant prostate cancer had frequent cases of cytokine release syndrome, which were manageable, and transient declines in PSA. Treatment-related deaths and radiographic responses were not observed. PSMA is a potential therapeutic target for T-cell redirection in prostate cancer.

Introduction: Cancer immunotherapies have limited efficacy in prostate cancer due to the immunosuppressive prostate microenvironment. Prostate specific membrane antigen (PSMA) expression is prevalent in prostate cancer, preserved during malignant transformation, and increases in response to anti-androgen therapies, making it a commonly targeted tumor associated antigen for prostate cancer. JNJ-63898081 (JNJ-081) is a bispecific antibody targeting PSMA-expressing tumor cells and CD3-expressing T cells, aiming to overcome immunosuppression and promoting antitumor activity. **Patients and Methods:** We conducted a phase 1 dose escalation study of JNJ-081 in patients with metastatic castration-resistance prostate cancer (mCRPC). Eligible patients included those receiving ≥1 prior line treatment with either novel androgen receptor targeted therapy or taxane for mCRPC. Safety, pharmacokinetics, and pharmacodynamics of JNJ-081, and preliminary antitumor response to treatment were evaluated. JNJ-081 was administered initially by intravenous (IV) then by subcutaneous (SC) route. **Results:** Thirty-nine patients in 10 dosing cohorts received JNJ-081 ranging from 0.3 μg/kg to 3.0 μg/kg IV and 3.0 μg/kg to 60 μg/kg SC (with step-up priming used at higher SC doses). All 39 patients experienced ≥1 treatment-emergent AE, and no treatment-related deaths were reported. Dose-limiting toxicities were observed in 4 patients. Cytokine release syndrome (CRS) was observed at higher doses with JNJ-081 IV or SC; however, CRS and infusion-related reaction (IRR) were reduced with SC dosing and step-up priming at higher doses. Treatment doses >30 μg/kg SC led to transient PSA decreases. No radiographic responses were observed. Anti-drug antibody responses were observed in 19 patients receiving JNJ-081 IV or SC. **Conclusion:** JNJ-081 dosing led to transient declines in PSA in patients with mCRPC. CRS and IRR could be partially mitigated by SC dosing, step-up priming, and a combination of both strategies. T cell redirection for prostate cancer is feasible and PSMA is a potential therapeutic target for T cell redirection in prostate cancer.

Clinical Genitourinary Cancer, Vol. 000, No.xxx, 1–10 © 2023 Elsevier Inc. All rights reserved.
Keywords: PSA, Immunotherapy, Cytokine release syndrome, Dose escalation, Immunosuppression

Abbreviations: ARSI, androgen receptor synthesis inhibitor; CRS, cytokine release syndrome; ECOG PS, European Eastern Cooperative Oncology Group Performance Status; IRR, infusion-related reaction; MABEL, minimum anticipated biological effect level; mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen; PSA, prostate-specific antigen; PCWG3, Prostate Cancer Clinical Trials Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumors.

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Submitted: Jan 4, 2023; Revised: Feb 16, 2023; Accepted: Feb 22, 2023; Epub: xxx

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https://doi.org/10.1016/j.clgc.2023.02.010

Please cite this article as: Emerson A. Lim et al, Phase 1 Study of Safety and Preliminary Clinical Activity of JNJ-63898081, a PSMA and CD3 Bispecific Antibody, for Metastatic Castration-Resistant Prostate Cancer, Clinical Genitourinary Cancer, https://doi.org/10.1016/j.clgc.2023.02.010

Introduction

The initial treatment for men with advanced prostate cancer is androgen-deprivation therapy (ADT). Despite the effectiveness of ADT, disease progression is inevitable with approximately 10–50% of men progressing to castration-resistant disease within 3 years of initial diagnosis.[1] Moreover, men with castration-resistant prostate cancer are at greater risk of developing metastatic disease, especially to bone (called metastatic castration-resistant prostate cancer, or mCRPC).[2,3] Available treatments for mCRPC have been shown to improve outcomes and include chemotherapy (docetaxel, cabazitaxel), inhibitors targeting androgen receptor signaling, androgen synthesis, and poly ADP ribose polymerase (PARP), radiotherapy (radium-223) and radioligand therapy (^{177}lutetium PSMA-617).[4-7]

Immune checkpoint inhibitors provide durable responses in various solid tumors but have limited efficacy in prostate cancer.[8-11] This is largely attributed to the immunosuppressive prostate tumor microenvironment characterized by the complex dynamics between cellular (including tumor stroma, regulatory T cells, tumor-associated macrophages) and molecular (including programmed cell death-ligand 1 [PD-L1], programmed cell death protein 1 [PD-1], transforming growth factor beta [TGF-beta], vascular endothelial growth factor [VEGF]) components.[12,13] Therapeutic strategies are needed to help overcome immunosuppression and allow prostate tumors to become more amenable to immunotherapy.

Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is expressed in normal prostatic tissue. PSMA expression is preserved in prostate cancer cells, especially in castration-resistant diseases. In addition, its expression is increased in tumors progressing on current anti-androgen therapies.[14-18] The tumor microenvironment in PSMA-positive prostate cancer may lack sufficient immune presence, perhaps explaining the limited efficacy of monotherapy with immune checkpoint inhibitors in prostate cancer. Because of the unique expression profile of PSMA in prostate cancer, several therapeutic platforms that target PSMA have been explored and validated, including CD3-redirection approaches to enhance immunogenicity.[19,20]

JNJ-63898081 (JNJ-081) is a humanized immunoglobulin G4 proline-alanine-alanine (IgG4 PAA) bispecific antibody, in which one arm binds to PSMA expressed on the cell surface, while the other arm binds to the CD3 receptor complex on T cells to promote antitumor activity. Here, we report results from a first-in-human, open-label, multicenter, phase 1 dose escalation study (NCT03926013) evaluating the safety and preliminary antitumor activity of JNJ-081 in patients with mCRPC.

Patients and Methods

Patients

Adults ≥18 years of age with a diagnosis of mCRPC and histologically confirmed adenocarcinoma were included. Adenocarcinoma with small-cell or neuroendocrine features was also allowed. Patients were required to have progressive disease per the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria, measurable or evaluable disease, received ≥1 line of prior novel androgen receptor signaling inhibitor (abiraterone acetate, apalutamide, enzalutamide) or taxane regimen for mCRPC, ECOG PS 0–1, and adequate organ function.

Study Design

Study 63898081EDI1001 was a first-in-human, open-label, multicenter, phase 1 study of JNJ-081 comprising a dose-escalation phase (Part 1) and dose expansion phase (Part 2). This study was conducted in accordance with the International Council for Harmonization Good Clinical Practice Standards and the Declaration of Helsinki. The protocol was approved by institutional and ethics committees. All patients provided written informed consent. Part 1 was initiated with an accelerated titration phase, followed by a standard titration phase with or without priming dose(s) (Figure 1). More than 1 priming dose was possible.

Dose escalation was initiated at 0.1 μg/kg JNJ-081 administered intravenously (IV) once a week. Subsequent dose levels were determined using a continuous reassessment method based on a Bayesian regression model. The dose escalation transitioned from accelerated to standard dose escalation when Grade ≥2 non-hematologic toxicity or Grade ≥3 hematologic toxicity occurred. After a dose level was deemed safe, drug dosage for patients enrolled in prior cohorts could be increased to that dose level. Subcutaneous (SC) injection as well as priming dose strategies were implemented in the standard titration phase to mitigate Grade ≥2 cytokine release syndrome (CRS). To mitigate the potential for infusion-related reactions (IRR) or CRS, all patients received their first dose of JNJ-081 with premedication consisting of corticosteroid, antipyretic, and antihistamine. Corticosteroids could be weaned for subsequent doses.

Study Assessments

Efficacy assessments using chest, abdomen, and pelvis imaging by CT/MRI and bone scan (99mTc) were performed every 8 weeks for the first 24 weeks, followed by every 12 weeks while on treatment. Pharmacokinetic, immunogenicity, or biomarker analyses were performed using serum and biopsy tissue. Pharmacokinetic and immunogenicity assays were performed using an electrochemiluminescence-based immunoassay format on the MSD platform. Immunogenicity or antidrug antibody testing used multitiered testing approach (screening, specificity, titration) with biotinylated JNJ-081 and SulfoTag-labelled JNJ-081 as capture and detection antibodies, respectively. Serum prostate-specific antigen (PSA) levels and systemic cytokine concentrations were also evaluated. Adverse events (AEs), including dose-limiting toxicities (DLTs) were recorded. AEs including CRS (AE of special interest) were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, v5.0.

Statistical Analysis

Response to treatment was evaluated by the investigator. Overall response rate (ORR) was defined as the proportion of participants who had a partial response (PR) or better according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1/PCWG3 criteria and was to be supplied with 2-sided 90% confidence interval. Duration of response (DOR) was defined as the interval between the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, or death due to any cause. Time to response was defined as the time from the date of first dose of study drug to the date of first documented response.

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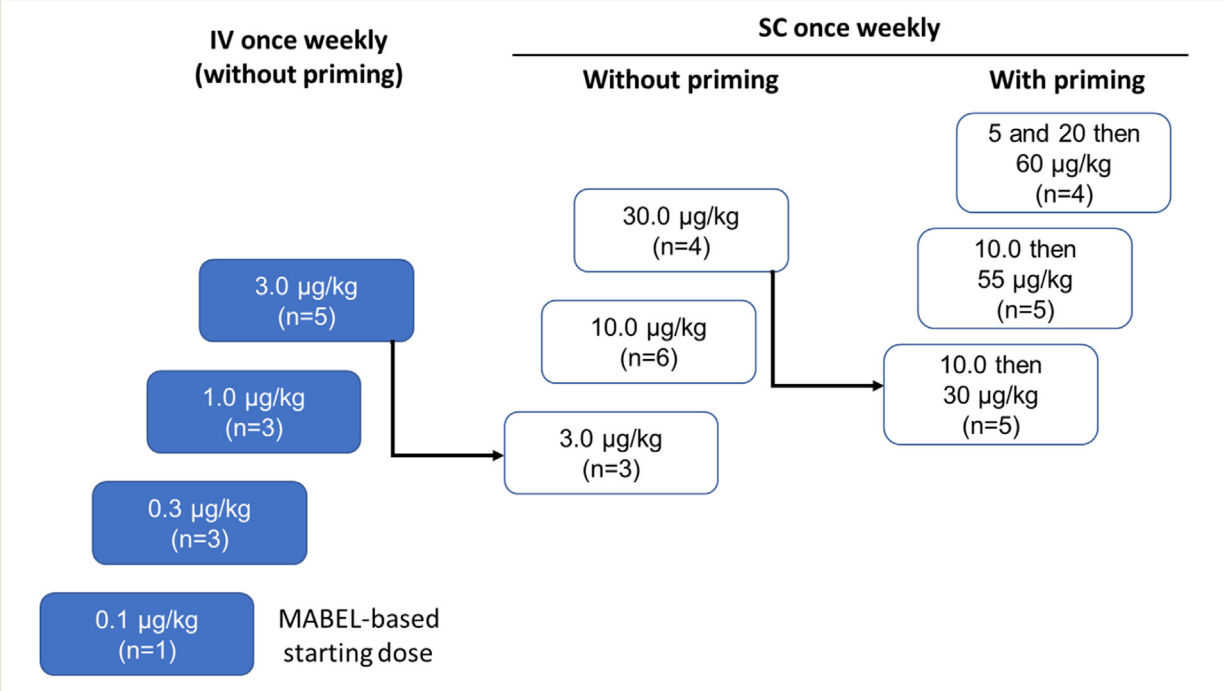
Figure 1 Dose escalation phase. IV, intravenous; MABEL; minimum anticipated biological effect level; SC, subcutaneous.



All safety and efficacy analyses were performed on data consisting of patients receiving at least 1 dose of the study drug and summarized using descriptive statistics. Additional statistical methods were provided in the study protocol.

Results

Patients

Thirty-nine patients with mCRPC were enrolled in the study, of which 38 patients (97.4%) were heavily pretreated with ≥3 lines of prior therapies (Table 1). All enrolled patients had adenocarcinoma; however, 1 included adenocarcinoma with small cell features. The dose escalation part of the study had 10 cohorts with treatment dose levels ranging from 0.1 µg/kg to 3 µg/kg IV and from 3 µg/kg to 60 µg/kg SC (Table 1). To mitigate CRS observed in the 30 µg/kg SC cohort, a single priming dose of 10 µg/kg was implemented on day 1, followed by treatment doses of either 30 µg/kg or 55 µg/kg SC once weekly in 2 subsequent dosing cohorts. Multi-dose priming was implemented with 5 µg/kg and 20 µg/kg on days 1 and 3, respectively, followed by doses of 60 µg/kg on day 8 and subsequently once a week. All 39 enrolled patients discontinued treatment predominantly due to progressive disease (89.7%; n = 35). Other reasons for discontinuation were withdrawal of consent by the patient (5.1%; n = 2), AEs, and lost to follow-up (2.6%; n = 1).

Safety

All 39 patients experienced at least 1 treatment-emergent AE (TEAE). DLTs were observed in 4 patients and included Grade 3 transaminitis (N = 2, following 30 µg/kg SC or 55 µg/kg SC doses), Grade 2 disseminated intravascular coagulation (N = 1, following fourth full treatment dose [60 µg/kg SC dose]), and Grade 3 hemolysis (N = 1, following 60 µg/kg SC dose). All DLTs occurred following a Grade 2 CRS events, except for hemolysis AE.

Serious TEAEs occurred in 18 (46.2%) patients (Table 2), with the most common being CRS (20.5%), pyrexia (7.7%), and back pain (5.1%). TEAEs leading to treatment discontinuation occurred in 1 patient each in priming with 10 µg/kg then treatment dose at 55 µg/kg SC (lethargy and pyrexia), and priming of 5 and 20 µg/kg then treatment dose of 60 µg/kg SC (disseminated intravascular coagulation). No treatment-related death was reported.

CRS was observed at higher doses with IV or SC administration (Table 3). No Grade ≥3 CRS events were reported. No notable CRS-related neurotoxicity was observed. Grade 2 CRS treated with tocilizumab generally resolved after a single dose. SC administration as well as step-up priming helped mitigate CRS during escalation to higher doses (Table 3). Grade 1 or 2 injection site reaction were also reported for SC administration.

The most frequent laboratory abnormalities reported as TEAEs were AST increased (15.4%), creatinine increased (15.4%), lipase increased (15.4%; no pancreatitis observed), ALT increased (12.8%), and neutrophils increased (12.8%). Among these laboratory TEAEs, grade ≥3 was reported for ALT and AST increased (7.7% each), and lipase increased (5.1%).

Efficacy

Of the 39 mCRPC participants exposed, 23 had RECIST evaluable disease. Overall, there were no radiographic responses (complete or partial response) per RECIST 1.1. The best overall

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Table 1 Patient Demographics and Baseline Characteristics

Characteristics	JNJ-081 Weekly IV (n = 12)	JNJ-081 Weekly SC (n = 27)	Total (n = 39)
Age, median (range), y	67.5 (43-82)	67 (50-80)	67 (43-82)
ECOG PS, n (%)			
0	7 (58.3)	9 (33.3)	16 (41.0)
1	5 (41.7)	18 (66.7)	23 (59.0)
Gleason score at initial diagnosis, n (%)			
7	6 (50.0)	9 (33.3)	15 (38.5)
≥8	6 (50.0)	14 (51.9)	20 (51.3)
Unknown	0	4 (14.8)	4 (10.3)
Metastases stage at initial diagnosis, n (%)			
M0	4 (33.3)	10 (37.0)	14 (35.9)
M1	6 (50.0)	12 (44.4)	18 (46.2)
Unknown	2 (16.7)	5 (18.5)	7 (17.9)
Prior cancer related therapy, n (%)			
Prostatectomy	5 (41.7)	9 (33.3)	14 (35.9)
Radiotherapy	7 (58.3)	21 (77.8)	28 (71.8)
Hormonal therapy	12 (100)	27 (100)	39 (100)
Orchietomy	1 (8.3)	0	1 (2.6)
GnRHa	11 (91.7)	23 (85.2)	34 (87.2)
First-generation anti-androgen	7 (58.3)	18 (66.7)	25 (64.1)
Novel ARSI	12 (100)	26 (96.3)	38 (97.4)
Chemotherapy – taxane-based	8 (66.7)	22 (81.5)	30 (76.9)
Other[a]	9 (75.0)	23 (85.2)	32 (82.1)

Abbreviations: ARSI = androgen receptor signaling inhibitor; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GnRHA = gonadotropin-releasing hormone agonist; IV = intravenous; SC = subcutaneous.
[a] Therapies other than hormonal therapy and chemotherapy, including atezolizumab, dexamethasone, dutasteride, granulocyte macrophage colony stimulating factor, niraparib, olaparib, pembrolizumab, prednisone, and zoledronic acid.

response observed was stable disease in 2 of 23 participants (13.0%) who had baseline target lesions. Transient PSA decreases were observed at treatment doses greater than 30 μg/kg SC. Two patients treated with 55 μg/kg had confirmed PSA decline of >50% (Figure 2A and 2B).

Pharmacokinetics, Pharmacodynamics, and Immunogenicity

Once weekly IV administration of JNJ-081 (0.1-3 μg/kg) led to increased C_{max} and AUC values (Figure 3A). The median t_{max} values were reached at the end of infusion (EOF) or EOF + 2 hours with IV administration, and from 24 to 168 hours following SC administration. Mean $t_{1/2}$ was 43.7 hours following 3 μg/kg IV dose and appear longer following SC administration. C_{max} and AUC values increased dose proportionally after once weekly SC administration of 3 to 30 μg/kg, and 30 to 60 μg/kg following priming dose.

Anti-drug antibodies (ADA) were detected in 2 of 12 (16.7%) patients with IV administration and 17 of 27 (63.0%) patients with SC administration (Table 4). Positive ADA status was observed in patients receiving 3 μg/kg IV (maximum titer 10), and in patients across all SC doses (maximum titer of 10485760). ADA generally corresponded with a decrease in serum concentrations of JNJ-081 with SC doses, particularly for patients with high titers. Intrapatient dose escalation in 3 patients did not overcome the reduced exposure after ADA seropositivity. A patient receiving 30 μg/kg had a PSA decrease of >30%; however, the decrease was transient, and the return to baseline and subsequent increase coincided with the onset of ADA seropositivity and a corresponding decrease in JNJ-081 serum levels (Figure 3B).

Dose-dependent cytokine increases were observed with IV administration. Cytokine increases after SC dosing were more variable and with lower magnitudes compared to IV administration at similar exposure levels. Serum cytokine levels of IFN-γ and IL-6 were 2 of the more notable and robust cytokines that demonstrated an increase in production after dosing with JNJ-081 (Figure 3C).

Discussion

In this study, we observed that JNJ-081 exhibited a manageable safety profile, and patients with mCRPC dosed with JNJ-081 had transient PSA responses. However, CRS events were observed at higher doses with IV or SC administration, but could be partially mitigated by SC dosing, step-up priming, and the combination of both strategies. In addition, ADA formation led to decreased JNJ-081 serum levels, which impacted drug exposure and efficacy.

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Table 2 Treatment-Emergent Adverse Events

n (%)	Weekly IV				Weekly SC (Without Priming)			Weekly SC (With Priming)			Total (n = 39)
	0.1 μg/kg (n = 1)	0.3 μg/kg (n = 3)	1 μg/kg (n = 3)	3 μg/kg (n = 5)	3 μg/kg (n = 3)	10 μg/kg (n = 6)	30 μg/kg (n = 4)	10 then 30 μg/kg (n = 5)	10 then 55 μg/kg (n = 5)	5 and 20, then 60 μg/kg (n = 4)	
Any TEAEs	1 (100)	3 (100)	3 (100)	5 (100)	3 (100)	6 (100)	4 (100)	5 (100)	5 (100)	4 (100	39 (100)
Related	1 (100)	3 (100)	3 (100)	5 (100)	3 (100)	6 (100)	4 (100)	5 (100)	5 (100)	4 (100)	39 (100)
Grade 3-4	0	1 (33.3)	1 (33.3)	4 (80.0)	0	2 (33.3)	2 (50.0)	4 (80.0)	2 (40.0)	1 (25.0)	17 (43.6)
Most common TEAEs (>40% in total group)											
Pyrexia	0	1 (33.3)	1 (33.3)	3 (60.0)	2 (66.7)	4 (66.7)	4 (100)	3 (60.0)	5 (100)	4 (100)	27 (69.2)
CRS	0	0	1 (33.3)	3 (60.0)	2 (66.7)	4 (66.7)	4 (100)	3 (60.0)	5 (100)	4 (100)	26 (66.7)
Injection site erythema	0	0	0	0	1 (33.3)	5 (83.3)	3 (75.0)	4 (80.0)	5 (100)	4 (100)	22 (56.4)
Chills	0	3 (100)	1 (33.3)	3 (60.0)	0	4 (66.7)	1 (25.0)	1 (20.0)	2 (40.0)	3 (75.0)	18 (46.2)
Fatigue	1 (100)	1 (33.3)	2 (66.7)	4 (80.0)	0	3 (50.0)	1 (25.0)	2 (40.0)	2 (40.0)	0	16 (41.0)
Serious TEAEs	0	1 (33.3)	1 (33.3)	3 (60.0)	0	2 (33.3)	3 (75.0)	3 (60.0)	3 (60.0)	2 (50.0)	18 (46.2)
Related	0	1 (33.3)	0	3 (60.0)	0	0	2 (50.0)	1 (20.0)	3 (60.0)	2 (50.0)	12 (30.8)
AEs leading to discontinuation	0	0	0	0	0	0	0	1 (20.0)	0	1 (25.0)	2 (5.1)
Related	0	0	0	0	0	0	0	0	0	1 (25.0)	1 (2.6)

Abbreviations: CRS = cytokine release syndrome; IV = intravenous; SC = subcutaneous; TEAE = treatment-emergent adverse event.
Database captured both the syndrome term CRS and individual signs and symptoms of CRS. Signs and symptoms of CRS are presented in Table 3 in addition to the report of CRS.

Therapies that harness the immune system to combat cancer have become more prevalent and viable in recent years.[19,21,22] One such approach is through bispecific molecules that facilitate a synapse between T cells and tumor antigens, leading to T cell activation and causing T cell-mediated lysis of target cells without the need for TCR-MHC interactions. This approach was first successfully used with blinatumomab for Philadelphia chromosome-negative relapsed or refractory acute lymphoblastic leukemia and has shown great promise with several bispecific agents for other hematologic malignancies[19,20,23-27] and tebentafusp for unresectable or metastatic uveal melanoma.[28]

The tumor microenvironment in mCRPC may lack a sufficient immune presence, which perhaps explains the lack of efficacy of checkpoint inhibitor monotherapy in prostate cancer.[29,30] T cell redirection could be an important approach to enhance the immune presence in the microenvironment of such tumors. Several other CD3-redirecting approaches targeting PSMA with mechanisms of action similar to that intended with JNJ-081 have entered clinical research for treating prostate cancer. These include BAY2010112 (also known as pasotuxizumab, a non-Fc-bearing CD3-PSMA bispecific T cell engager [BiTE] molecule),[31] AMG 160 (a PSMA-targeted, half-life extended BiTE molecule),[32] ES414 (an Fc-competent bivalent bispecific CD3-PSMA molecule),[19,32] and HPN424 (a tri-specific T cell-activating construct targeting CD3, PSMA, and human serum albumin).[33] Preliminary clinical data from a phase 1 study of pasotuxizumab indicated that this strategy was tolerated at doses up to 80 μg/day with continuous intravenous infusion and induced radiographic responders in patients with castration-resistant prostate cancer.[31] Efficacy with AMG 160 was also reported with a confirmed PSA 50 response of 27.6% and a confirmed radiographic partial response of 13.3% in patients with mCRPC who had measurable lesions at baseline.[34]

Although PSMA expression in normal tissues other than the prostate is relatively low, its RNA or protein expression is observed in normal epithelial tissues including kidney, liver, small intestine, salivary, and mammary gland as well as in endothelial cells.[14,26] This expression pattern of PSMA enables bispecific agents, such as JNJ-081 and other PSMA-target CD3 redirecting agents, to engage T cells and PSMA-expressing cells, which could cause T cell activation beyond tumor sites and CRS events. Preliminary data reported for all investigational PSMA-targeted CD3 redirecting agents indicate frequent observations of CRS, mainly manifested as pyrexia and occasionally accompanied with hypotension. Therefore, administration of these redirecting agents require corticosteroid premedication at least with initial dosing. Reports of immune effector cell-associated neurotoxicity syndrome (ICANS) were also rare for these group of agents unlike the CD3 redirecting agents for hematologic targets.[31-33]

The most commonly reported serious TEAE for JNJ-081 was CRS, which emerged in the third dosing cohort after initiating the study. Based on preclinical reports that the *in vivo* efficacy of JNJ-081 was observed at certain dose levels, we investigated various strategies to mitigate CRS. In this study, JNJ-081 was administered by IV and SC to determine the effects of routes of administration

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Table 3 Treatment-Emergent Adverse Events of CRS and IRR/ISR

n (%)	Weekly IV				Weekly SC (Without Priming)			Weekly SC (With Priming)			Total (n = 39)
	0.1 μg/kg (n = 1)	0.3 μg/kg (n = 3)	1 μg/kg (n = 3)	3 μg/kg (n = 5)	3 μg/kg (n = 3)	10 μg/kg (n = 6)	30 μg/kg (n = 4)	10 then 30 μg/kg (n = 5)	10 then 55 μg/kg (n = 5)	5 and 20, then 60 μg/kg (n = 4)	
CRS	0	0	1 (33.3)	3 (60.0)	2 (66.7)	4 (66.7)	4 (100)	3 (60.0)	5 (100)	4 (100)	26 (66.7)
Grade 2	0	0	0	3 (60.0)	0	1 (16.7)	3 (75.0)	1 (20.0)	4 (80.0)	1 (25.0	13 (33.3)
Most common CRS symptoms[a]											
Pyrexia	0	0	1 (33.3)	3 (60.0)	2 (66.7)	4 (66.7)	4 (100)	3 (60.0)	5 (100)	4 (100)	26 (66.7)
Hypotension	0	0	0	2 (40.0)	0	1 (16.7)	2 (50.0)	1 (20.0)	4 (80.0)	1 (25.0)	11 (28.2)
Chills	0	0	0	0	0	3 (50.0)	1 (25.0)	1 (20.0)	2 (40.0)	3 (75.0)	10 (25.6)
Tachycardia	0	0	0	2 (40.0)	0	1 (16.7)	1 (25.0)	0	1 (20.0)	1 (25.0)	6 (15.4)
Hypoxia	0	0	0	2 (40.0)	0	0	0	1 (20.0)	1 (20.0)	1 (25.0)	5 (12.8)
IRR/ISR	0	2 (66.7)	0	4 (80.0)	3 (100)	6 (100)	4 (100)	5 (100)	5 (100)	4 (100)	33 (84.6)
Most common IRR/ISR symptoms[a]											
Injection site erythema	0	0	0	0	1 (33.3)	5 (83.3)	3 (75.0)	4 (80.0)	5 (100)	4 (100.0)	22 (56.4)
Injection site pruritus	0	0	0	0	0	4 (66.7)	2 (50.0)	2 (40.0)	1 (20.0)	1 (25.0)	10 (25.6)
Injection site pain	0	0	0	0	1 (33.3)	3 (50.0)	0	0	2 (40.0)	1 (25.0)	7 (17.9)
Chills	0	1 (33.3)	0	3 (60.0)	0	0	0	0	0	0	4 (10.3)

Abbreviations: CRS = cytokine release syndrome; ISR = infusion/injection site reaction; IRR = infusion/injection related reaction; IV = intravenous; SC = subcutaneous; TEAE = treatment-emergent adverse event.
[a] More than 10% of patients in total group, as reported by the investigator.

Table 4 ADA Incidence by Cohort

Cohort	Dose	ADA-Positive/Total Patients
1	IV 0.1 μg/kg	0/1
2	IV 0.3 μg/kg	0/3
3	IV 1 μg/kg	0/3
4	IV 3 μg/kg	2/5
5	SC 3 μg/kg	2/3
6	SC 10 μg/kg	4/6
7	SC 30 μg/kg	3/4
8	SC 10 then 30 μg/kg	3/5
9	SC 10 then 55 μg/kg	2/5
10	SC 5 and 20, then 60 μg/kg	3/4

Abbreviations: ADA, anti-drug antibodies; IV, intravenous; SC, subcutaneous.

on CRS. Grade 2 CRS repeatedly occurred at a dose level of JNJ-081 that was 10-fold higher when administered by SC than IV, and furthermore, was approximately 2-fold higher with priming. As a result, SC administration, priming, and the combination of these strategies coupled with corticosteroid premedication could greatly mitigate CRS to achieve higher treatment doses. Further research is needed to better refine the necessary number of priming doses, and the increments between priming doses and the frequency of priming doses.

A gradual increase in serum concentration of JNJ-081 was observed following SC administration with t_{max} ranging from 24 to 168 hours. SC administration appeared to prolong the apparent

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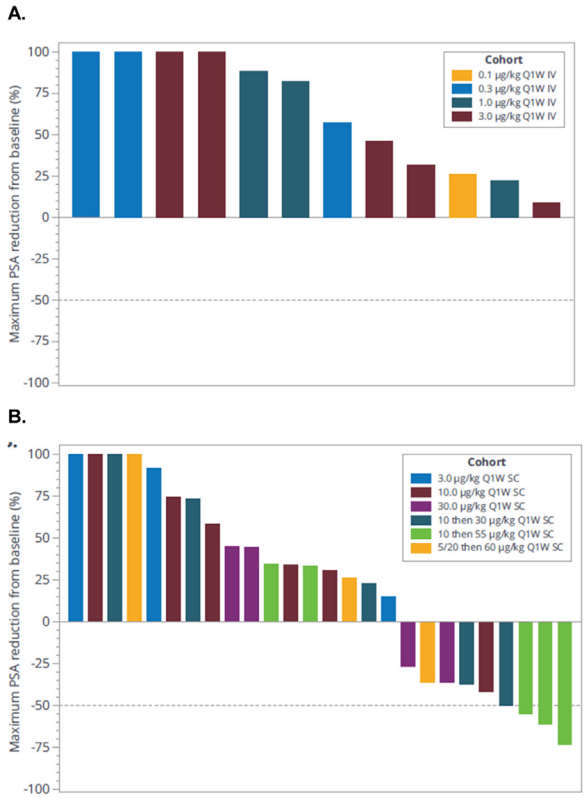
Figure 2 Maximum change in PSA. (A) IV dose and (B) SC dose. IV, intravenous; PSA, prostate-specific antigen; Q1W, once a week; SC, subcutaneous.



$t_{1/2}$ of JNJ-081 compared with IV administration as shown by a shallower decline of the terminal slope in the PK curve, resulting in more sustained exposure with smaller peak to trough concentration ratio. This phenomenon is often observed with extravascular administration of drugs when the rate of absorption is slower than the rate of elimination.[35] The gradual PK increase from SC absorption and relatively stable JNJ-081 levels compared with IV administration likely contributed to a decrease in cytokine release.[36] As shown in Figure 3C, the change from IV to SC administration introduced more muted and variable IFN-γ and IL-6 production with JNJ-081.

Based on the emerging ADA that negatively impacted PK exposure, this clinical study was terminated early. Full patient enrollment was not achieved for Part 1, and no patients were enrolled in Part 2. The limited enrollment data is a constraint on generalizing safety and antitumor efficacy profiles. However, the sample size is customary with early-phase oncology clinical trials evaluating first-in-human investigational agents and provides insights into the safety, tolerability, and efficacy of PSMA-targeted CD3 redirecting agents. In this study, all patients eventually discontinued treatment, primarily due to disease progression. Moreover, early termination of the study prevented many planned pharmacodynamic and biomarker assessments. Despite the small number of patients in cohorts from this study, the evidence suggests that the introduction of SC step-up dosing could be a viable option to manage cytokine and mitigate CRS in future solid tumor CD3 redirector clinical trials.

At doses greater than 30 µg/kg SC, JNJ-081 demonstrated a transient, substantial decrease in PSA levels. Higher dosing of JNJ-081 yielded larger PSA reduction, with greater than 50% decreases observed with doses over 55 µg/kg. These results were generally consistent with reported data regarding other PSMA-targeted CD3 redirecting bispecifics for mCRPC that are currently in development.[13,31]

Compared with BiTEs, ES414 and HPN424, JNJ-081 more resembled an endogenous human IgG antibody. However, immunogenicity (as measured by the presence of ADA) still occurred and was more prevalent with SC administration at higher doses. Further, systemic exposure of JNJ-081 was greatly reduced after ADA formation which could not be restored with intra-patient dose escalation. Loss of systemic exposure could also be responsible for transient PSA decreases. These results are consistent with previous findings.[31,34,37] As with other bispecific antibodies, increased immunogenicity associated with SC administration of JNJ-081 may be the result of slower distribution, the difference in volume compared with IV administration, and greater variability in drug

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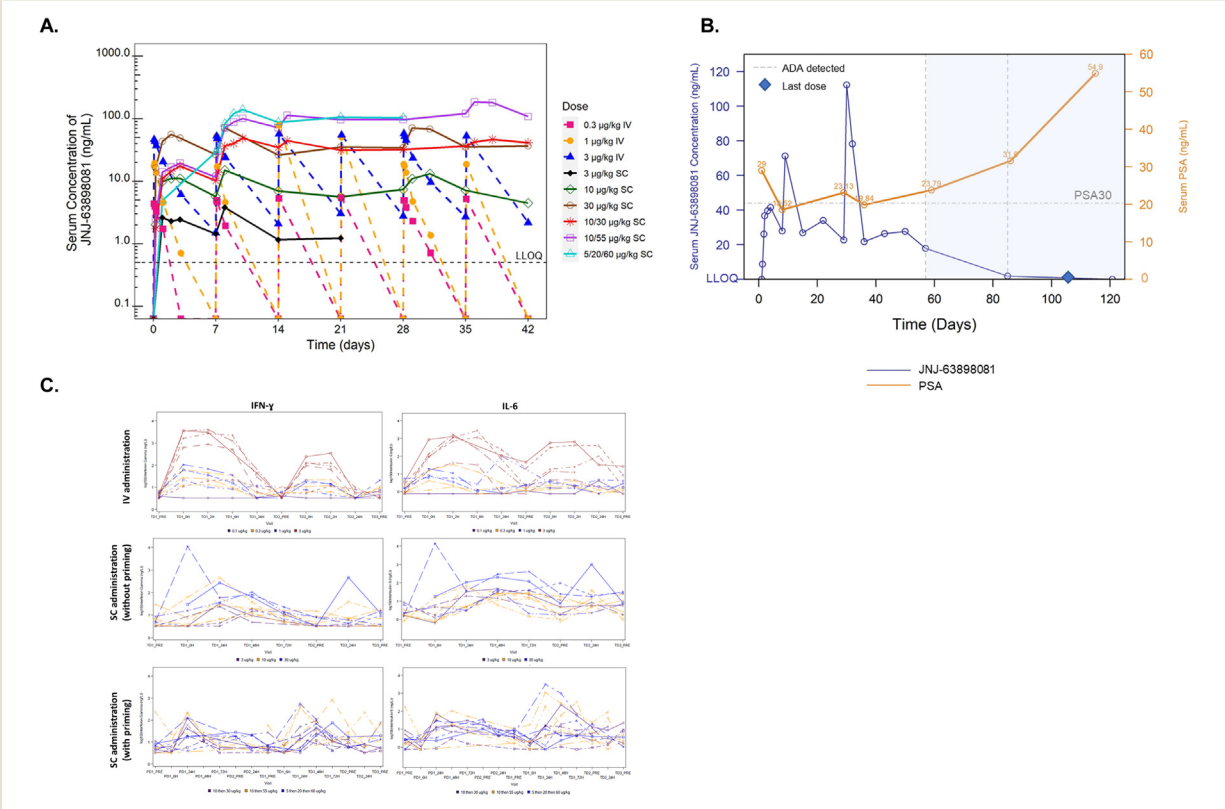
Figure 3 Pharmacokinetics and pharmacodynamics of JNJ-081. (A) Mean serum concentration-time profiles of JNJ-081 after IV or SC administration. Data not shown when n < 3. (B) Serum concentration-time profiles of JNJ-081 (blue, left y-axis) and PSA (orange, right y-axis) of a participant who was ADA positive on Days 57 and 85. (C) Changes in peripheral cytokines with IV and SC doses. H, hours; IL-6, Interleukin 6; IFN-γ, Interferon gamma; IV, intravenous; PD, priming dose; PRE, predose; PSA, prostate-specific antigen; Q1W, once a week; SC, subcutaneous; TD, treatment dose.



exposure levels between individuals. Moreover, skin cells possess highly specialized apparatus for foreign antigen presentation.[38]

The transient decreases in PSA in 2 patients receiving JNJ-081 and the reported clinical activity of other PSMA-directed bispecific antibodies[13] suggest that PSMA remains a viable target for T cell engagement to treat mCRPC. Further investigation may target methods to reduce CRS and, presumably, increase the likelihood of achieving maximum tolerated dose and optimal antitumor efficacy. These may include antibody component manipulation to further increase half-life, optimal dosing delivery for SC administration, and prophylactic (rather than symptomatic) treatment for CRS.

Conclusions

JNJ-081 demonstrated transient decreases in PSA in patients with mCRPC, with a manageable safety profile. Grade 2 CRS was observed at higher doses and was partially mitigated by SC and step-up dosing. ADA formation was frequent with SC administration. Additionally, ADA positivity generally corresponded with decrease in serum JNJ-081 concentrations in patients receiving SC doses, particularly for those with high titers. PSMA remains a potential therapeutic target for T cell redirection in treating prostate cancer.

Clinical Practice Points

- Patients with metastatic castration-resistant prostate cancer (mCRPC) have a poor prognosis and although available treatments have improved outcomes in patients, the disease remains uniformly fatal.
- Although therapies with immune checkpoint inhibitors have shown efficacy in other solid tumors, these immunotherapies lack efficacy in patients with mCRPC.
- A challenge in developing effective immunotherapies for prostate cancer is likely due to the various immunosuppressive mechanisms present in the prostate tumor microenvironment.
- A potential therapeutic approach to overcome immunosuppression is inducing or enhancing tumor-specific immune responses through T-cell redirection.
- PSMA is a membrane bound antigen prevalent in prostate cancer and its expression is preserved during prostate cancer progression, making it a suitable T-cell redirecting target.
- JNJ-63898081 (JNJ-081) is a bispecific antibody designed to bind PSMA-expressing tumor cells and CD3-expressing T cells to promote antitumor activity via immune synapse formation.
- In this first-in-human, phase 1 dose escalation study, administration of JNJ-081 was associated with transient declines in

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serumprostate specific antigen levels in patients with mCRPC. In addition, DLTs, mainly CRS which was manageable, were limited in duration and no treatment-related deaths were reported.

- This study indicates that T-cell redirection is feasible for the treatment of prostate cancer and PSMA remains a potential therapeutic target for T-cell redirection.

CRediT authorship contribution statement

Emerson A. Lim: Writing – review & editing. **Michael T. Schweizer:** Writing – review & editing. **Kim N. Chi:** Writing – review & editing. **Rahul Aggarwal:** Writing – review & editing. **Neeraj Agarwal:** Writing – review & editing. **James Gulley:** Writing – review & editing. **Edward Attiyeh:** Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **James Greger:** Conceptualization, Resources, Data curation, Supervision, Investigation, Methodology, Project administration, Writing – review & editing. **Shujian Wu:** Formal analysis, Supervision, Writing – review & editing. **Pharavee Jaiprasart:** Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **John Loffredo:** Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Nibedita Bandyopadhyay:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Hong Xie:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Aaron R. Hansen:** Writing – review & editing.

Acknowledgments

The authors thank all patients for their participation in this study and acknowledge the collaboration and commitment of the investigators and their staff. Writing assistance was provided by Paul D. Cao, PhD, of Janssen Global Services, LLC. Additional editorial support was provided by Namit Ghildyal, PhD, of Janssen Global Services, LLC. The study was funded by Janssen Research & Development, LLC.

Disclosures

EA Lim reports other support from Pfizer outside the submitted work; *MT Schweizer* reports personal fees from Janssen and Resverlogix, as well as grants from Zenith Epigenetics, Bristol Myers Squibb, Merck, Immunomedics, Janssen, AstraZeneca, Pfizer, Madison Vaccines, Tmunity, and Hoffmann-La Roche outside the submitted work; *R Aggarwal* reports honoraria from Clovis Oncology, advisory roles for AstraZeneca, Dendreon, and Janssen, research funding from AbbVie, Amgen, Cancer Targeted Technology, Janssen, Merck, Novartis, Xynomic Pharmaceuticals, and Zenith Epigenetics, and compensation for travel, accommodations, and expenses from Xynomic Pharmaceuticals; *N Agarwal* reports consultancy to Astellas, Astra Zeneca, Aveo, Bayer, Bristol Myers Squibb, Calithera, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Foundation Medicine, Genentech, Gilead, Janssen, Merck, MEI Pharma, Nektar, Novartis, Pfizer, Pharmacyclics, and Seattle Genetics, and additionally reports institutional research funding from Astra Zeneca, Bavarian Nordic, Bayer, Bristol Myers Squibb, Calithera, Celldex, Clovis, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech, Glaxo Smith Kline, Immunomedics, Janssen, Medivation, Merck, Nektar, New Link Genetics, Novartis, Pfizer, Prometheus, Rexahn, Roche, Sanofi, Seattle Genetics, Takeda, and Tracon; *KN Chi and J Gulley* have nothing to disclosed; AR Hansen reports research funding to the institution from GSK, Merck, Pfizer, MedImmune/Genentech, Roche, Janssen, BMS, AstraZeneca, Astellas, Boehringer Ingelheim, and Bayer and consulting role/advisory boards for GSK, Merck, and Eisai; *E Attiyeh, J Greger, S Wu, P Jaiprasart, J Loffredo, N Bandyopadhyay, H Xie* are employees of Janssen Research and Development.

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Journal for ImmunoTherapy of Cancer

First-in-human, phase 1 study of PF-06753512, a vaccine-based immunotherapy regimen (VBIR), in non-metastatic hormone-sensitive biochemical recurrence and metastatic castration-resistant prostate cancer (mCRPC)

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To cite: Autio KA, Higano CS, Nordquist L, *et al*. First-in-human, phase 1 study of PF-06753512, a vaccine-based immunotherapy regimen (VBIR), in non-metastatic hormone-sensitive biochemical recurrence and metastatic castration-resistant prostate cancer (mCRPC). *Journal for ImmunoTherapy of Cancer* 2023;**11**:e005702. doi:10.1136/jitc-2022-005702

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jitc-2022-005702).

Accepted 07 December 2022

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ABSTRACT

Background This phase 1 study evaluated PF-06753512, a vaccine-based immunotherapy regimen (PrCa VBIR), in two clinical states of prostate cancer (PC), metastatic castration-resistant PC (mCRPC) and biochemical recurrence (BCR).

Methods For dose escalation, patients with mCRPC received intramuscular PrCa VBIR (adenovirus vector and plasmid DNA expressing prostate-specific membrane antigen (PSMA), prostate-specific antigen (PSA), and prostate stem cell antigen (PSCA)) with or without immune checkpoint inhibitors (ICIs, tremelimumab 40 or 80 mg with or without sasanlimab 130 or 300 mg, both subcutaneous). For dose expansion, patients with mCRPC received recommended phase 2 dose (RP2D) of PrCa VBIR plus tremelimumab 80 mg and sasanlimab 300 mg; patients with BCR received PrCa VBIR plus tremelimumab 80 mg (Cohort 1B-BCR) or tremelimumab 80 mg plus sasanlimab 130 mg (Cohort 5B-BCR) without androgen deprivation therapy (ADT). The primary endpoint was safety.

Results Ninety-one patients were treated in dose escalation (mCRPC=38) and expansion (BCR=35, mCRPC=18). Overall, treatment-related and immune-related adverse events occurred in 64 (70.3%) and 39 (42.9%) patients, with fatigue (40.7%), influenza-like illness (30.8%), diarrhea (23.1%), and immune-related thyroid dysfunction (19.8%) and rash (15.4%), as the most common. In patients with mCRPC, the objective response rate (ORR, 95% CI) was 5.6% (1.2% to 15.4%) and the median radiographic progression-free survival (rPFS) was 5.6 (3.5 to not estimable) months for all; the ORR was 16.7% (3.6% to 41.4%) and 6-month rPFS rate was 45.5% (24.9% to 64.1%) for those who received RP2D

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The use of immunotherapy in the treatment of prostate cancer (PC) has been far less successful compared with more 'immunologically responsive' cancers; only the vaccine sipuleucel-T has demonstrated modest survival benefit and is approved for the treatment of metastatic castration-resistant PC (mCRPC).

WHAT THIS STUDY ADDS

⇒ This phase 1 study (NCT02616185) evaluated PF-06753512, a vaccine-based immunotherapy regimen (VBIR) for PC (PrCa VBIR) that combines a vaccine prime/boost strategy with immune checkpoint inhibitors (ICIs), in two clinical states of PC, mCRPC and biochemical recurrence (BCR).

⇒ PF-06753512 overall demonstrated safety signals similar to other ICI combination trials, significant side effects were seen in some patients with BCR, a modestly prolonged radiographic progression-free survival was observed in patients with mCRPC, and a prompt and durable ≥50% decline in baseline prostate-specific antigen was observed without the use of androgen deprivation therapy in some patients with BCR.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ PrCa VBIR stimulated antigen-specific immunity in most patients, and the results are suggestive of immune-mediated antitumor activity with PrCa VBIR, particularly in BCR; therefore, further investigation of vaccine and ICI combinations in patients with PC is warranted.

J Immunother Cancer: first published as 10.1136/jitc-2022-005702 on 22 March 2023. Downloaded from http://jitc.bmj.com/ on April 24, 2023 at Fred Hutchinson Cancer Research Center - Arnold Library. Protected by copyright.

with measurable disease (n=18). 7.4% of patients with mCRPC achieved a ≥50% decline in baseline PSA (PSA-50), with a median duration of 4.6 (1.2–45.2) months. In patients with BCR, 9 (25.7%) achieved PSA-50; the median duration of PSA response was 3.9 (1.9–4.2) and 10.1 (6.9–28.8) months for Cohorts 5B-BCR and 1B-BCR. Overall, antigen specific T-cell response was 88.0% to PSMA, 84.0% to PSA, and 80.0% to PSCA.

Conclusions PrCa VBIR overall demonstrated safety signals similar to other ICI combination trials; significant side effects were seen in some patients with BCR. It stimulated antigen-specific immunity across all cohorts and resulted in modest antitumor activity in patients with BCR without using ADT.

Trial registration number NCT02616185.

INTRODUCTION

Immunotherapy with checkpoint inhibition has significantly improved the treatment of many solid tumors, especially for microsatellite instable solid tumors.[1] Using immunotherapy in the treatment of prostate cancer (PC) has been far less successful compared with more 'immunologically responsive' cancers, such as lung cancer, melanoma, and renal cell carcinoma.[2–8] At present, only the vaccine sipuleucel-T has demonstrated modest survival benefit, leading to its approval for the treatment of metastatic castration-resistant PC (mCRPC).[9] Responses to checkpoint inhibitor therapy in patients with mCRPC are generally limited to those patients with microsatellite instability.[10] In PC, there remains an unmet need for novel immunologic strategies to provide long-term disease control, with manageable safety profiles, in the recurrent and metastatic setting.

The natural history of recurrent PC can be viewed as a series of clinical states beginning with localized disease, followed by a state of biochemical recurrence (BCR), with progression to radiographically visible metastatic, hormone-sensitive disease; ultimately, mCRPC, an advanced form of the disease, then ensues.[11–13] The use of androgen deprivation therapy (ADT) serves as the backbone of treatment for those with high-risk BCR, and all patients with hormone-sensitive and castration-resistant metastatic disease. The various clinical disease states of PC have distinct biological characteristics. These same clinical stages may harbor different immunological profiles that could influence response to immunotherapy.[3 8 14–18] Therefore, there remains uncertainty surrounding the optimal patient populations in which to develop and assess vaccine-based immunotherapies.[3 8 14–18]

PC expresses specific tumor-associated antigens, such as prostate-specific antigen (PSA), prostate-specific membrane antigen (PSMA), and prostatic acid phosphatase (PAP), which are attractive targets for antigen-based PC vaccines.[2 4 7] Apart from sipuleucel-T, other vaccination strategies, such as PROSTVAC,[19] Prostate GVAX,[20 21] and TG4010,[22] which incorporate a variety of antigens and delivery systems, have been unsuccessful therapeutically.[19] In more recent vaccine development, the incorporation of immune checkpoint inhibitors (ICIs) is proposed to induce, expand, and maintain T-cell function leading to better antitumor immune responses, perhaps by overcoming the 'immunologically cold' environment of PC.[3 5]

PF-06753512 is a vaccine-based immunotherapy regimen (VBIR) for PC (PrCa VBIR) in development for the treatment of patients in distinct clinical states of PC. PrCa VBIR combines a vaccine with ICIs, and uses novel methods of administration of these compounds, including electroporation of antigens encoded within plasmid DNA (pDNA), along with subcutaneous (SC) administration of ICIs. PrCa VBIR contains an adenovirus (AdC68) vector expressing three selected PC-specific antigens, PSA, PSMA, and prostate stem cell antigen (PSCA); pDNA (PF-06755990); and an anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody, tremelimumab (PF-06753388). Multiple overexpressed PC-specific antigens were selected to improve the probability that patients will benefit from the vaccine.[23 24] AdC68 was used for priming vaccination, as antigen-specific T-cell responses have been induced by adenovirus vectors.[25 26] The rationale for this combinatorial approach is to promote the induction, expansion, and long-term maintenance of T-cell derived, anti-PC immune responses at the site of metastatic disease. In preclinical models, T-cell responses were amplified at each prime and boost vaccination with PrCa VBIR.[27] If effective, PrCa VBIR could potentially avoid the significant toxicity of androgen deprivation in BCR and delay the need for chemotherapy in mCRPC.

The purpose of this phase 1 study (NCT02616185) was to explore the safety, antitumor activity, immune response, pharmacokinetics (PK), and pharmacodynamics (PD) of escalating doses of PrCa VBIR (PF-06753512) in patients with PC.

METHODS

Study design

This was a phase 1, open-label, multicenter, multiple-dose, safety, PK, PD, and immunogenicity study. The study enrolled and treated patients at 11 study centers in the USA between December 30, 2015, and February 23, 2021. The study was divided into two parts: Part 1, dose escalation enrolling patients with mCRPC, followed by Part 2, dose expansion enrolling patients with mCRPC and BCR (figure 1).

The PrCa VBIR regimen comprised the following components: (1) a priming immunization with a replication-deficient adenovirus (AdC68) vector, derived from a chimpanzee-originated AdC68 expressing three selected PC-specific antigens (PSA, PSMA, and PSCA), administered intramuscularly; (2) DNA plasmid booster vaccinations, encoding the same antigens, administered intramuscularly with an electroporation device (TriGrid Delivery System); (3) SC administration of tremelimumab; and (4) for some cohorts, a programmed cell death protein 1 (PD-1) monoclonal antibody, sasanlimab (PF-06801591), was given SC. All intramuscular injections (AdC68 and the DNA booster vaccine) were given

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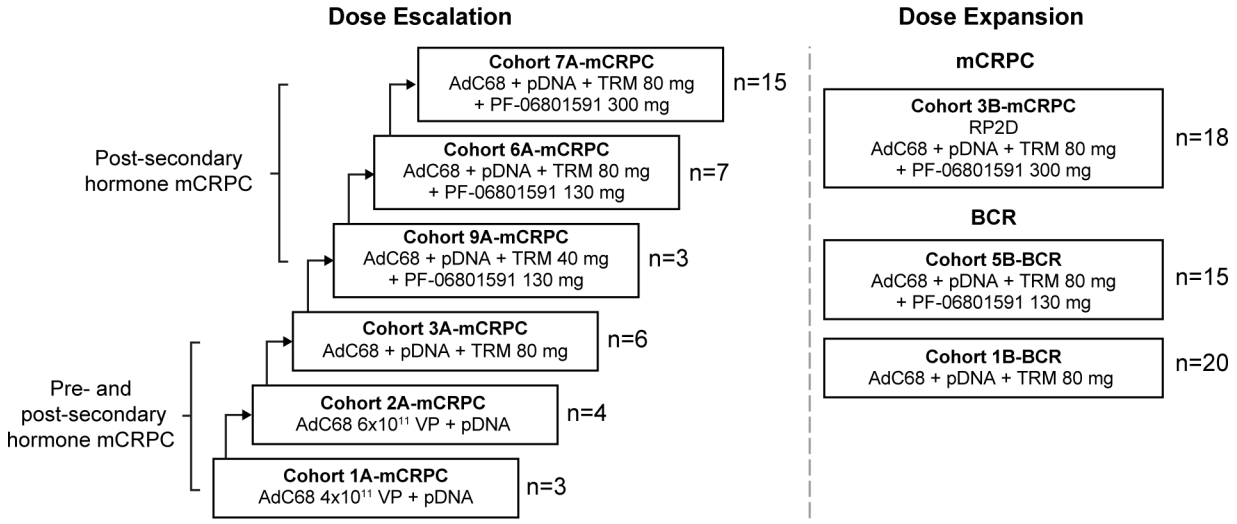

Figure 1 Study design. The dose for AdC68 was 6×10^{11} VP if not specified. Post-secondary hormone was defined as a failed androgen receptor-targeted therapy.
AdC68, adenovirus vector; BCR, biochemical recurrence; mCRPC, metastatic castration-resistant prostate cancer; pDNA, plasmid DNA; RP2D, recommended phase 2 dose; TRM, tremelimumab; PF-06801591, sasanlimab; VP, viral particles.

bilaterally in the deltoid muscles or in the vastus lateralis muscles of the quadriceps. SC injections (tremelimumab and sasanlimab) were given near the vaccinated muscles and the vaccine draining lymph nodes.

In the dose-escalation portion enrolling only patients with mCRPC, a 3+3 design was used. A cycle of PrCa VBIR included AdC68 priming dose (intramuscularly) on Day 1, followed by three pDNA boosts (5 mg fixed dose, intramuscularly) using an electroporation device at 4-week intervals for 12 weeks (16 weeks total). AdC68 dose of 4×10^{11} viral particles (VP) was given to Cohort 1A-mCRPC and 6×10^{11} VP to Cohort 2A-mCRPC. Since toxicity was determined to be acceptable in the first two cohorts, the AdC68 dose of 6×10^{11} VP was used for all subsequent cohorts. From Cohort 3A-mCRPC, the PrCa VBIR cycle included SC tremelimumab every 4 weeks (Q4W). For Cohorts 3A-mCRPC, 6A-mCRPC, and 7A-mCRPC, SC tremelimumab was given at 80 mg Q4W; for Cohort 9A-mCRPC, SC tremelimumab was dosed at 40 mg Q4W. Starting with Cohorts 6A-mCRPC through 9A-mCRPC, the PrCa VBIR cycle also included the anti-PD-1 antibody sasanlimab given SC Q4W, starting at 130 mg (Cohorts 6A-mCRPC and 9A-mCRPC) and escalated up to 300 mg (Cohort 7A-mCRPC).

In the dose-expansion portion, PrCa VBIR alone (AdC68 6×10^{11} VP, pDNA, SC tremelimumab 80 mg) and in combination with sasanlimab were evaluated in two populations: (1) patients with mCRPC who had disease progression despite abiraterone and/or enzalutamide treatment were treated with PrCa VBIR plus SC sasanlimab 300 mg (Cohort 3B-mCRPC); or (2) patients with BCR were treated with PrCa VBIR alone (Cohort 1B-BCR) or PrCa VBIR plus SC sasanlimab 130 mg (Cohort 5B-BCR). After completing two cycles of treatment (treatment duration was approximately 8 months), a maintenance treatment period with pDNA and tremelimumab administered every 2 months was provided as long as patients were deriving clinical benefit. Patients continued to receive sasanlimab Q4W where applicable. Treatment continued until disease progression, participant refusal, or unacceptable toxicity occurred.

Blood samples were collected from patients who received tremelimumab and sasanlimab for PK, PD, and immunogenicity assessments at scheduled times (details see online supplemental materials).

The study was approved by either institutional review boards or an independent ethics committee at each study center. There was no patient involvement in the study design. The study was conducted in accordance with all local legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients, Guidelines for Good Clinical Practice, and the Declaration of Helsinki. All patients provided written informed consent.

Patients

Eligible patients were men aged ≥18 years with a histological or cytological diagnosis of adenocarcinoma of the prostate accompanied by adequate bone marrow, renal, and liver function. Patients were excluded if they met any of the following conditions: a diagnosis of neuroendocrine PC or a neuroendocrine component; metastases to the brain or liver; Eastern Cooperative Oncology Group performance status ≥2; prior malignancy other than PC <3 years, excluding successfully-treated basal cell carcinoma or squamous cell carcinoma of the skin; systemic anticancer therapy <4 weeks or 5 half-lives; chemotherapy in mCRPC; sipuleucel-T and PROSTVAC <12 months; or investigational agents, immunosuppressive dose of corticosteroids, or other immunosuppressive medication <30 days.

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For patients with mCRPC, those in Cohorts 1A-mCRPC, 2A-mCRPC, and 3A-mCRPC had progressed on ADT, but were not required to have prior novel androgen receptor-directed therapy (eg, enzalutamide or abiraterone); those in Cohorts 7A-mCRPC through 9A-mCRPC and 3B-mCRPC were required to have prior therapy with enzalutamide and/or abiraterone, testosterone <50 ng/dL, disease progression per modified Prostate Cancer Working Group 3 (PCWG3) criteria, and currently being treated with a gonadotrophin-releasing hormone agonist or antagonist (unless surgically castrated). Measurable disease based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria was not required for patients with mCRPC; however, for patients with bone-only metastatic disease, this was required to be evaluable using PCWG3 criteria.

Patients with BCR (Cohorts 1B-BCR and 5B-BCR) were required to meet the following criteria: definitive local therapy for primary diagnosis; rising PSA with a minimum PSA of 0.2 ng/mL; PSA doubling time (PSADT) <10 months, testosterone >150 ng/dL; and no metastatic disease on conventional imaging (CT/MRI or bone scintigraphy).

Endpoints

Dose-escalation portion

The primary endpoint was incidence and grade of treatment-emergent adverse events (TEAEs), including dose-limiting toxicities (DLTs), as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V.4.03. Secondary endpoints included: immune response such as T cells specific to the three selected PC tumor-antigens, laboratory abnormalities, tremelimumab and sasanlimab single-dose PK parameters, and the incidence and titers of anti-drug antibodies (ADA) against tremelimumab and sasanlimab (sampling time for PK and ADA assessments see online supplemental materials). Exploratory endpoints were: objective response rate (ORR) per RECIST V.1.1; antitumor response and tumor control duration based on total measurable tumor burden per immune-related RECIST V.1.1 (irRECIST); bone metastatic disease as evaluated per PCWG3 criteria; radiographic progression-free survival (rPFS) as assessed by RECIST V.1.1 and PCWG3; and baseline and changes from baseline for PSA and PSADT.

Dose-expansion portion

The primary endpoints were: rates of TEAEs, including DLTs, and laboratory abnormalities. Secondary endpoints included: PSA-50 response rate (defined as the proportion of patients whose on-study locally measured PSA declined from baseline by ≥50% at two consecutive measurements ≥3 weeks apart prior to other systematic anticancer therapy) and duration of response (DOR); baseline and changes from baseline for PSA and PSADT; and the incidence and titers of ADA against tremelimumab and sasanlimab. Immune response, including T cells specific to the three selected PC tumor-antigens, was assessed as an exploratory endpoint.

Dose-escalation and expansion portions

For patients with mCRPC in Cohort 3B-mCRPC and 7A-mCRPC who were treated at the same dose (AdC68+DNA plasmid booster vaccine+tremelimumab 80 mg + sasanlimab 300 mg), additional secondary endpoints were: ORR and DOR per RECIST; antitumor response and tumor control duration based on total measurable tumor burden per irRECIST; and rPFS by RECIST, irRECIST, and PCWG3 criteria.

Specific T-cell response analysis was conducted on Cohort 5B-BCR, and on Cohort 7A-mCRPC and 3B-mCRPC.

Statistical analyses

Details on sampling, sample size, and analysis populations are in online supplemental materials. The results are presented as overall, all patients with mCRPC, and patients with BCR.

Safety was assessed with adverse events (AEs) and serious AEs (SAEs) described by Medical Dictionary for Regulatory Activities (V.23.1) preferred term and graded by NCI CTCAE (V.4.03). Immune-related AEs (irAEs) were defined as immune-related, based on the need for immunosuppressive therapy such as steroids, or endocrine replacement therapy. The definition of irAE also required that no alternative clinical explanation for the AE could be found, other than immune-related. In the first 28 days following the first AdC68 vaccination, the occurrence of specific hematologic and non-hematologic AEs (not considered related to disease or disease progression) potentially attributable to the drug combination was classified as a DLT (definitions see online supplemental materials).

Antitumor activity was assessed through radiologic tumor assessments, including bone scintigraphy and CT or MRI conducted at baseline, during treatment, at suspected disease progression, and at the time of withdrawal from treatment. Assessment of tumor response was per RECIST and irRECIST, and bone metastatic disease assessed per PCWG3. Progression-free survival was estimated using the Kaplan-Meier method.

Blood samples for PK analyses were assayed for all analytes using validated analytical methods. Plasma PK parameters were estimated using non-compartmental analysis, and PK parameters were summarized descriptively.

Analyses of immunogenicity and PD endpoints were summarized descriptively. Peripheral blood mononuclear cell (PBMC) samples were assayed for antigen-specific T-cell response against PSMA, PSCA, and PSA antigens by applying a modified enzyme-linked immunospot (ELISpot) assay including an initial in vitro expansion. Numbers of interferon (IFN)-γ secreting spot-forming cells were counted and scored as a positive T-cell response

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Table 1 Baseline demographics and characteristics

	BCR (N=35)	mCRPC (N=56)	Total (N=91)
Mean (range) age, years	67.4 (52–79)	70.1 (54–88)	69.1 (52–88)
Race, n (%)			
White	32 (91.4)	47 (83.9)	79 (86.8)
Black	3 (8.6)	8 (14.3)	11 (12.1)
Asian	0 (0.0)	1 (1.8)	1 (1.1)
ECOG PS, n (%)			
0	34 (97.1)	35 (62.5)	69 (75.8)
1	1 (2.9)	21 (37.5)	22 (24.2)
Median (range) Gleason score	7.0 (4–9)	8.0 (6–10)	7.0 (4–10)
Measurable disease	N=35	N=54	N=89
Yes	0 (0.0)	24 (44.4)	24 (27.0)
No	35 (100)	30 (55.6)	65 (73.0)
Median (range) local PSA, ng/mL	2.8 (0.5–20.6)	16.2 (0.7–1500.0)	6.7 (0.5–1500.0)
Prior surgery, n (%)	31 (88.6)	38 (67.9)	69 (75.8)
Prior radiation therapy, n (%)	27 (77.1)	37 (66.1)	64 (70.3)
Prior systemic therapy, n (%)	19 (54.3)	56 (100.0)	75 (82.4)
Abiraterone	1 (2.9)*	41 (73.2)	42 (46.2)
Enzalutamide	0 (0.0)	33 (58.9)	33 (36.3)
Apalutamide	1 (2.9)*	2 (3.6)	3 (3.3)
Darolutamide	0 (0.0)	0 (0.0)	0 (0.0)

Safety population. Measurable disease based on the RECIST criteria was not required for patients with mCRPC; however, for patients with bone-only metastatic disease, this must be evaluable using PCWG3 criteria.
*Two patients in the BCR cohorts (patient 057 in Cohort 1B-BCR and patient 091 in Cohort 5B-BCR) received anti-androgen hormone suppressing medication within 2–4 years prior to study entry.
BCR, biochemical recurrence; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRPC, metastatic castration-resistant prostate cancer; PCWG3, Prostate Cancer Working Group 3; PSA, prostate-specific antigen; RECIST, the Response Evaluation Criteria in Solid Tumors.

if there was a ≥2-fold count at any time point post vaccination compared with baseline.

Software used was SAS V.9.4 (SAS Institute, North Carolina, USA). T-cell response analysis was calculated using R V.3.6.1.

RESULTS

Patient disposition and demography

Overall, 91 patients were treated in the dose escalation (mCRPC: n=38) and dose expansion (n=53; BCR: n=35, mCRPC: n=18). Most patients were white (86.8%), with a median (range) age of 70.0 (52–88) years and a median Gleason score of 7.0 (table 1). The median (range) duration of treatment, in months, was 3.94 (0.03–47.11) for all patients, 3.22 (0.03–46.49) for patients with mCRPC, 22.06 (0.95–47.11) for Cohort 1B-BCR (patients with BCR), and 2.79 (0.03–17.48) for Cohort 5B-BCR (patients with BCR). Median number of cycles was two for all patients (including patients with mCRPC), three for Cohort 1B-BCR, and one for Cohort 5B-BCR; the corresponding treatment duration (4 months per cycle) was 8, 12, and 4 months. The median (range) duration of follow-up, in months, was 9.8 (1–51) for all patients, 8.5 (1–51) for patients with mCRPC, and 12.9 (2–48) for patients with BCR.

Safety

Overall, one patient in Cohort 6A-mCRPC (mCRPC) had a DLT of Grade 4 myositis and Grade 3 myasthenia gravis. Both events were attributable to AdC68, tremelimumab, and sasanlimab, which resulted in permanent discontinuation of study treatment.

mCRPC

In patients with mCRPC, all-causality AEs were reported in 55 (98.2%) and SAEs in 16 (28.6%) patients. The most common all-causality AEs were anemia (46.4%), fatigue (41.1%), and arthralgia (39.3%). Treatment-related AEs (TRAEs) were reported in 51 (91.1%) and serious TRAEs in 11 (19.6%) patients. The most common TRAEs were fatigue (35.7%), nausea (21.4%), and diarrhea (21.4%). Grade 3 or 4 TRAEs developed in 23 (41.1%) patients, and 1 patient had a Grade 5 TRAE of pulmonary embolism as a complication of myasthenia gravis (table 2).

Permanent discontinuations due to all-causality AEs occurred in 16 (28.6%) patients, among whom, 13 (23.2%) were due to TRAEs. The non-serious AEs leading to discontinuation were Grade 3 rash maculopapular, amylase increased, hyperglycemia, rash papular, and weight decreased; and Grade 4 lipase increased. The SAEs leading to discontinuation were Grade 2 myositis;

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Table 2 Summary of TRAEs occurring in ≥20% of patients in Cohort 1B-BCR, Cohort 5B-BCR, and all patients with mCRPC

	BCR														
	Cohort 1B-BCR (N=20)					Cohort 5B-BCR (N=15)					mCRPC (N=56)				
N (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total
Any TRAEs	7 (35.0)	6 (30.0)	5 (25.0)	1 (5.0)	19 (95.0)	3 (20.0)	2 (13.3)	6 (40.0)	3 (20.0)	15 (100.0)	15 (26.8)	13 (23.2)	17 (30.4)	5 (8.9)	51 (91.1)
Endocrine disorders															
Hyperthyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (20.0)	1 (6.7)	0 (0.0)	0 (0.0)	4 (26.7)	5 (8.9)	1 (1.8)	0 (0.0)	0 (0.0)	6 (10.7)
Hypothyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	2 (13.3)	1 (6.7)	0 (0.0)	4 (26.7)	3 (5.4)	4 (7.1)	0 (0.0)	0 (0.0)	7 (12.5)
Gastrointestinal disorders															
Diarrhea	2 (10.0)	1 (5.0)	0 (0.0)	0 (0.0)	3 (15.0)	3 (20.0)	1 (6.7)	2 (13.3)	0 (0.0)	6 (40.0)	6 (10.7)	2 (3.6)	4 (7.1)	0 (0.0)	12 (21.4)
Nausea	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (6.7)	3 (20.0)	0 (0.0)	0 (0.0)	4 (26.7)	9 (16.1)	3 (5.4)	0 (0.0)	0 (0.0)	12 (21.4)
General disorder and administration site conditions															
Fatigue	7 (35.0)	2 (10.0)	0 (0.0)	0 (0.0)	9 (45.0)	4 (26.7)	1 (6.7)	3 (20.0)	0 (0.0)	8 (53.3)	11 (19.6)	7 (12.5)	2 (3.6)	0 (0.0)	20 (35.7)
Influenza-like illness	9 (45.0)	3 (15.0)	0 (0.0)	0 (0.0)	12 (60.0)	3 (20.0)	1 (6.7)	1 (6.7)	0 (0.0)	5 (33.3)	9 (16.1)	2 (3.6)	0 (0.0)	0 (0.0)	11 (19.6)
Injection site pain	6 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (30.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	2 (3.6)	0 (0.0)	0 (0.0)	2 (3.6)
Fever	4 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (12.5)	1 (1.8)	0 (0.0)	0 (0.0)	8 (14.3)
Laboratory investigations															
ALT increased	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	3 (20.0)	0 (0.0)	2 (13.3)	0 (0.0)	5 (33.3)	6 (10.7)	2 (3.6)	1 (1.8)	0 (0.0)	9 (16.1)
Amylase increased	2 (10.0)	1 (5.0)	0 (0.0)	0 (0.0)	3 (15.0)	5 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (33.3)	6 (10.7)	2 (3.6)	1 (1.8)	1 (1.8)	10 (17.9)
AST increased	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	4 (26.7)	1 (6.7)	0 (0.0)	1 (6.7)	6 (40.0)	5 (8.9)	2 (3.6)	2 (3.6)	0 (0.0)	9 (16.1)
Lipase increased	1 (5.0)	2 (10.0)	2 (10.0)	0 (0.0)	5 (25.0)	3 (20.0)	1 (6.7)	1 (6.7)	0 (0.0)	5 (33.3)	3 (5.4)	0 (0.0)	5 (8.9)	2 (3.6)	10 (17.9)
Metabolism and nutrition disorders															
Hyponatremia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)	0 (0.0)	1 (6.7)	1 (6.7)	4 (26.7)	7 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	7 (12.5)
Hypophosphatemia	0 (0.0)	0 (0.0)	4 (20.0)	0 (0.0)	4 (20.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (6.7)	0 (0.0)	3 (5.4)	0 (0.0)	0 (0.0)	3 (5.4)
Musculoskeletal and connective tissue disorders															
Arthralgia	3 (15.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (15.0)	3 (20.0)	1 (6.7)	0 (0.0)	0 (0.0)	4 (26.7)	4 (7.1)	2 (3.6)	1 (1.8)	0 (0.0)	7 (12.5)
Myalgia	3 (15.0)	2 (10.0)	0 (0.0)	0 (0.0)	5 (25.0)	2 (13.3)	1 (6.7)	0 (0.0)	0 (0.0)	3 (20.0)	4 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (7.1)
Nervous system disorders															
Headache	3 (15.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (15.0)	2 (13.3)	3 (20.0)	0 (0.0)	0 (0.0)	5 (33.3)	5 (8.9)	1 (1.8)	0 (0.0)	0 (0.0)	6 (10.7)
Skin and subcutaneous tissue disorders															
Pruritus	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	3 (20.0)	2 (13.3)	0 (0.0)	0 (0.0)	5 (33.3)	9 (16.1)	1 (1.8)	0 (0.0)	0 (0.0)	10 (17.9)

Safety population. Treatment was received for each cohort. Patients with mCRPC were in Cohorts 1A-mCRPC through 9A-mCRPC and 3B-mCRPC. Treatment included AdC68 vector 4×10^{11} VP (Cohort 1A-mCRPC only) or 6×10^{11} VP (all other cohorts), plasmid DNA boosts 5 mg (all cohorts), tremelimumab 40 mg (Cohort 9A-mCRPC only) or 80 mg (all other cohorts), and sasanlimab 130 mg (Cohorts 6A-mCRPC and 9A-mCRPC) or 300 mg (Cohorts 7A-mCRPC and 3B-mCRPC). Patients with BCR in Cohort 1B-BCR were treated with AdC68 vector 6×10^{11} VP, plasmid DNA boosts 5 mg, and tremelimumab 80 mg. Patients with BCR in Cohort 5B-BCR were treated with AdC68 vector 6×10^{11} VP, plasmid DNA boosts 5 mg, tremelimumab 80 mg, and sasanlimab 130 mg.
Grade 5 treatment-related AEs occurred in two patients: pulmonary embolism in a patient with mCRPC, and immune-mediated myocarditis in a patient from Cohort 5B-BCR.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCR, biochemical recurrence; mCRPC, metastatic castration-resistant prostate cancer; TRAE, treatment-related adverse event; VP, viral particle.

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Grade 3 colitis and diarrhea; Grade 4 myasthenia gravis (DLT), and Grade 5 pulmonary embolism.

The irAEs occurred in 23 (41.1%) patients, 12 (21.4%) had Grade 3 irAEs (colitis, rash, hepatitis, and myositis), 1 (1.8%) had Grade 4 irAEs of myasthenia gravis and myositis, and none had Grade 5 irAEs. The most common irAEs were thyroid dysfunction (23.2%), hypothyroidism (12.5%), hyperthyroidism (10.7%), and diarrhea (10.7%).

BCR

In patients with BCR (Cohorts 1B-BCR and 5B-BCR), all-causality AEs were reported in 20 (100%) and 15 (100%) patients, and SAEs were reported in 2 (10.0%) and 6 (40.0%) patients. The most common all-causality AEs were fatigue (60.0%), influenza-like illness (60.0%), and arthralgia (40.0%) in Cohort 1B-BCR, and diarrhea (53.3%), fatigue (53.3%), and increased aspartate aminotransferase (AST; 46.7%) in Cohort 5B-BCR. TRAEs and serious TRAEs were reported in 19 (95.0%) and zero patients in Cohort 1B-BCR, and 15 (100%) and 6 (40.0%) patients in Cohort 5B-BCR. The most common TRAEs were influenza-like illness (60.0%), fatigue (45.0%), and injection site pain (30.0%) in Cohort 1B-BCR; and fatigue (53.3%), increased AST (40.0%), and diarrhea (40.0%) in Cohort 5B-BCR. In Cohorts 1B-BCR and 5B-BCR, Grade 3 or 4 TRAEs developed in 6 (30.0%) and 9 (60.0%) patients, and Grade 5 TRAE in 0 and 1 (immune-mediated myocarditis) patient (table 2).

In Cohort 1B-BCR, 1 (5.0%) patient discontinued due to a Grade 4 TRAE of uveitis. In Cohort 5B-BCR, of the 10 (66.7%) patients who permanently discontinued due to AEs, 9 (60.0%) patients had TRAEs. The non-serious TRAEs leading to discontinuation were Grade 2 muscular weakness, diarrhea, and hyperthyroidism; and Grade 3 alanine aminotransferase increased, fatigue, influenza-like illness, and a non-TRAE of right kidney clear cell carcinoma. The treatment-related SAEs leading to discontinuation were Grade 3 hypothyroidism and syncope, Grade 4 colitis and immune-related myocarditis, and Grade 5 immune-related myocarditis.

The irAEs occurred in 4 (20.0%) patients in Cohort 1B-BCR, with 1 patient having Grade 4 immune-related uveitis and no other Grade ≥3 irAEs. In Cohort 5B-BCR, 12 (80.0%) patients had irAEs, with immune-related thyroid dysfunction as the most common (8, 53.3%); of the 12 patients, 4 had Grade 3 irAEs (rash, colitis, adrenal insufficiency, pituitary dysfunction, thyroid dysfunction, and hepatitis), 2 had Grade 4 irAEs (colitis, hepatitis, myocarditis, and myositis), and 1 had Grade 5 immune-mediated myocarditis.

Death

Overall, 6 (6.6%) patients died; 2 (2.2%, immune-mediated myocarditis and pulmonary embolism) were considered treatment-related. The six TEAEs with fatal outcome included neoplasm progression in two patients (one patient with mCRPC in Cohort 3B-mCRPC and one patient with mCRPC in Cohort 7A-mCRPC), sepsis in one patient with mCRPC in Cohort 3B-mCRPC, immune-mediated myocarditis in one patient with BCR in Cohort 5B-BCR, and pulmonary embolism in one patient with mCRPC in Cohort 6A-mCRPC.

Clinical response

mCRPC

Of 54 patients with mCRPC in the modified intention-to-treat population inclusive of those without RECIST measurable disease (n=30, 55.6%) (table 1), at a median follow-up of 8.5 (range 1–51) months, 1 patient in Cohort 3B-mCRPC had a confirmed complete response (CR, the CR was a 1.5-cm para-aortic lymph node in this patient who withdrew from study therapy early after Grade 3 diarrhea), 1 patient each in Cohorts 7A-mCRPC and 3B-mCRPC had a confirmed partial response (PR), and 8 (4 in Cohort 3B-mCRPC, 1 each in Cohorts 2A-mCRPC, 3A-mCRPC, 6A-mCRPC, and 7A-mCRPC) had stable disease (SD) (figure 2, online supplemental table S1). ORR was 5.6% (n/N=3/54, 95% CI: 1.2% to 15.4%) and disease control (confirmed and unconfirmed CR+PR+SD+non-CR/non-progressive disease) rate was 29.6%. Of the 24 (44.4%) patients with mCPRC who had RECIST measurable disease at baseline (table 1), the ORR was 12.5% (3/24). The median (range) duration of SD was 5.4 (1.4–13.3) months, the median (range) DOR (CR+PR) was 5.6 (3.9–7.4) months, and the median (95% CI) rPFS (defined as time from start date of treatment to the date of first documented progression of disease by PCWG3-defined bone progression or RECIST, or death due to any cause, whichever came first) was 5.6 (3.5 to not estimable) months in patients with mCRPC (online supplemental figure S1). Three patients had progression in bone per PCWG3 criteria. Overall, the PSA-50 response rate was 7.4% (4/54, based on PSA assessments performed at the study center's local laboratory) (table 3). The best response for PSA from baseline is shown in online supplemental figure S2.

Patients with mCRPC treated at the recommended phase 2 dose (RP2D, that is, Cohorts 7A-mCRPC and 3B-mCRPC) had an ORR of 9.4% (n/N=3/32, 95% CI: 2.0% to 25.0%). The median DOR was 5.6 (3.9–7.4) months, the median rPFS was 5.6 (95% CI: 2.0 to NE) months, and the rPFS rate was 45.5% (95% CI: 24.9% to 64.1%) at 6 months and 30.4% (95% CI: 7.6% to 57.6%) at 12 months. The PSA-50 response rate was 6.3% (2/32, local laboratory assessments). Measurable disease at baseline was confirmed in 18 (56.3%) out of the 32 patients with mCRPC in these two cohorts. If only including these 18 patients, ORR was 16.7% (n/N=3/18, 95% CI: 3.6% to 41.4%).

BCR

Of patients with BCR, the PSA-50 response rate was 25.0% (5/20) in Cohort 1B-BCR and 26.7% (4/15) in Cohort 5B-BCR, and the median (range) duration of PSA-50 response was 10.1 (6.9–28.8) months and 3.9 (1.9–4.2)

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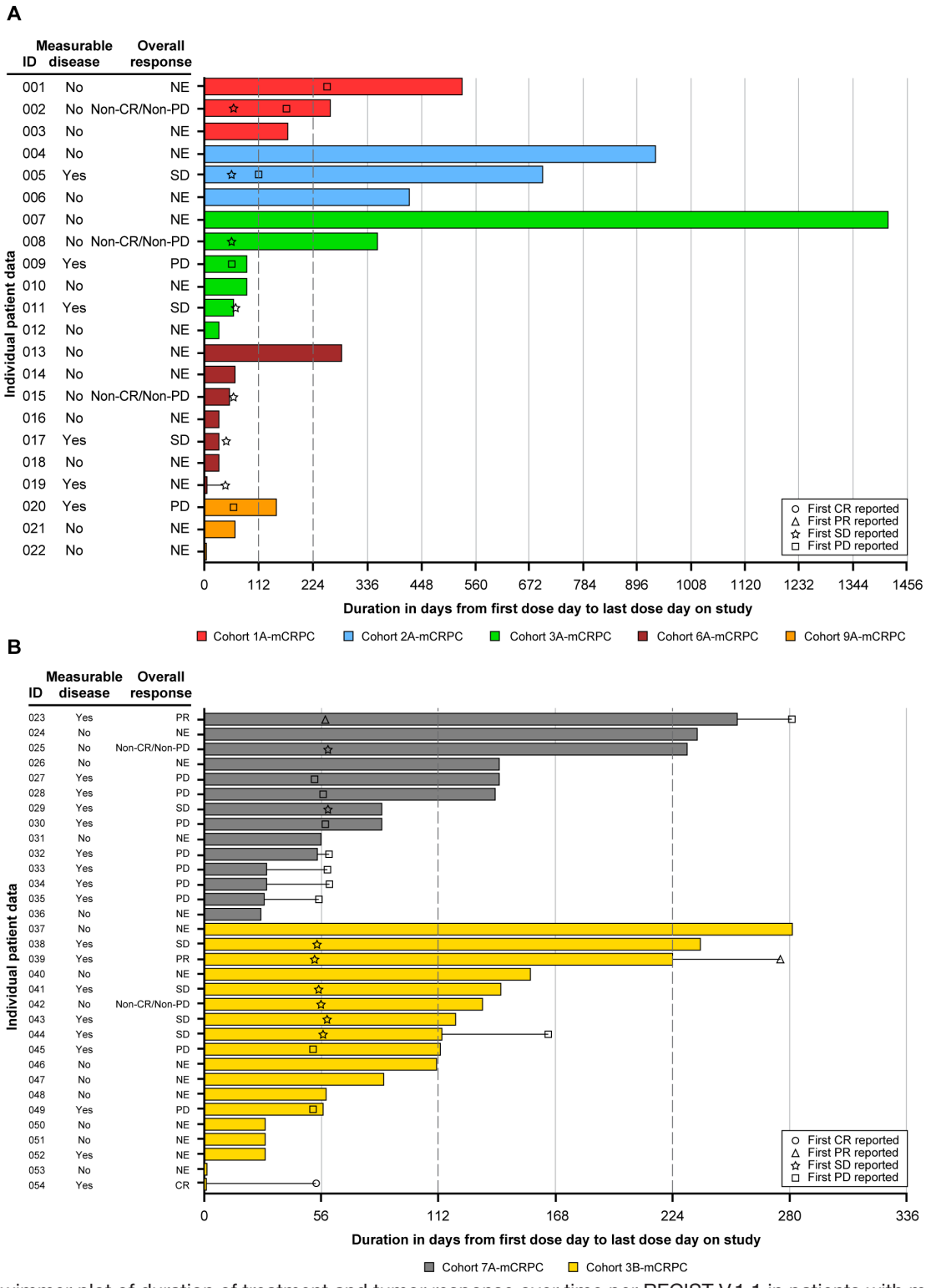

Figure 2 Swimmer plot of duration of treatment and tumor response over time per RECIST V.1.1 in patients with mCRPC. (A) Patients with mCRPC excluding Cohorts 7A-mCRPC and 3B-mCRPC. (B) Patients with mCRPC in Cohorts 7A-mCRPC and 3B-mCRPC.

mITT population. Treatment of each cohort see the footnote of table 2. Measurable disease at baseline was defined as showing new or progressive metastatic lymph node and/or local recurrence or visceral metastatic disease (with the exception of metastases to the liver) on CT or MRI scans. Duration of treatment was defined as (last dose date–first dose date+1). One patient from Cohort 3B-mCRPC achieved a confirmed CR (CR was 1.5-cm para-aortic lymph node, patient withdrew from study therapy after early Grade 3 diarrhea).

CR, complete response; mCRPC, metastatic castration-resistant prostate cancer; mITT, modified intention-to-treat; NE, not evaluated; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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Table 3 Summary of PSA parameters

	BCR		
	Cohort 1B-BCR (N=20)	Cohort 5B-BCR (N=15)	All mCRPC (N=54)
N (%) of patients achieving local PSA-50 response rate	5 (25.0)	4 (26.7)	4 (7.4)
Median (range) duration of PSA-50 response, months	10.1 (6.9 to 28.8)	3.9 (1.9 to 4.2)	4.6 (1.2 to 45.2)
Median (range) time to PSA-50 response, months	8.3 (1.9 to 10.4)	2.8 (1.9 to 6.4)	3.2 (0.9 to 5.5)
Median (range) PSA doubling time at baseline, months	1.768 (–10.04 to 7.73)	1.615 (–10.28 to 20.72)	1.3 (–80.6 to 14.3)
Median (range) change from baseline in PSA doubling time, months	4.800 (–31.92 to 44.66)	8.078 (–58.53 to 23.27)	1.3 (–2034.3 to 85.23)

Data were for the pharmacodynamic population. Treatment of each cohort see the footnote of table 2. A successful PSA response was defined as a decline from baseline PSA by at least 50%. A PSA response was confirmed by a second consecutive value at least 3 weeks later. Baseline was defined as the most recent non-missing value prior to dosing.
For other PSA parameters, baseline values were calculated from the PSA values at screening and Cycle 1 Day 1. PSA doubling time at the post-treatment visit was calculated from Cycle 1 Day 1 and all post-treatment PSA values.
BCR, biochemical recurrence; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

months, respectively (table 3). Minimum percent change from baseline for PSA assessed at local laboratory are shown in online supplemental figure S1.

PK

Serum PK parameters determined included the maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration versus time curve (AUC) from time 0 to 672 hours ($AUC_{0–672h}$), and observed accumulation ratio for trough concentrations after multiple dosing ($R_{ac,\ Ctrough}$). $AUC_{0–672h}$, C_{max}, and accumulation ratio $R_{ac,\ Ctrough}$ were presented as geometric mean (geometric % coefficient of variation), and T_{max} was presented as median (range).

For tremelimumab administered at 80 mg SC (n=6), on Cycle 1 Day 1, $AUC_{0–672h}$ was 2,389,000 (32) ng×hour/mL; C_{max} was 4360 (31) ng/mL; and T_{max} was 307 (165–477) hours; on Cycle 2 Day 1 (n=33), $R_{ac,\ Ctrough}$ was 1.454 (73). For sasanlimab administered at 300 mg SC, on Cycle 1 Day 1, $AUC_{0–627h}$ (n=13) was 10,250,000 (44) ng×hour/mL; C_{max} (n=14) was 19,960 (40) ng/mL; and T_{max} (n=14) was 188 (67.3–378) hours; on Cycle 2 Day 1, $R_{ac,\ Ctrough}$(n=15) was 0.7794 (220). For sasanlimab administered at 130 mg SC (n=11), on Cycle 1 Day 1, $AUC_{0–627h}$ was 4,289,000 (44) ng×hour/mL; C_{max} was 8612 (44) ng/mL; and T_{max} was 165 (71.0–380) hours; on Cycle 2 Day 1, $R_{ac,\ Ctrough}$ (n=8) was 0.2734 (253) (table 4).

Immunogenicity and PD

A total of 84 patients were evaluable for ADA against tremelimumab. Of these 84 patients, 17 (20.2%) were tremelimumab-induced ADA-positive, with a median onset at Day 84 (sampling time for ADA assessments see online supplemental materials). Of the 17 patients who were ADA-positive and the 67 patients who were ADA-negative, the numbers of patients who experienced Type I hypersensitivity reaction were 2 (11.8%) and 9 (13.4%), respectively. A Type I hypersensitivity reaction was defined as any event occurring on the same day of drug injection, including headache, nausea, fever, chills, dizziness, pruritus, musculoskeletal chest pain, non-cardiac chest pain, and back pain. Injection site reactions were experienced in 4 (23.5%) and 5 (7.5%) patients, respectively.

Of 58 patients evaluable for ADA against sasanlimab, 13 (22.4%) patients were sasanlimab-induced/boosted ADA-positive, with a median onset at Day 142. Of these 13 patients who were ADA-positive and the 45 patients who were ADA-negative, patients who experienced Type I hypersensitivity reaction were 3 (23.1%) and 13 (28.9%), respectively; injection site reactions were experienced in 0 and 6 (13.3%) patients, respectively. Three patients had ADA for both tremelimumab and sasanlimab. There was no apparent effect of ADA on exposure to tremelimumab or sasanlimab.

T-cell responses to ≥1 antigen (PSMA, PSCA, or PSA), based on ELISpot measurements of IFN-γ release, were seen in all patients across cohorts assessed in BCR and mCRPC. The range of positive T-cell responses for each antigen were: PSMA 85.7% to 90.9%, PSCA 71.4% to 90.9%, and PSA 72.7% to 92.9% (online supplemental table S2). T-cell response in patients with mCRPC (Cohorts 7A-mCRPC, 3B-mCRPC) and BCR (Cohort 5B-BCR) treated at the RP2D are shown in figure 3 and online supplemental figures S3 and S4.

DISCUSSION

This phase 1 open-label study evaluated the safety, antitumor activity, PK, and PD of increasing dose levels of three PrCa VBIR components alone and in combination with increasing doses of sasanlimab. An RP2D was

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Table 4 Serum tremelimumab and sasanlimab pharmacokinetics parameters

	Tremelimumab 80 mg SC (N=6)	Sasanlimab 300 mg SC (N=14)	Sasanlimab 130 mg SC (N=11)
$AUC_{0\text{-}672h}$, ng×hour/mL			
n	6	13	11
Geometric mean (geometric CV, %)	2,389,000 (32)	10,250,000 (44)	4,289,000 (44)
Arithmetic mean (SD)	2,480,000 (666,930)	11,040,000 (4,117,100)	4,621,000 (1,778,300)
Median (range)	2,645,000 (1,330,000–3,270,000)	9,810,000 (3,940,000–17,600,000)	4,410,000 (1,820,000–8,010,000)
C_{max}, ng/mL			
n	6	14	11
Geometric mean (geometric CV, %)	4360 (31)	19,960 (40)	8612 (44)
Arithmetic mean (SD)	4520 (1246.8)	21,250 (7241.6)	9266 (3491.3)
Median (range)	4635 (2600–6100)	21,050 (8970–31,100)	9710 (3540–16,300)
T_{max}, hour			
n	6	14	11
Median (range)	307 (165–477)	188 (67.3–378)	165 (71.0–380)
$R_{ac,\ Ctrough}$	N=35	N=16	N=8
n	33	15	8
Geometric mean (geometric CV, %)	1.454 (73)	0.7794 (220)	0.2734 (253)
Arithmetic mean (SD)	1.671 (0.7129)	1.269 (0.8723)	0.7980 (1.3647)
Median (range)	1.530 (0.101–3.10)	1.210 (0.0507–2.85)	0.1540 (0.0988–3.89)

$AUC_{0\text{-}672h}$, area under the serum concentration-time profile from time 0 to 672 hours; C_{max}, maximum serum concentration; n, number of patients included in the summary statistics; N, total number of patients in the indicated population; $R_{ac,\ Ctrough}$, observed accumulation ratio for C_{trough} at Day 29 to Day 1; T_{max}, time for C_{max}.
AUC, area under the curve; CV, coefficient of variation; SC, subcutaneous.

then evaluated in patients with mCRPC, who continued on ADT, and in high-risk BCR, where patients were not treated with ADT. These seemingly disparate populations were selected to evaluate what the optimal recurrent PC population for cancer vaccination should be. It has been theorized that earlier clinical states of PC, such as BCR (rising PSA but no metastatic disease detected on conventional imaging) may harbor a less immune-suppressed microenvironment, which might allow an antitumor response to vaccination. In the current study, there was no meaningful tumor regression (based on RECIST) in patients with mCRPC; however, an encouraging signal of activity was observed in patients with BCR. The observed one death related to myocarditis in patients with BCR was concerning given that this population is at low risk for cancer-associated death. However, increasing dose levels of the study treatment were generally tolerated, with overall toxicities comparable to other ICI combination trials in patients with PC.[28 29]

Suggestive evidence for increased immunoresponsiveness in early-stage PC can be seen in neoadjuvant trials. In the preoperative setting, studies have demonstrated that ADT rapidly changes the tumor microenvironment with an influx of T regulatory cells.[30] By comparison, a pilot neoadjuvant trial of PROSTVAC (vaccine using poxviral-based vectors with transgenes for PSA and three costimulatory molecules for T cells) without ADT demonstrated a decrease in tumor-infiltrating lymphocytes T regulatory cells and increase in T effector helper cells (CD4+FOXP3−).[31] Similarly, neoadjuvant sipuleucel-T (an autologous dendritic cell vaccine using PBMCs activated ex vivo with PAP and fused with granulocyte-monocyte colony stimulating factor) without ADT before prostatectomy led to a threefold increase in CD4+FOXP3 T-cell infiltrate.[32] In a trial of patients with BCR, T-cell responses were generally greater when vaccination with sipuleucel-T was administered before ADT compared with the reverse.[33] Collectively, the data suggest that there may be advantages to vaccination in the absence of ADT, which is a potential approach in the BCR population. In this setting, both ADT and monitoring alone are standards of care, unlike in mCRPC, where obtaining castrate levels of testosterone (ie, ADT) is an essential component of therapy.

The subpopulation of patients with BCR in this trial had PSA reductions of >50% with durable response (those patients with BCR who received one ICI and VBIR had a median duration of 6.9 months; those patients with BCR who received two ICIs and VBIR had a median duration of 4.1 months). The PSA-50 rates were similar in those who received one versus two ICIs as part of PrCa VBIR, although the time to which PSA-50 was achieved was faster for those patients treated with two ICIs than one ICI. In those patients with mCRPC treated at the same expansion

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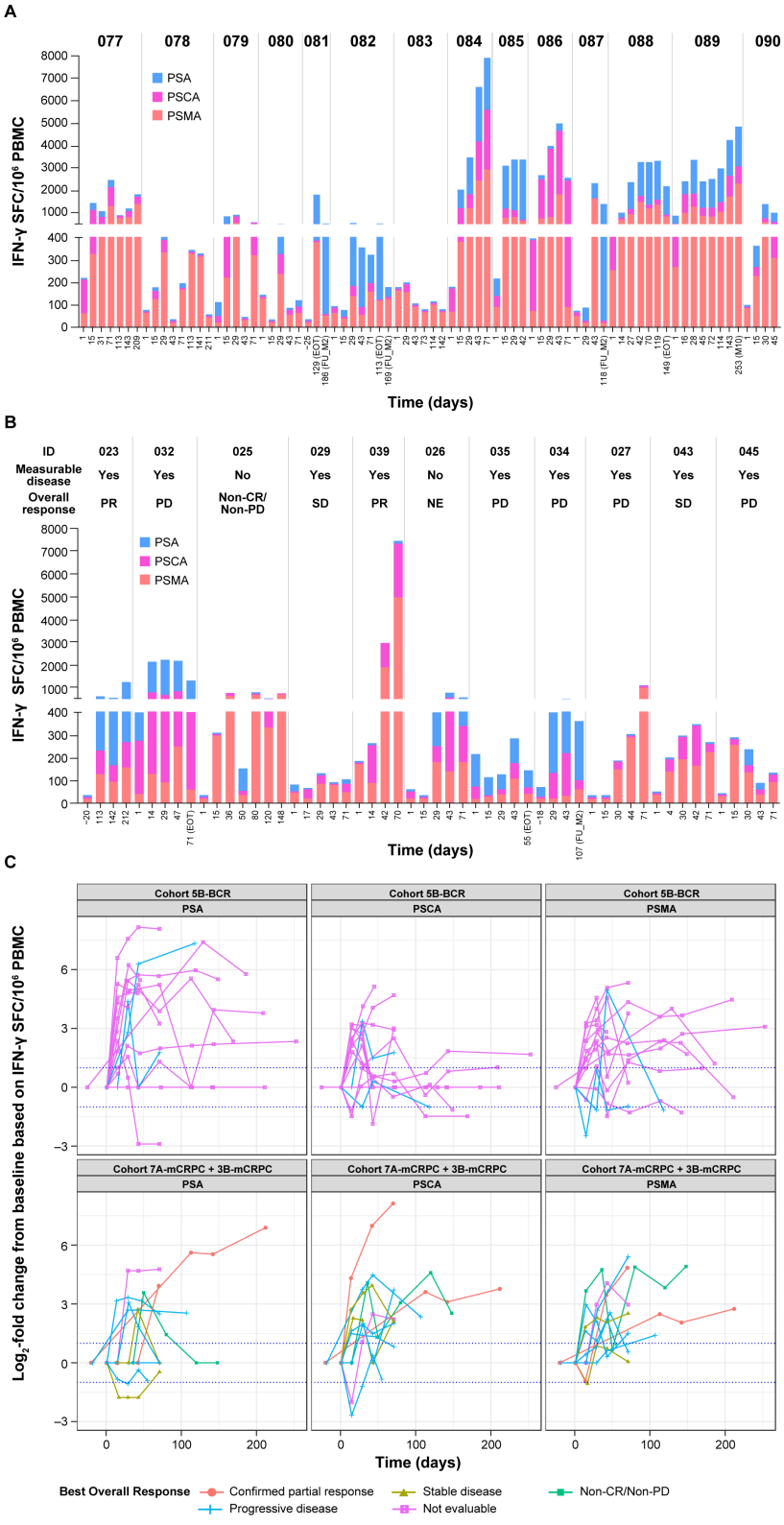

Figure 3 T-cell immune response. (A) Patients with BCR in Cohort 5B. (B) Patients with mCRPC in Cohorts 7A and 3B. (C) Fold changes from baseline of each antigen. Patients with mCRPC in Cohorts 7A-mCRPC and 3B-mCRPC were treated at the RP2D, which was AdC68 6×10^{11} VP, the DNA booster vaccine, tremelimumab 80 mg, and sasanlimab 300 mg. For patients with BCR in Cohort 5B-BCR, the treatment was AdC68 6×10^{11} VP, the DNA booster vaccine, tremelimumab 80 mg, and sasanlimab 130 mg.

BCR, biochemical recurrence; CR, complete response; EOT, end of treatment; IFN, interferon; mCRPC, metastatic castration-resistant prostate cancer; NE, not evaluated; PBMC, peripheral blood mononuclear cell; PD, progressive disease; PR, partial response; PSA, prostate-specific antigen; PSCA, prostate stem cell antigen; PSMA, prostate-specific membrane antigen; RP2D, recommended phase 2 dose; SD, stable disease; SFC, spot-forming cells; VP, viral particle.

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dose (Cohorts 7A-mCRPC and 3B-mCRPC, n=32), the ORR was 9.4% (16.7% for the 18 patients with measurable disease at baseline) and the estimated median rPFS was 5.6 months.

In mCRPC, a disease that is dominated by bone metastases that are not measurable by RECIST, outcomes such as ORR underestimate the effectiveness of therapy. In comparison, measurement of rPFS, which incorporates bone assessments per PCWG3 criteria, is a more accurate reflection of disease control in PC. While comparison to historic databases has significant limitations, previously reported rPFS rates for patients with mCRPC and progression on an androgen receptor signaling inhibitor, subsequently treated with chemotherapy, have ranged from 3.7 months[34] to 5.2 months.[35] The CARD trial showed that in patients with mCRPC who were previously treated with docetaxel and abiraterone or enzalutamide, the median rPFS of the cabazitaxel group was 8.0 months and the comparator (an androgen signaling-targeted inhibitor) group was 3.7 months.[36] As such, the 5.6-month rPFS in the current study appears somewhat favorable. In general, the biologic/therapeutic effects of cancer vaccines may take longer to be observed, and may carry durable benefit going forward, and thus require longer follow-up time periods than typically expected with conventional treatment. For patients with BCR, metastasis-free survival would take many years of follow-up, which is an obvious limitation of efficacy analyses in an early-phase study.

PrCa VBIR uses multiple antigens as part of the prime/boost strategy to improve clinical efficacy. All patients demonstrated post-treatment T-cell responses to ≥1 antigen (PSMA, PSCA, or PSA; figure 3), suggestive of immune activation by PrCa VBIR. The ICIs were administered concurrently with vaccination priming and boosting in this trial, which may account for enhanced T-cell activation. Nevertheless, a correlation between T-cell responses and drug regimen or tumor control (rPFS) was not observed, possibly due to limited data. T-cell response against tumor-associated antigens alone may not be sufficient for conferring antitumor activity or clinical benefit, as shown in the phase 3 PROSTVAC trial[19]; potential underlying reasons include tumor heterogeneity rendering some areas not accessible by the administered vaccine and immune escape due to exhaustion of T effector cells or upregulation of additional inhibitory molecules such as lymphocyte-activation gene-3 and T-cell immunoglobulin and mucin domain-containing protein-3, which are not covered by the treatment regimens.[37] The novel delivery by electroporation of pDNA encoding selected antigens depends on the induction of a transient state of cell membrane permeability. Delivery by electroporation has been demonstrated to increase DNA vaccine potency both preclinically and clinically.[38–42]

The safety profile for PrCa VBIR+/− anti-PD-1 reflected common non-immunological TRAEs as well as irAEs. Approximately 40% of patients with mCRPC experienced an irAE, most commonly thyroid dysfunction, colitis, and rash. In patients with BCR, one (Cohort 1B-BCR, n=20) versus two (Cohort 5B-BCR, n=15) ICIs were evaluated with vaccination, and while the numbers are small, there were more irAEs in the cohort receiving dual ICIs (20% one ICI vs 80% two ICIs). The irAEs also led to higher discontinuation rates in the dual-ICI cohorts relative to single ICI (5% vs 60%).

Although more irAEs may be anticipated when administering two as compared with a single ICI, the magnitude of the difference (two-fold) was not expected. The high percentage of irAEs with dual checkpoint inhibition plus vaccination in the patient with BCR population could limit the use of dual ICIs in combination with a vaccine. The selection of an anti-CTLA-4 rather than anti-PD-1 for the single-agent ICI cohorts was based on preclinical data demonstrating amplified T-cell responses with tremelimumab.[27] Administration of ICIs SC was intended to amplify nodal antigen presenting cell and T-cell activity to draining lymph nodes, although nodal immune cell activity was not studied. In addition to enhancing potential activation at the site of draining lymph nodes with SC administration, it had been postulated that there may be less systemic toxicity. With the caveats of a small study, however, there was no clear signal of improved safety or preferred PK with SC ICI administration compared with historic intravenous administration.[28]

In summary, in this phase 1, open-label study, PrCa VBIR overall demonstrated safety signals similar to other ICI combination trials in mCRPC, with a modestly prolonged rPFS that did not warrant further study; patients with BCR (who did not receive concurrent ADT) treated with dual ICI had more irAEs than those with mCRPC, but some had prompt and durable PSA-50 responses without the use of ADT, which is noteworthy, as many patients seek an ADT-sparing approach. Future trials using immunotherapy combinations with a dual checkpoint inhibitor backbone in BCR should be carried out with careful oversight in this population with a long natural history of disease, as the potential risks must be carefully balanced with potential benefit. The sponsor will not develop PrCa VBIR further for strategic reasons; however, this study provides evidence for proof-of-principle that immunotherapy using vaccine strategies should be further studied in PC.

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Acknowledgements This work was sponsored by Pfizer. Medical writing support was provided by Anne Marie McGonigal, PhD, and Shuang Li, PhD, of Engage Scientific Solutions and funded by Pfizer.

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Contributors All authors were involved in the trial conception/design, or the acquisition, analysis, or interpretation of data. All authors contributed to the drafting of the manuscript and approved the final version. The authors were thankful for the statistical programming support provided by Fang Yuan at Pfizer Global Biometrics and Data Management. This paper is dedicated to the memory of Dr Nicholas Vogelzang, who died in September 2022 during its revision. Dr Vogelzang was strongly committed to the improvement of cancer patients' lives through his untiring work in the field. His enthusiasm and contributions will be greatly missed.

Competing interests This work was sponsored by Pfizer. KAA: PI/research funding to institution: Amgen, AstraZeneca, CytomX, Eli Lilly and Company, GlaxoSmithKline, Parker Institute for Cancer Immunotherapy, Pfizer, Trishula. CSH: consulting fees: Astellas, AstraZeneca, Bayer, Blue Earth Diagnostics, Carrick Therapeutics, Clovis Oncology, Ferring Pharmaceuticals, Genentech, Hinova, Janssen, Menarini, Merck Sharp & Dohme, Myovant Sciences, Novartis, Pfizer; contracted research support: Aragon Pharmaceuticals, Astellas, AstraZeneca, Bayer, Clovis Oncology, eFFECTOR Therapeutics, Emergent BioSolutions, Ferring Pharmaceuticals, Medivation, Roche; ownership interest: CTI BioPharma; honoraria: Astellas. LN and X-HZ: nothing to disclose. LJA: consulting or advisory role: AADi; research funding (institution as recipient): Amgen, Astellas, Aveo, Bayer, BioNTech, Bristol Myers Squibb, Calithera Biosciences, Eisai, Eli Lilly and Company, Epizyme, Exelixis, Genentech/Roche, Inovio, Merck, Novartis, Peloton Therapeutics, Pfizer, Seattle Genetics, Surface Oncology; other relationship: Pfizer; uncompensated relationships: Exelixis. TZ: PI/research funding: AbbVie/StemCentrx, Acerta, Astellas, AstraZeneca, Eli Lilly and Company, Janssen, Merck, Merrimack, Mirati Therapeutics, Novartis, OmniSeq, Personal Genome Diagnostics, Pfizer, Regeneron; speaker: Genomic Health (end 2020), Sanofi-Aventis (end 2020); advisory board/consultant: Amgen, Aptitude Health, AstraZeneca, Aveo, Bayer, Bristol Myers Squibb, Calithera Biosciences, Clinical Care Options, Dendreon, Eisai, Eli Lilly and Company, Exelixis, Janssen, Merck, MJH Associates, Peerview, Pfizer, Pharmacyclics, QED Therapeutics, Sanofi-Aventis, Seattle Genetics, Vaniam; employee/stockholder: Archimmune Therapeutics (spouse), Capio Biosciences (spouse), Nanorobotics (spouse). HB: consultancy: Caris, Idera, Myovant, Novocure, Tracon; speaker's bureau: Guardant360. NJV: PI/research funding: none; advisory boards: Caris, Clovis, Eisai, Fujifilm, Gilead Sciences, Merck, OnQuality Pharmaceuticals, Pfizer-Myovant, Sanofi-Aventis, Seagen; speaker's bureau: Aveo, Bayer, Caris, Janssen, PER, Pfizer-Myovant, Sanofi, Seagen. SMP: PI funding: Janssen, Merck, Pfizer, UroGen Pharma. MTS: paid consultant and/or received honoraria: AstraZeneca, Pharmaln, Resverlogix, Sanofi; research funding to institution: Ambrx, AstraZeneca, Bristol Myers Squibb, F. Hoffman-La Roche, Immunomedics, Janssen, Madison Vaccines, Merck, Pfizer, SignalOne Bio, Tmunity, Zenith Epigenetics. RAM: research funding: Bayer. SB, NC, OB, RL, MK, I-MW, JZ, S-YT, and KAK: employees of Pfizer with stock and/or stock options. KC, HC, and RH: employees of Pfizer at the time of the study. DPP: stock and other ownership interests: Bellicum Pharmaceuticals, TYME Technologies; consulting or advisory role: Advanced Accelerator Applications, Amgen, Astellas, AstraZeneca, Bayer, Bicycle Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Eli Lilly and Company, Exelixis, Gilead Sciences, Incyte, Ipsen, Janssen, Mirati Therapeutics, Monopteros Therapeutics, Pfizer, Pharmacyclics, Regeneron, Roche, Seattle Genetics, UroGen Pharma; research funding: Advanced Accelerator Applications (Inst), Agensys (Inst), Astellas Medivation (Inst), AstraZeneca (Inst), Bayer (Inst), BioXcel Therapeutics (Inst), Bristol Myers Squibb (Inst), Clovis Oncology (Inst), Eisai (Inst), Endocyte (Inst), Eli Lilly and Company (Inst), Genentech (Inst), Gilead Sciences (Inst), Innocrin Pharma (Inst), MedImmune (Inst), Medivation (Inst), Merck (Inst), Mirati Therapeutics (Inst), Novartis (Inst), Pfizer (Inst), Progenics (Inst), Replimune (Inst), Roche (Inst), Sanofi (Inst), Seattle Genetics (Inst); expert testimony: Celgene, Sanofi.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Memorial Sloan Kettering Cancer Center Institutional Review Board (15-325A), the Yale University Institutional Review Board (1512016984), the Western Institutional Review Board (20151318), the Duke University Health System Institutional Review Board (00067872), the University of Pittsburgh IRB (15-118), the National Cancer Institute IRB (16C0079), the Thomas Jefferson University Office of Human Research (16C.471), the Atlantic Health System IRB (1295262), and the Biomedical Research Alliance of New York (18-11-398-03).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): a multicentre, open-label, phase 2 trial

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Lancet Oncol 2022; 23: 362–73

Published Online February 4, 2022 https://doi.org/10.1016/S1470-2045(21)00757-9

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Summary

Background Metastatic castration-resistant prostate cancers are enriched for DNA repair gene defects (DRDs) that can be susceptible to synthetic lethality through inhibition of PARP proteins. We evaluated the anti-tumour activity and safety of the PARP inhibitor niraparib in patients with metastatic castration-resistant prostate cancers and DRDs who progressed on previous treatment with an androgen signalling inhibitor and a taxane.

Methods In this multicentre, open-label, single-arm, phase 2 study, patients aged at least 18 years with histologically confirmed metastatic castration-resistant prostate cancer (mixed histology accepted, with the exception of the small cell pure phenotype) and DRDs (assessed in blood, tumour tissue, or saliva), with progression on a previous next-generation androgen signalling inhibitor and a taxane per Response Evaluation Criteria in Solid Tumors 1.1 or Prostate Cancer Working Group 3 criteria and an Eastern Cooperative Oncology Group performance status of 0–2, were eligible. Enrolled patients received niraparib 300 mg orally once daily until treatment discontinuation, death, or study termination. For the final study analysis, all patients who received at least one dose of study drug were included in the safety analysis population; patients with germline pathogenic or somatic biallelic pathogenic alterations in *BRCA1* or *BRCA2* (*BRCA* cohort) or biallelic alterations in other prespecified DRDs (non-*BRCA* cohort) were included in the efficacy analysis population. The primary endpoint was objective response rate in patients with *BRCA* alterations and measurable disease (measurable *BRCA* cohort). This study is registered with ClinicalTrials.gov, NCT02854436.

Findings Between Sept 28, 2016, and June 26, 2020, 289 patients were enrolled, of whom 182 (63%) had received three or more systemic therapies for prostate cancer. 223 (77%) of 289 patients were included in the overall efficacy analysis population, which included *BRCA* (n=142) and non-*BRCA* (n=81) cohorts. At final analysis, with a median follow-up of 10·0 months (IQR 6·6–13·3), the objective response rate in the measurable *BRCA* cohort (n=76) was 34·2% (95% CI 23·7–46·0). In the safety analysis population, the most common treatment-emergent adverse events of any grade were nausea (169 [58%] of 289), anaemia (156 [54%]), and vomiting (111 [38%]); the most common grade 3 or worse events were haematological (anaemia in 95 [33%] of 289; thrombocytopenia in 47 [16%]; and neutropenia in 28 [10%]). Of 134 (46%) of 289 patients with at least one serious treatment-emergent adverse event, the most common were also haematological (thrombocytopenia in 17 [6%] and anaemia in 13 [4%]). Two adverse events with fatal outcome (one patient with urosepsis in the *BRCA* cohort and one patient with sepsis in the non-*BRCA* cohort) were deemed possibly related to niraparib treatment.

Interpretation Niraparib is tolerable and shows anti-tumour activity in heavily pretreated patients with metastatic castration-resistant prostate cancer and DRDs, particularly in those with *BRCA* alterations.

Funding Janssen Research & Development.

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Introduction

Patients with metastatic castration-resistant prostate cancer who have progressed on a next-generation androgen signalling inhibitor and taxane chemotherapy (docetaxel, cabazitaxel, or both) have few treatment options.[1,2] DNA repair gene defects (DRDs), seen in approximately 12–23% of tumours in patients with metastatic prostate cancer when considering both germline and somatic alterations,[3–5] are associated with cancer development, aggressiveness, and progression.[6] These DRD-altered tumours are not only frequent in metastatic disease, but are also associated with poor prognosis and potential resistance to systemic therapies.[7] Developing more effective treatments to improve survival for these patients is therefore a critical unmet need.

Cancers with DRDs, particularly those with defects in homologous recombination repair, are highly sensitive to the blockade of DNA single-strand break repair via inhibition of the PARP family of nuclear proteins, which

Research in context

Evidence before this study

At the time that the GALAHAD study was designed, docetaxel and the androgen signalling inhibitors abiraterone acetate and enzalutamide were the only established treatment options for patients with metastatic castration-resistant prostate cancer, but there remained a subset of patients who either did not initially respond or became refractory to these agents and for whom no approved therapeutic options were available. Given that genomic instability is a hallmark of cancer that has been documented in this patient population, we evaluated the medical literature by searching PubMed from database inception up to Aug 31, 2016, with (castration) AND (resistant) AND ("prostatic neoplasm" OR "prostate cancer") AND ("genomic instability" OR "DNA repair" OR "DNA repair defect") as search terms of interest with no additional restrictions (eg, to English language publications only). The search yielded 33 results. Only two of these were clinical trial publications, which presented results from an early phase 1 study of veliparib and the phase 2 TOPARP study of olaparib—both PARP inhibitors—in this disease setting. Veliparib was reported to have low efficacy, but the high response rate observed among patients with specified DNA repair gene defects (DRDs) in the TOPARP study provided a compelling rationale for assessing the clinical activity and safety of other such agents in a genetically selected patient population. Coauthors of the current study also contributed appropriate citations of importance that were not detected by the original search strategy or that were found in subsequent literature, with an emphasis on randomised clinical trials, systematic reviews, meta-analyses, and prospective observational studies. Taken together, the findings indicated that PARP inhibitors show notable activity in cancers with DRDs. In articles published since the GALAHAD study was initiated, further clinical activity has since been reported in metastatic castration-resistant prostate cancers with selected DRDs for the PARP inhibitors olaparib, rucaparib, and talazoparib (for which key primary publications are cited in the present work), but not yet for niraparib, which is also a potent and highly selective PARP inhibitor with established efficacy and tolerability in other cancers.

Added value of this study

To our knowledge, the GALAHAD study is the first to show the anti-tumour activity of niraparib in patients with metastatic castration-resistant prostate cancer and DRDs who previously progressed on both androgen signalling inhibitors and taxanes, with notable activity particularly in the cohort of patients with defects in *BRCA1* or *BRCA2*.

Implications of all the available evidence

This final analysis of the GALAHAD study suggests that in patients with heavily pretreated metastatic castration-resistant disease, niraparib could offer promising clinical activity with a manageable safety profile. These findings motivate the further assessment of niraparib alone or in combination with other agents to improve treatment options and underscore the importance of biological disease profiling in informing treatment decisions.

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See **Online** for appendix

are involved in single-strand DNA break repair.[8] PARP inhibitors, such as olaparib, rucaparib, and talazoparib, have been studied in patients with metastatic castration-resistant prostate cancer and DRDs in previous phase 2 and 3 studies.[9–13] Olaparib is approved in the EU for *BRCA1*-mutated or *BRCA2*-mutated metastatic castration-resistant prostate cancer[14] and by the US Food and Drug Administration (FDA) for patients with metastatic castration-resistant prostate cancer and DRDs progressing after treatment with enzalutamide, abiraterone, or both,[15] whereas rucaparib is approved for patients with *BRCA1*-mutated or *BRCA2*-mutated metastatic castration-resistant prostate cancer who have been treated with an androgen signalling inhibitor therapy and a taxane.[16]

Niraparib, a potent and highly selective inhibitor of PARP-1 and PARP-2, is approved by the FDA for the maintenance treatment of select patient populations with ovarian, fallopian tube, and primary peritoneal cancers.[17,18] Here, we report the final anti-tumour activity and safety results of a multicentre, open-label, phase 2 study of niraparib in patients with metastatic castration-resistant prostate cancer and tumour DRDs, whose disease had progressed on androgen signalling inhibitor therapy and taxane chemotherapy (docetaxel, cabazitaxel, or both).

Methods

Study design and participants

GALAHAD is an open-label, phase 2 study at 115 hospitals or health-care centres in 15 countries (appendix pp 8–9), which consisted of the following phases: prescreening, screening, treatment, follow-up, and long-term extension.

Male patients aged at least 18 years with histologically confirmed metastatic castration-resistant prostate cancer (mixed histology was acceptable, with the exception of the small cell pure phenotype, which was excluded) were eligible if they had a predefined DRD and disease progression on an androgen signalling inhibitor and taxane chemotherapy (docetaxel, cabazitaxel, or both). Disease progression was defined as progression of metastatic prostate cancer in the setting of castrate levels of testosterone of up to 50 ng/dL on a gonadotropin-releasing hormone analogue or with history of bilateral orchiectomy at study entry, with progression specifically defined as prostate-specific antigen (PSA) progression or radiographic progression of soft tissue by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or bone disease by Prostate Cancer Working Group 3 (PCWG3) criteria.[19,20] Patients were also required to have an Eastern Cooperative Oncology Group (ECOG)

performance status of 2 or less. Patients with measurable and non-measurable disease were enrolled. Exclusion criteria included previous treatment with a PARP inhibitor or platinum-based chemotherapy regimen, and a known history or current diagnosis of myelodysplastic syndrome or acute myeloid leukaemia. The full eligibility criteria are available in the protocol (appendix).

All patients provided written informed consent. Independent ethics committees or institutional review boards of each participating institution approved this study. The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol is available in the appendix.

Procedures

Patients were prescreened using a blood sample (Resolution Bioscience, Kirkland, WA, USA) or tumour tissue sample (Foundation Medicine, Cambridge, MA, USA[21]) for evaluation of DRD alterations. The Resolution Bioscience assay, Resolution HRD, is a targeted hybrid capture, next-generation sequencing assay that detects single-nucleotide variants, indels, and copy number variation (including homozygous deletions) in genes involved in homologous recombination repair using cell-free DNA from plasma. The specific genes of interest for DRD consisted of eight candidates: *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FANCA*, *HDAC2*, and *PALB2*. In addition, three genes that are commonly mutated in metastatic castration-resistant prostate tumours were evaluated: *AR*, *CDKN2A*, and *TP53*. This Resolution Bioscience assay can also identify patients with monoallelic and biallelic pathogenic alterations in the genes of interest. Patients were eligible to enter the screening phase if a deleterious germline or somatic alteration was found in at least one of the following genes: *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FANCA*, *HDAC2*, and *PALB2*. Patients were considered DRD-positive if they had an alteration with known pathogenic consequences including homozygous deletions; rearrangements; and nonsense, missense, frame-shift, and splice-site mutations. After the assay was developed to distinguish between biallelic and monoallelic DRD, patients who had been enrolled with monoallelic or non-pathogenic DRD were excluded from the final analysis according to an approved protocol amendment (amendment 3; October, 2017). As such, only patients with germline pathogenic or biallelic pathogenic alterations in *BRCA1* or *BRCA2* (*BRCA* cohort) or other prespecified non-*BRCA* genes (non-*BRCA* cohort) were included in the final analysis. Additional details on testing methods are available in the appendix (p 4).

All patients received niraparib 300 mg orally in the form of 100 mg capsules (Quotient Sciences, Boothwyn, PA, USA) starting on day 1 of cycle 1 (once daily dosing, with a cycle defined as 28 days) until treatment discontinuation due to disease progression, unacceptable toxicity or adverse events, diagnosis of myelodysplastic syndrome or acute myeloid leukaemia, investigator decision in the best interest of the patient, patient withdrawal of consent, death, or study termination. Monitoring for the need of dose adjustments or interruptions (eg, with laboratory measurements) was at the discretion of the investigator, based on the severity of the adverse events experienced. Patients who were not surgically castrated continued regularly prescribed gonadotropin-releasing hormone analogue.

During the treatment phase, study visits occurred weekly for the first month, biweekly for the second month, and monthly thereafter. CT or MRI and ^{99m}technetium bone scans were performed during screening, every 8 weeks for 24 weeks, and then every 12 weeks thereafter. Circulating tumour cell (CTC) counts were assessed at every cycle until cycle 7 and then at the end-of-treatment visit. PSA assessments were done every 4 weeks until cycle 7 and then every three cycles thereafter.

The follow-up phase began after completion of the treatment phase. If a patient discontinued treatment without radiographic progression, imaging was done every 12 weeks (or within 2 weeks before or after this timepoint) until radiographic progression was documented. The long-term extension phase began after completion of the primary analysis, at which point patients could elect to discontinue treatment or continue niraparib until disease progression. Throughout the study, adverse events were evaluated and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03 or later). Safety evaluations included incidence, severity, and types of adverse events, as well as deaths. Adverse events were classified as treatment-emergent adverse events if they were reported on or after the date of first dose until 30 days (inclusive) after the last dose of study drug. Drug-related adverse events were determined by investigators if they were considered related to the study drug. Appropriate supportive measures to address adverse events could be administered at the discretion of investigators per institutional standards of care. A full schedule of study assessments and procedures is available in the protocol in the appendix.

Outcomes

The primary endpoint was investigator-assessed objective response rate (defined as the proportion of patients with a confirmed partial response or complete response as defined by RECIST version 1.1,[19] according to the sum of target tumour lesion diameters, with no evidence of bone progression on bone scan per PCWG3 criteria[20]) in patients with *BRCA* alterations and measurable disease (the measurable *BRCA* cohort). The primary endpoint was amended early on in this study (amendment 2; January, 2017) from a composite response endpoint to objective response rate to comply with feedback from health authorities, and hence the primary efficacy analysis included only these participants with measurable disease; additional details regarding this amendment are available in the study protocol in the appendix. Patients with non-measurable disease were still included in the

study to increase the size of the safety population and to assess the activity of niraparib in this population.

Secondary efficacy endpoints were objective response rate in patients with non-*BRCA* alterations (*ATM*, *BRIP1*, *CHEK2*, *FANCA*, *HDAC2*, and *PALB2*) and measurable disease; CTC response (CTC0) defined as CTC=0 per 7·5 mL blood at 8 weeks post-baseline in patients with CTC count greater than 0 (1 or more) at baseline;[22,23] overall survival (time from enrolment to death from any cause); radiographic progression-free survival (time from enrolment to radiographic progression or death from any cause, whichever occurred first); time from enrolment to radiographic progression; time to PSA progression (defined as time from enrolment to first date of documented PSA progression based on PCWG3 criteria); time to symptomatic skeletal event (defined as time from enrolment to tumour-related spinal cord compression, radiotherapy to bone to relieve skeletal symptoms, surgery to bone or need for tumour-related orthopaedic surgical intervention, or symptomatic or pathological fracture); duration of objective response (defined as time from complete response or partial response to radiographic progression of disease, unequivocal clinical progression, or death, whichever occurred first); and safety. With the exception of objective response rate in patients with non-*BRCA* alterations and measurable disease, all secondary endpoints were assessed in both the *BRCA* and non-*BRCA* populations.

Prespecified exploratory endpoints included the composite response rate, defined as either an objective response for patients with measurable disease, CTC conversion (defined as CTC count ≥5 per 7·5 mL blood at baseline and <5 per 7·5 mL blood post-therapy nadir), or at least a 50% decline in PSA (PSA_{50}). Both CTC conversion and PSA_{50} were also assessed separately as prespecified exploratory analyses.

Statistical analysis

Statistical analysis followed Simon's two-stage design for phase 2, single-arm clinical trials.[24] Specifically for the non-*BRCA* cohort, a futility analysis for objective response rate based on this design was implemented, in which Simon's stage 1 was assessed after approximately 14 patients with measurable disease were evaluated for objective response rate with at least one post-treatment scan and a confirmatory scan; enrolment was to be terminated for this cohort if two or fewer responses were observed in the first stage. Otherwise, enrolment was specified to proceed to the second stage with a total of 45 patients enrolled for the two stages combined, and the null hypothesis was to be rejected if ten or more responses were observed. For the primary endpoint, the null hypothesis of an objective response rate of 15% or less was tested against the alternate hypothesis of an objective response rate of 32% or higher. With approximately 120 patients with biomarker-positive measurable disease (75 *BRCA* and 45 non-*BRCA*) planned for enrolment, the study had more than 90% power to show that the lower limit of the 95% CI for the primary endpoint of objective response rate exceeded 15% in the measurable *BRCA* cohort. Activity of niraparib was to be declared if the lower bound of the two-sided 95% exact CI for objective response rate was higher than 15% in this cohort. For the secondary endpoint of objective response rate in patients with non-*BRCA* alterations, the null hypothesis of an objective response rate of 15% or less was tested against the alternate hypothesis of an objective response rate of 32% or higher, with a one-sided α of 0·05 and power of 80%.

Objective response in soft tissue disease was evaluated in both *BRCA* and non-*BRCA* patients with measurable disease within the efficacy analysis population of patients who fulfilled the final biomarker assay criteria for this study; however, as prespecified, the primary endpoint was specifically evaluated in the cohort of *BRCA* patients with measurable disease, and the final primary endpoint analysis was planned for approximately 6 months after the last patient with measurable disease in the *BRCA* cohort was enrolled. For analysis of objective response rate, patients who discontinued treatment before any efficacy assessments were considered non-responders; patients with no imaging available for a particular study visit were considered not evaluable for that visit, and patients without valid baseline data were considered not evaluable. Anti-tumour activity, such as PSA response, CTC conversion or response, and composite response rate, was analysed separately for the *BRCA* and non-*BRCA* cohorts, with corresponding criteria for identification of non-responders and non-evaluable patients based on discontinuation or availability of laboratory measurements. Response rates were calculated along with exact two-sided 95% CIs. Time-to-event endpoints were summarised by Kaplan-Meier curves with median times and 95% CIs, as well as descriptive event-free rates analysed as prespecified. Analyses of additional study outcomes, such as the prespecified calculation of treatment compliance in the form of relative dose intensity, are described in further detail in the appendix (p 4).

Post-hoc analyses included objective response rate by baseline characteristics of interest (such as in subgroups of patients with visceral disease at baseline, patients who experienced stable disease for more than 6 months, or patients with three or more previous lines of therapy), specific evaluation of stable disease (defined as neither sufficient decrease in target lesions to qualify for partial response, nor sufficient increase to qualify for progressive disease, with respect to smallest sum of target lesion diameters while on study), and biomarker analyses for non-DRD alterations of interest (*AR* and *TP53* alteration) were also done using the available data. For the post-hoc analysis of patients with *AR* and *TP53* alterations, differences in objective response rates were assessed using Pearson's χ^2 test and p values were adjusted using false discovery rate correction for multiple testing (Benjamini-Hochberg procedure).

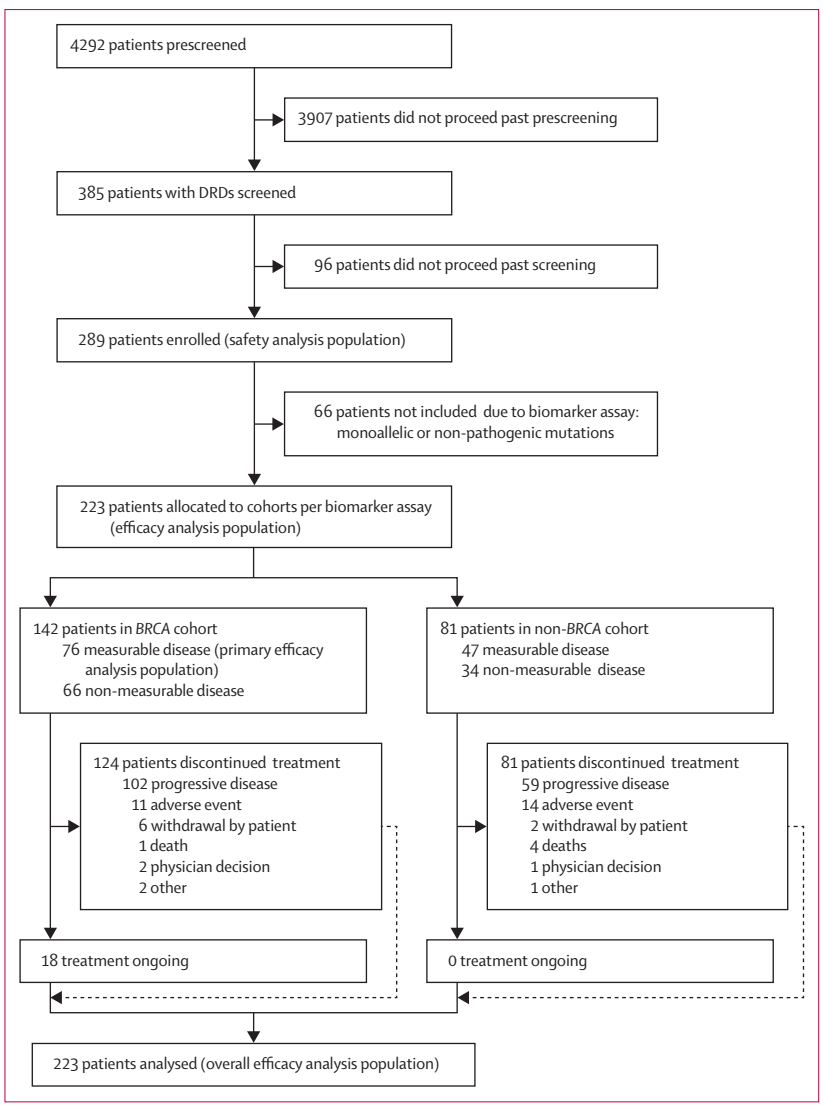

Figure 1: **Trial profile**
DRD=DNA repair gene defect.

Safety and treatment compliance were analysed in the safety analysis population (ie, all patients who received at least one dose of the study drug). Adverse events and serious adverse events were reported and summarised. Sensitivity analyses with censoring rules were done if warranted. Additional details from the statistical analysis plan are available in the appendix. Statistical analyses were performed using SAS (version 15.1).

This study is registered with ClinicalTrials.gov, NCT02854436, and with the European Clinical Trials database, EudraCT 2016-002057-38).

Role of the funding source

The sponsor and employees of the sponsor of this study participated in the study design, data collection, data analysis, and data interpretation, with writing and editorial assistance also funded by the sponsor. All authors participated in the writing process and provided critical input.

Results

385 patients were screened for this study; of these, 289 (75%) patients were enrolled between Sept 28, 2016, and June 26, 2020. All 289 patients were included in the safety analysis population, and 223 (77%) of 289 patients were included in the efficacy analysis population, based on DRD eligibility from the validated biomarker assay (142 with *BRCA* alterations [139 biallelic, three monoallelic germline pathogenic] and 81 with biallelic non-*BRCA* alterations; figure 1). 66 (23%) of 289 patients with monoallelic or non-pathogenic DRD from the safety analysis were not included in the final efficacy analysis. Additional information on the prescreening results is available in the appendix (p 5). For patients with measurable disease, 76 with *BRCA* alterations (primary efficacy population) and 47 with non-*BRCA* alterations were enrolled, which fulfilled the numbers required per study sample size estimation for evaluation of objective response rate. The types and frequencies of genotypes observed in the efficacy analysis are reported in the appendix (p 10).

Based on the Simon's two-stage design, enrolment proceeded through both stages to fulfill the estimated sample size requirements. At the clinical cutoff date of Jan 26, 2021, 271 (94%) of 289 patients had discontinued treatment, with reasons summarised in the appendix (p 11). Seven (9%) of 76 patients in the primary efficacy cohort (patients with *BRCA* alterations and measurable disease) discontinued therapy before their first study evaluation due to progressive disease (n=4), urosepsis leading to death (n=1), or withdrawal of consent (n=1 due to fear of COVID-19; n=1 received radium-223 due to bone disease burden). The median treatment duration was 6·5 months (IQR 3·3–9·4) in the *BRCA* cohort and 3·6 months (1·8–5·6) in the non-*BRCA* cohort. Dose adjustments and interruptions are summarised in the appendix (p 12), with most treatment dose reductions occurring due to an adverse event.

Patients were heavily pretreated and showed advanced disease in both the *BRCA* and non-*BRCA* populations (table 1). Nearly all patients had bone metastases and, in the primary efficacy population (the measurable *BRCA* cohort), a notable proportion of patients had visceral disease, including liver and lung metastases, as well as many patients having nodal disease.

At baseline, 182 (63%) of 289 patients in the safety analysis population had received at least three previous systemic therapies for metastatic prostate cancer; 94 (33%) had received two previous androgen signalling inhibitor therapies, and 107 (37%) had received two previous taxane-based chemotherapies. The demographics and baseline characteristics of the safety analysis population are presented in the appendix (p 13). The final activity results

for the overall *BRCA* cohort (with a median follow-up of 10·1 months [IQR 7·5–13·4]) are shown in tables 2 and 3 and the appendix (pp 6, 7, 14).

The primary endpoint, objective response rate per protocol in the measurable *BRCA* cohort, was met in 26 of 76 patients (34·2%, 95% CI 23·7–46·0; table 2) with a median follow-up of 10·0 months (IQR 6·6–13·3). Of the 76 patients in the measurable *BRCA* cohort, 35 (46%) had at least a 30% decrease of maximum change from baseline in the sum of longest target lesion diameters relative to baseline (appendix p 6). Median duration of objective response was 5·55 months (95% CI 3·91–7·20; table 3); eight (31%) of 26 responses were ongoing at the time of data cutoff.

Figure 2 and table 3 present radiographic progression-free survival, with 87 (61%) events at the time of data cutoff, and overall survival, with 88 (62%) events in the overall *BRCA* cohort. 12-month event-free survival in the overall *BRCA* cohort was 56·4% (95% CI 47·2–64·6), and 24-month event-free survival was 15·2% (7·7–25·1). Approximately a quarter of patients reached CTC0 (table 3). 85 (60%) of 142 patients in the *BRCA* cohort and 42 (55%) of 76 patients in the measurable *BRCA* cohort experienced PSA progression, and 46 (32%) of 142 patients and 23 (30%) of 76 patients had a documented symptomatic skeletal event in these cohorts, respectively.

The exploratory endpoint of composite response rate in the overall *BRCA* cohort is also presented in table 3. More than 40% of patients in the overall *BRCA* cohort had PSA_{50} and CTC conversion (also exploratory), and approximately two thirds of evaluable patients experienced a decrease in PSA levels from baseline (table 3; appendix p 7). Similar outcomes in composite response rate were obtained in the *BRCA* cohort for patients with measurable and non-measurable disease (appendix p 14).

Of note, two patients (both with biallelic alterations) in the measurable *BRCA* cohort had a complete response. One patient with visceral (adrenal) and nodal disease at baseline maintained the complete response for 9·7 months, and a second patient with nodal disease at baseline experienced a complete response that persisted for 9·5 months based on imaging, despite having received only 2·1 months of treatment that was discontinued due to an adverse event of anaemia (grade 3). In a post-hoc analysis, of the 30 patients in the measurable *BRCA* cohort who had visceral disease at baseline, 11 (37%) had an objective response. Furthermore, a post-hoc analysis of the 20 patients who experienced stable disease for more than 6 months in this study showed that 14 (70%) were in the *BRCA* cohort. 16 (21%) of the 76 patients in the measurable *BRCA* cohort continued treatment after radiographic progression with no unequivocal clinical progression because they were considered to still be benefiting from therapy.

For the measurable non-*BRCA* cohort (n=47; median follow-up of 8·6 months [IQR 4·8–14·0]), objective response rate per protocol and median duration of response (none of which are ongoing) are shown in table 2. An objective response was recorded in five of 47 patients (10·6%; 95% CI 3·5–23·1) in this cohort.

The corresponding maximum changes in the sum of target tumour lesion diameters from baseline in the

	BRCA cohort (n=142)	Measurable *BRCA* cohort (n=76)	Non-*BRCA* cohort (n=81)	Measurable non-*BRCA* cohort (n=47)
Age, years	67·0 (63·0–73·0)	66·0 (62·0–73·0)	70·0 (66·0–75·0)	71·0 (59·0–86·0)
Bodyweight, kg	82·7 (15·5)	80·5 (13·4)	79·9 (16·1)	77·6 (13·0)
Race				
White	101 (71%)	57 (75%)	54 (67%)	33 (70%)
Asian	9 (6%)	6 (8%)	6 (7%)	3 (6%)
Black or African American	5 (4%)	3 (4%)	0	0
Other	3 (2%)	0	2 (2%)	0
Multiple	1 (1%)	0	2 (2%)	1 (2%)
Not reported	11 (8%)	5 (7%)	8 (10%)	4 (9%)
Unknown	12 (8%)	5 (7%)	9 (11%)	6 (13%)
PSA at baseline, ng/mL	141·5 (41·0–512·4)	197·0 (40·1–653·9)	161·7 (43·7–611·1)	196·0 (43·7–662·3)
Patients with alterations in a single gene*				
BRCA1	4 (3%)	3 (4%)	··	··
BRCA2	127 (89%)	69 (91%)	··	··
ATM	··	··	37 (46%)	21 (45%)
BRIP1	··	··	1 (1%)	1 (2%)
CHEK2	··	··	5 (6%)	2 (4%)
FANCA	··	··	18 (22%)	10 (21%)
HDAC2	··	··	8 (10%)	5 (11%)
PALB2	··	··	0	0
ECOG performance status score				
0	48 (34%)	25 (33%)	18 (22%)	9 (19%)
1	78 (55%)	44 (58%)	47 (58%)	27 (57%)
2	16 (11%)	7 (9%)	16 (20%)	11 (23%)
Extent of disease progression at study entry				
Bone	127 (89%)	61 (80%)	79 (98%)	45 (96%)
Visceral	33 (23%)	30 (39%)	20 (25%)	16 (34%)
Liver	24 (17%)	23 (30%)	13 (16%)	12 (26%)
Lung	15 (11%)	13 (17%)	10 (12%)	7 (15%)
Lymph node	79 (56%)	67 (88%)	39 (48%)	33 (70%)
Soft tissue	22 (15%)	21 (28%)	16 (20%)	15 (32%)
Disease status				
Measurable	76 (54%)	76 (100%)	47 (58%)	47 (100%)
Non-measurable	66 (46%)	0	34 (42%)	0
Gleason score at diagnosis				
<8	39/135 (29%)	20/73 (27%)	26/77 (34%)	15/43 (35%)
≥8	96/135 (71%)	53/73 (73%)	51/77 (66%)	28/43 (65%)
Previous therapies for prostate cancer†				
Two	59 (42%)	29 (38%)	22 (27%)	10 (21%)
Three	54 (38%)	31 (41%)	31 (38%)	18 (38%)
Four	21 (15%)	12 (16%)	19 (23%)	12 (26%)
Five	7 (5%)	3 (4%)	9 (11%)	7 (15%)
Six	1 (1%)	1 (1%)	0	0

(Table 1 continues on next page)

	BRCA cohort (n=142)	Measurable *BRCA* cohort (n=76)	Non-*BRCA* cohort (n=81)	Measurable non-*BRCA* cohort (n=47)
(Continued from previous page)				
Previous androgen signalling inhibitor therapies				
One	97 (68%)	51 (67%)	45 (56%)	23 (49%)
Two	44 (31%)	25 (33%)	31 (38%)	21 (45%)
Three	1 (1%)	0	5 (6%)	3 (6%)
Previous taxane-based chemotherapies				
One	100 (70%)	51 (67%)	41 (51%)	21 (45%)
Two	42 (30%)	25 (33%)	40 (49%)	26 (55%)

Data are reported as median (IQR), mean (SD), n (%), or n/N (%). The measurable *BRCA* cohort (n=76) is the primary efficacy population and the *BRCA* and non-*BRCA* cohorts combined (n=223) is the overall efficacy analysis population. PSA=prostate-specific antigen. ECOG=Eastern Cooperative Oncology Group. *All patients with *PALB2* had co-occurring alterations and are thus not listed here; patient numbers and percentages might not add up to 100% because some patients had more than one gene alteration and are thus not listed here. †Number of androgen signalling inhibitors, taxane-based chemotherapies, cytotoxic chemotherapies, and other therapies received; specifically, previous therapies could include taxane-based chemotherapy for metastatic prostate cancer with evidence of disease progression, or next-generation androgen signalling inhibitor therapy for either metastatic prostate cancer with evidence of disease progression or non-metastatic castration-resistant prostate cancer with evidence of subsequent metastasis.

Table 1: **Baseline characteristics of patients in the overall efficacy analysis population**

	Measurable *BRCA* cohort* (n=76)	Measurable non-*BRCA* cohort† (n=47)
Objective response rate	26 (34·2%; 23·7–46·0)	5 (10·6%; 3·5–23·1)
Complete response	2 (3%)	0
Partial response	24 (32%)	5 (11%)

Data are n (%; 95% CI) or n (%). *Primary efficacy analysis cohort. †Objective response rate in measurable non-*BRCA* patients was a secondary efficacy endpoint.

Table 2: **Objective response rates**

overall non-*BRCA* cohort (n=81) are presented in the appendix (p 6).

Figure 2 and table 3 also present radiographic progression-free survival in the non-*BRCA* cohort, with 57 (70%) events at the time of data cutoff, and overall survival, with 65 (80%) events. 12-month event-free survival was 41·3% (95% CI 30·0–52·2), and 24-month event-free survival was 11·1% (4·4–21·2). Fewer than 10% of patients reached CTC0 in this cohort; 39 (48%) of 81 patients had PSA progression, and 19 (23%) of 81 patients had a documented symptomatic skeletal event.

The exploratory endpoint of composite response rate in the non-*BRCA* cohort is also presented in table 3, and the maximum change in PSA from baseline is presented in the appendix (p 7). Response by either PSA_{50} or CTC conversion (also exploratory) among non-*BRCA* patients with non-measurable disease is provided in the appendix (p 14).

In post-hoc analyses of the non-*BRCA* cohort, two (13%) of 16 patients with visceral disease and four (80%) of five patients who had received three or more lines of therapy experienced an objective response in the non-*BRCA* cohort; six patients in this cohort experienced stable disease for more than 6 months. 15 (32%) of 47 patients continued treatment after radiographic progression with no unequivocal clinical progression.

Of note, 11 (8%) of 142 patients in the *BRCA* cohort and seven (9%) of 81 patients in the non-*BRCA* cohort had co-expression of two or more eligible DRD biomarkers. Moreover, in addition to being DRD-positive, 162 (74%) of 220 patients with available plasma DNA results had alterations in the *AR* gene and 49 (22%) of 220 had alterations in *TP53*, of whom 42 (19%) had both *TP53* and *AR* alterations. These additional alterations in plasma DNA were similarly distributed between the *BRCA* and non-*BRCA* cohorts, and no substantial difference in objective response rate was observed in subgroups of patients with or without co-occurring alterations (appendix pp 15–16).

Safety results are summarised in table 4 and the appendix (pp 17–25, 28–30). Almost all patients in the safety population experienced at least one treatment-emergent adverse event. The most common adverse events (of any grade) were nausea (169 [58%] of 289), anaemia (156 [54%]), and vomiting (111 [38%]). Of the grade 3 or worse treatment-emergent adverse events reported in 217 (75%) of 289 patients, most were haematological, with both the most common grade 3 or worse adverse events overall and grade 3 or worse adverse events of special interest being anaemia (95 [33%] of 289), thrombocytopenia (47 [16%]), and neutropenia (28 [10%]). These events were manageable with one or more of: treatment interruptions, dose reductions, or supportive measures such as blood transfusions. One patient experienced neutropenic sepsis. The most common non-haematological grade 3–4 treatment-emergent adverse events were fatigue and nausea. 134 (46%) of 289 patients had at least one serious treatment-emergent adverse event, with haematological events being the most common (17 [6%] of 289 with thrombocytopenia and 13 [4%] of 289 with anaemia; appendix pp 21–23). Similarly, of 43 (15%) of 289 patients with drug-related serious treatment-emergent adverse events, the most common were thrombocytopenia (four [3%] of 142 in the *BRCA* cohort and seven [9%] of 81 in the non-*BRCA* cohort) and anaemia (three [2%] of 142 in the *BRCA* cohort and three [4%] of 81 in the non-*BRCA* cohort; appendix p 24). The most common adverse events overall by *BRCA* and non-*BRCA* cohorts are also summarised in the appendix (p 20).

Estimated relative dose intensities are presented in the appendix (pp 26–27), including a breakdown of relative dose intensities in responders versus non-responders in the primary efficacy analysis population (appendix p 26). In the safety population, 128 (44%) of 289 patients had an adverse event leading to a dose reduction; consistent with the aforementioned findings, 87 (68%) of 128 patients had haematological events

	BRCA cohort (n=142)	Measurable *BRCA* cohort (n=76)	Non-*BRCA* cohort (n=81)
CTC response*, n/N (%)	31/131 (24%)	18/71 (25%)	6/71 (8%)
Overall survival, months	13·01 (11·04–14·29)	10·87 (9·49–13·77)	9·63 (8·05–13·44)
Radiographic progression-free survival, months	8·08 (5·55–8·38)	5·52 (5·29–7·59)	3·71 (1·97–5·49)
Time to radiographic progression, months	8·08 (5·75–8·97)	5·55 (5·36–8·08)	3·78 (2·00–5·55)
Time to PSA progression, months	5·13 (4·60–5·59)	5·55 (4·60–8·31)	3·65 (2·83–3·71)
Time to symptomatic skeletal event, months	13·80 (10·41–NE)	13·80 (9·07–NE)	10·35 (8·18–NE)
Duration of objective response, months	6·28 (3·65–9·23)	5·55 (3·91–7·20)	5·16 (2·14–NE)
Composite response rate†, n/N (%; 95% CI)	82/142 (58%; 49·2–66·0)	46/76 (61%; 48·7–71·6)	12/81 (15%; 7·9–24·5)
CTC conversion‡, n/N (%; 95% CI)	55/117 (47%; 37·7–56·5)	28/64 (44%; 31·4–56·7)	9/60 (15%; 7·1–26·6)
PSA_{50}, n/N (%; 95% CI)	61/142 (43%; 34·7–51·5)	31/76 (41%; 29·7–52·7)	4/81 (5%; 1·4–12·2)

Data are median (95% CI) unless otherwise indicated. CTC=circulating tumour cell. PSA=prostate-specific antigen. NE=not estimable. PSA_{50}=at least 50% decline in prostate-specific antigen. *Defined per protocol and statistical analysis plan as CTC=0 per 7·5 mL blood at 8 weeks post-baseline in patients with baseline CTC count >0. †Defined as an objective response for patients with measurable disease, CTC conversion (defined as CTC count ≥5 per 7·5 mL blood at baseline and <5 per 7·5 mL blood post-therapy nadir), or PSA_{50}. ‡Among patients with baseline CTC count ≥5.

Table 3: **Secondary and exploratory efficacy endpoints**

(appendix p 28), which were manageable with one or more of the following: dose reductions, interruptions, or appropriate supportive measures (administered at the discretion of investigators per institutional standards of care). Among patients evaluated for anti-tumour activity, 70 (95%) of 74 patients with dose reductions in the *BRCA* cohort and 37 (93%) of 40 patients with dose reductions in the non-*BRCA* cohort had dose reductions due to adverse events versus other reasons; 103 (46%) of 223 patients received at least one transfusion (platelets or packed red blood cells), and the incidence of transfusions was similar between the *BRCA* and non-*BRCA* cohorts (data not shown). Other supportive measures included colony-stimulating factors, which were administered to 12 (4%) of 289 patients, and erythropoietin, which was administered to 15 (5%) of 289 patients. 37 (13%) of 289 patients were deemed to have discontinued treatment due to drug-related toxicities (treatment-emergent adverse events deemed related to study drug). The most common drug-related toxicities leading to discontinuation were thrombocytopenia (in seven patients with *BRCA* alterations and three patients with non-*BRCA* alterations) and anaemia (in six patients with *BRCA* alterations and one patient with non-*BRCA* alteration; appendix p 25).

Adverse events leading to death are summarised in the appendix (p 29). Of the 16 deaths related to adverse events, two events (one patient with urosepsis in the *BRCA* cohort and one patient with sepsis in the non-*BRCA* cohort) were deemed possibly related to niraparib treatment. 208 (72%) of 289 patients died during the study; reasons for deaths are summarised in the appendix (p 30). The only sensitivity analysis warranted was for COVID-19, but there was only one patient with a COVID-19-related adverse event (non-serious) and one death due to COVID-19 in this study (appendix p 30).

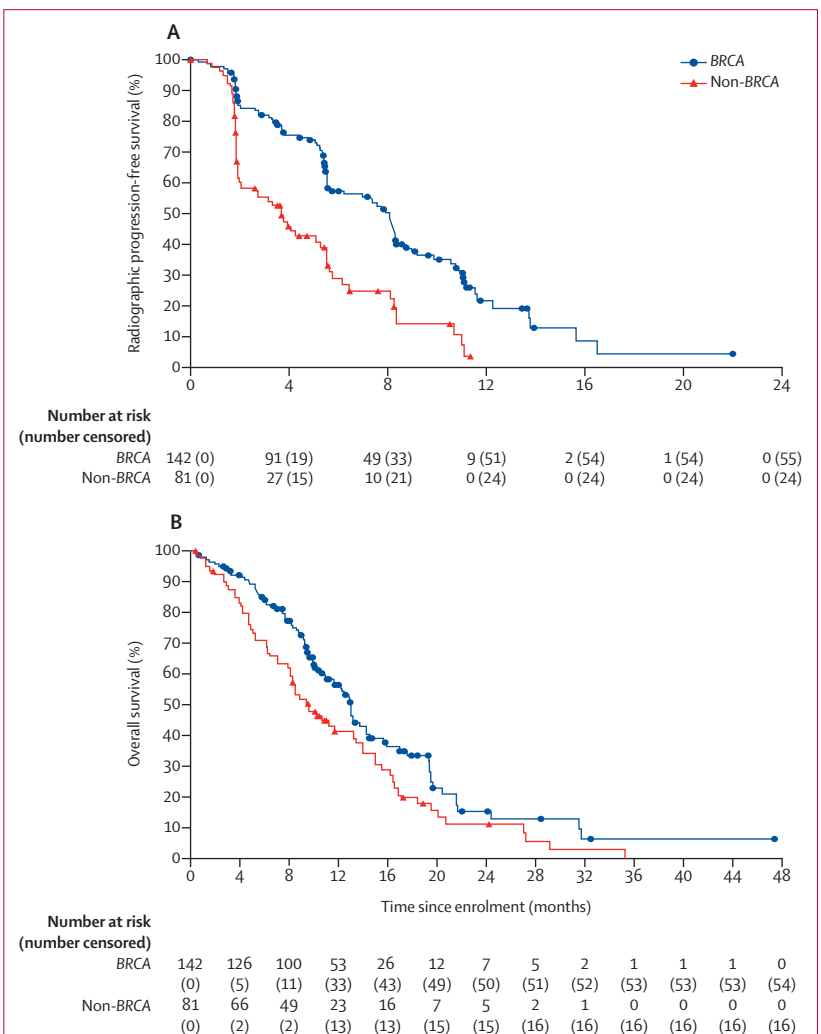

Figure 2: **Radiographic progression-free survival (A) and overall survival (B) in the *BRCA* and non-*BRCA* cohorts**
Symbols represent censored patients.

	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	154 (53%)	15 (5%)	0	0
Vomiting	101 (35%)	10 (3%)	0	0
Constipation	95 (33%)	5 (2%)	1 (<1%)	0
Fatigue	87 (30%)	19 (7%)	0	0
Decreased appetite	85 (29%)	8 (3%)	0	0
Anaemia	61 (21%)	92 (32%)	2 (1%)	1 (<1%)
Thrombocytopenia	52 (18%)	24 (8%)	23 (8%)	0
Back pain	51 (18%)	13 (4%)	0	0
Arthralgia	38 (13%)	6 (2%)	0	0
Asthenia	37 (13%)	11 (4%)	0	0
Neutropenia	27 (9%)	17 (6%)	11 (4%)	0
Bone pain	23 (8%)	9 (3%)	0	0
Hypertension	22 (8%)	12 (4%)	0	0
Blood alkaline phosphatase increased	15 (5%)	11 (4%)	0	0
Stomatitis	15 (5%)	6 (2%)	0	0
Leukopenia	14 (5%)	11 (4%)	3 (1%)	0
γ-glutamyl transferase increased	13 (4%)	11 (4%)	1 (<1%)	0
Lymphopenia	11 (4%)	12 (4%)	1 (<1%)	0
Hypophosphataemia	7 (2%)	6 (2%)	1 (<1%)	0
Spinal cord compression	1 (<1%)	7 (2%)	0	0
General physical health deterioration	1 (<1%)	7 (2%)	1 (<1%)	4 (1%)

Data are shown as n (%). A total of 288 patients had one or more recorded treatment-emergent adverse events. Data are presented for grade 1–2 treatment-emergent adverse events with a combined incidence of ≥20% or any higher-grade (grade 3–5) treatment-emergent adverse events with an incidence of ≥2%.

Table 4: **Treatment-emergent adverse events in the safety analysis set (n=289)**

Discussion

The results of this multicentre, open-label, phase 2 study establish the anti-tumour activity of niraparib in patients with metastatic castration-resistant prostate cancer and DRDs who have progressed on both androgen signalling inhibitors and taxanes. Treatment with niraparib was manageable, and adverse events observed were consistent with the known safety profile of niraparib, with no new safety signals.

The activity of niraparib in the measurable *BRCA* cohort is notable given the heavily pretreated, end-stage patient population with few therapeutic options. These findings are especially remarkable considering the high percentage of patients with visceral metastasis, in particular to the liver, which is strongly associated with poor survival;[25] the high percentage of patients with three or more lines of previous therapy; and that some patients in the *BRCA* cohort even achieved a complete response. Further evidence of benefit was shown by the proportion of patients experiencing stabilisation of disease for more than 6 months in both the *BRCA* and non-*BRCA* cohorts, which is a clinically meaningful finding given this heavily pretreated advanced disease state. Also notable was that patients in both cohorts, some with multiple poor prognostic features, continued to derive clinical benefit from niraparib after radiographic progression (in line with the importance of considering the totality of a patient's disease before discontinuing a drug rather than strictly at the first evidence of progression in any site, as recommended by PCWG3[21]). Objective response rate, median radiographic progression-free survival and overall survival, and composite response rate were greater in the *BRCA* cohort than in the non-*BRCA* cohort, including a median radiographic progression-free survival time that was approximately double that in the non-*BRCA* cohort. Interestingly, our exploratory endpoint of composite response rate was largely similar between the subgroups of patients with measurable versus non-measurable disease in both cohorts (particularly in the *BRCA* cohort). Taken together, these results extend the evidence on the activity of PARP inhibitors in patients with metastatic castration-resistant prostate cancer and DRD-altered tumours whose disease has progressed on approved life-prolonging therapies, and also highlight the importance of biological profiling of an individual patient's disease in metastatic castration-resistant prostate cancer.[8,21] Of note, to our knowledge, this trial is the first to prospectively test the CTC0 endpoint, which has been shown to strongly associate with survival.[22]

The dose of niraparib used in this study (300 mg oral; once daily dosing) was chosen based on the previously evaluated pharmacokinetics, clinical activity, and safety profile of niraparib and is the approved dose for patients with ovarian cancer.[17,26] As expected, grade 3 or worse treatment-emergent adverse events were largely haematological and manageable with supportive measures (such as blood transfusions and growth factor treatment), dose interruptions, and dose reductions. Rates of treatment interruptions and reductions were higher than the previously reported rates for other PARP inhibitors.[9–13] This finding is consistent with the more advanced disease stage of patients in the GALAHAD trial, who had all progressed on androgen signalling inhibitor therapy and taxane chemotherapy and also tended to be on later lines of therapy, with the majority having received three or more lines of previous therapy. Moreover, the present study applied more stringent dose interruption criteria (for example, skipping a dose was also considered a dose interruption). Thus, the finding that at least half of the patients in both the *BRCA* and non-*BRCA* cohorts maintained the full dose (300 mg) of niraparib throughout the study supports the overall tolerability of this regimen. Relative dose intensity was also generally high, including in the primary efficacy cohort, and was higher for those who had an objective response in that cohort compared with those who did not.

The clinical activity of niraparib shown in this study's specific patient population (noting particular activity observed in the *BRCA* cohort) can be further contextualised by results of studies of other PARP inhibitors that point to a benefit for both minimally and heavily pretreated patients with metastatic castration-resistant prostate cancer and particular DRD alterations. Of note, in the phase 3 PROfound study that evaluated patients treated with the PARP inhibitor olaparib versus those treated with the

physician's choice of an androgen signalling inhibitor, olaparib treatment resulted in a median radiographic progression-free survival of 7·4 months versus 3·6 months (hazard ratio 0·34, 95% CI 0·25–0·47; p<0·001), median overall survival of 19·1 months versus 14·7 months (0·69, 0·50–0·97; p=0·02 at final analysis), and confirmed objective response rate of 33% (28 of 84) versus 2% (one of 43; odds ratio 20·86, 95% CI 4·18–379·18; p<0·001) compared with the control treatment in a cohort of patients with alterations in *BRCA1, BRCA2,* or *ATM*.[10,11] Rucaparib, which was investigated in the phase 2 TRITON-2 study, led to an objective response rate of 47·5% and a median time to PSA progression of 6·5 months, with a better response seen in patients with *BRCA* alterations compared with those with alterations in other genes such *ATM* or *CDK12*.[12,13] In the phase 2 TALAPRO-1 study, patients with certain gene alterations reported to sensitise to PARP inhibitors were enrolled and treated with talazoparib. The objective response rate was 29·8% (31 of 104; 95% CI 21·2–39·6) with talazoparib treatment after a median follow-up of 16·4 months.[9]

The limitations of the present study include that some patients developed progressive disease before completing their first disease evaluation, consistent with the advanced stage and aggressiveness of the disease in the enrolled population. Additionally, tissue-based assays rely on sufficient high-quality biopsy samples, which might be difficult to obtain, and further challenges ensue when archival samples are found to be unsuitable or unavailable for analysis. In this study, a commercially available tissue-based assay was initially used to select patients, but due to the aforementioned challenges, a blood-based assay was subsequently implemented, with early prescreening rates and biomarker logic finalisation then addressed during a brief study pause. As such, a notable number of patients in GALAHAD were prescreened using blood-based assay. Such assays could offer valuable data, especially for metastatic prostate cancer for which tumour biopsies are challenging to acquire and biopsies are largely limited to bone that has considerable issues with the quality of materials. However, liquid biopsies also have limitations. Given the lack of parallel next-generation sequencing of corresponding white blood cells in this study, clonal haematopoietic alterations of indeterminate potential could have presented as a biological confounding factor.[27] Additionally, blood-based assays might show false negative results in blood samples with low plasma circulating tumour DNA content, especially for mutations that are difficult to detect such as homozygous deletions. Conversely, circulating tumour DNA assays could select for patients with higher percentages of circulating tumour DNA, which was previously found to be a predictive factor for a poorer prognosis.[28] Nevertheless, the number of patients enrolled for efficacy evaluation in GALAHAD (n=223 with specifically germline pathogenic or biallelic DRD alterations, of a total of 4218 with any biomarker sample submitted) represents an incidence of DRD alterations that is within expectations. Finally, 22% of the GALAHAD study population had *TP53* alterations, which are also associated with overall poor prognosis.

Additional studies, including those designed to evaluate niraparib-based regimens in appropriate biomarker-identified populations at earlier stages of disease, are underway to expand on the present findings. The phase 3 MAGNITUDE study is evaluating niraparib in combination with abiraterone acetate plus prednisone as first-line therapy in patients with metastatic castration-resistant disease with or without DRD.[29] The phase 3 AMPLITUDE study will also evaluate niraparib in combination with abiraterone acetate plus prednisone in a biomarker-selected population with metastatic castration-sensitive disease.[30]

In conclusion, these results suggest that niraparib has promising clinical activity with a manageable safety profile when administered as a monotherapy for treatment-refractory metastatic castration-resistant prostate cancer with *BRCA* alterations or select non-*BRCA* alterations. Such findings underscore the need for and importance of molecular testing to inform management along with continued research to establish treatment paradigms with appropriately targeted therapies for patients with prostate cancer. Efforts to investigate and better understand predictive markers and signatures of both response and resistance to treatment with PARP inhibitors such as niraparib are needed to guide therapy selection and optimise treatment outcomes.

Contributors

All authors in their role as GALAHAD study investigators or Janssen Research & Development investigators contributed to study design, study conduct, data analysis, and data interpretation. All authors participated in drafting and revising the manuscript and approved the final version before submission. MRS, GEM, and XZ verified all data. All authors had full access to all data for the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MRS has received grants or contracts to their institution from Bayer, Janssen, Pfizer, AstraZeneca, and Lilly; has received consulting fees from Astellas Pharma, Novartis, Janssen, AstraZeneca, Bayer, Lilly, and Pfizer; and has participated on data safety monitoring boards, advisory boards, or both for Janssen, Pfizer, and AstraZeneca. HIS has a leadership role in Asterias Biotherapeutics; holds stock and other ownership interests in Asterias Biotherapeutics; received grants or contracts to their institution from Epic Sciences, Illumina, Menarini Silicon Biosystems, ThermoFisher, and AIQ Pharma; provided consulting to Ambry Genetics Corporation/Konica Minolta, Amgen (uncompensated), Bayer, ESSA Pharma (uncompensated), Menarini Silicon Biosystems (uncompensated), Pfizer, Sun Pharmaceuticals, and WCG Oncology; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sidney Kimmel Cancer Center—Jefferson Health; has received support for attending meetings or travel from Amgen, Bayer, ESSA Pharma, Menarini Silicon Biosystems, Epic Sciences, Pfizer, WCG Oncology, and Phosplatin; has patents planned, issued, or pending via their institution with BioNTech, Elucida Oncology, MabVax Therapeutics, and Y-mAbs Therapeutics; and has other financial or non-financial interests in Elsevier, Prostate Cancer Foundation (via institution), National Cancer Institute (via institution), Department of Defense (via institution), MabVax Therapeutics, and BioNTech. SS has received grants from Amgen, Advanced Accelerator Applications (a Novartis company), Merck Sharp & Dohme,

AstraZeneca, and Genentech; has received grants and personal fees from AstraZeneca, Bristol Myers Squibb, and Merck Sharp & Dohme; and participated on a data safety monitoring board for Advanced Accelerator Applications (a Novartis company). EE has received grants or contracts, consulting fees, and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sanofi, Astellas, Pfizer, Myovant, Merck Sharp & Dohme, AstraZeneca, and Novartis, and has participated on data safety monitoring boards, advisory boards, or both for Sanofi, Astellas, Pfizer, Myovant, Merck Sharp & Dohme, AstraZeneca, and Novartis. PNL Jr has received grants or contracts from Janssen to their institution. EYY has received grants or contracts from Bayer, Dendreon, Merck Sharp & Dohme, Seagen, Taiho, Blue Earth, and Lantheus; and has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Bayer, Clovis, Janssen, Merck Sharp & Dohme, Seagen, Sanofi, AbbVie, Advanced Accelerator Applications (a Novartis company), and Exelixis. DJG has received grants or contracts to their institution from Astellas, Bristol Myers Squibb, Calithera, Exelixis, Janssen, Novartis, Pfizer, and Sanofi; has received consulting fees from Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Constellation, Exelixis, Flatiron, IdeoOncology, Janssen, Merck, Myovant Sciences, Physician Education Resource, Pfizer, PlatformQ, Propella, RevHealth, Sanofi, Seattle Genetics, WebMD, and Xcures; has received payment or honoraria for lectures, presentation, speakers bureaus, manuscript writing, or educational events from Bayer, EMD Serono, Exelixis, Ipsen, Michael J Hennessey, Pfizer, Sanofi, UroGPO, and UroToday; has received payment for expert testimony from Wilmer Hale Attorneys; has received support for attending meetings or travel from Bayer, Exelixis, Sanofi, and UroToday; has participated on data safety monitoring boards, advisory boards, or both for Astellas, AstraZeneca, Janssen, and Modra; and holds a leadership or fiduciary role in the American Association for Cancer Research (senior editor), AstraZeneca (CAPI-281 study coordinator), Bristol Myers Squibb (study coordinator), Capio Biosciences (scientific advisory board), Millennium Medical Publishing (co-editor-in-chief, *Clinical Advances in Hematology & Oncology*), NCI Genitourinary (study coordinator), Nektar Therapeutics (study coordinator), and Pfizer (study coordinator). KNC has received grants or contracts to their institution from Janssen, AstraZeneca, Merck, Novartis, and Point Biopharma; has received consulting fees from Astellas, AstraZeneca, Janssen, Merck Sharp & Dohme, Novartis, Point Biopharma, and Roche; and has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Astellas, Janssen, Merck Sharp & Dohme, AstraZeneca, and Novartis. FS has received grants or contracts, consulting fees, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events, and has received equipment, materials, drugs, medical writing, gifts, or other services from Janssen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Myovant, Sanofi, Novartis, and Pfizer; and has participated on data safety monitoring boards, advisory boards, or both for Janssen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Myovant, Sanofi, Novartis, and Pfizer. DO has received grants or contracts from AstraZeneca, Bayer, and Janssen; has received consulting fees from Clovis, Daiichi Sankyo, AstraZeneca, Bayer, Roche, Merck Sharp & Dohme, and Janssen; has received support for attending meetings or travel from AstraZeneca, Janssen, and Roche; and has participated on data safety monitoring boards, advisory boards, or both for Janssen, AstraZeneca, and Bayer. DCD has received consulting fees from Angle, Axiom, Janssen, Astellas, Medivation, Pfizer, Genzyme, and Agensys; and has other financial or non-financial interests (research support) in the US Department of Defense, the American Society of Clinical Oncology, the Prostate Cancer Foundation, Stand Up to Cancer, Janssen, Astellas, Medivation, Agensys, Genentech, and CreaTV. GEM, BME, KAU, PF, and AL-G are employees of Janssen Research & Development. GEM and PF own stocks with Janssen. XZ was an employee of Janssen at the time of this study. KAU has been listed as an inventor on a patent as an employee of Janssen Research & Development. KF has received consulting fees from AAA, Astellas, AstraZeneca, Bayer, Novartis, Janssen, Amgen, Pfizer, Orion, Curevac, and Sanofi; has received payment or honoraria from lectures, presentations, speakers bureaus, manuscript writing, or educational events from Astellas, AstraZeneca, Bayer, Janssen, Novartis, Merck Sharp & Dohme, Bristol Myers Squibb, and Orion; and has participated on data safety monitoring boards, advisory boards, or both for Astellas, AstraZeneca, Bayer, Novartis, Janssen, Amgen, Pfizer, Sanofi, Orion, and Curevac. OS declares no competing interests.

Data sharing

The full study protocol is available in the appendix. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access Project site at http://yoda.yale.edu. De-identified patient-level data will be made available to qualified researchers upon request, after signing of a data transfer agreement with Janssen Research & Development. Requests for data sharing, including a research proposal, can also be made to the corresponding author.

Acknowledgments

This study was funded by Janssen Research & Development. We thank the patients who participated in this study, along with their families, and the study teams who were involved at each participating institution. Statistical analysis support was provided by Eugene Zhu and George Wang of Janssen Research & Development (Raritan, NJ, USA). Medical writing and editorial assistance were provided by Michelle Kwon and Danyang Zhou of Cello Health Communications/MedErgy (Yardley, PA, USA), which was provided in accordance with Good Publication Practice (GPP3) guidelines and funded by Janssen Research & Development. HIS is in receipt of the following National Instititutes of Health (NIH) grants: NIH/National Cancert Institute (NCI) Prostate SPORE Grant P50-CA92629 and NIH/NCI Cancer Center Support Grant P30 CA008748.

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journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Maxton E. Thoman, Keyan Salari on pp. 31–33 of this issue

Pembrolizumab Plus Docetaxel and Prednisone in Patients with Metastatic Castration-resistant Prostate Cancer: Long-term Results from the Phase 1b/2 KEYNOTE-365 Cohort B Study

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Article info

Article history:
Accepted February 22, 2022

Associate Editor:
James Catto

Abstract

Background: Patients with metastatic castration-resistant prostate cancer (mCRPC) frequently receive docetaxel after they develop resistance to abiraterone or enzalutamide and need more efficacious treatments.
Objective: To evaluate the efficacy and safety of pembrolizumab plus docetaxel and prednisone in patients with mCRPC.

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https://doi.org/10.1016/j.eururo.2022.02.023
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Keywords:
Docetaxel
Metastatic castration-resistant prostate cancer
Pembrolizumab
Prednisone

Design, setting, and participants: The trial included patients with mCRPC in the phase 1b/2 KEYNOTE-365 cohort B study who were chemotherapy naïve and who experienced failure of or were intolerant to ≥4 wk of abiraterone or enzalutamide for mCRPC with progressive disease within 6 mo of screening.
Intervention: Pembrolizumab 200 mg intravenously (IV) every 3 wk (Q3W), docetaxel 75 mg/m^2 IV Q3W, and prednisone 5 mg orally twice daily.
Outcome measurements and statistical analysis: The primary endpoints were safety, the prostate-specific antigen (PSA) response rate, and the objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by blinded independent central review (BICR). Secondary endpoints included time to PSA progression; the disease control rate (DCR) and duration of response (DOR) according to RECIST v1.1 by BICR; ORR, DCR, DOR, and radiographic progression-free survival (rPFS) according to Prostate Cancer Working Group 3–modified RECIST v1.1 by BICR; and overall survival (OS).
Results and limitations: Among 104 treated patients, 52 had measurable disease. The median time from allocation to data cutoff (July 9, 2020) was 32.4 mo, during which 101 patients discontinued treatment, 81 (78%) for disease progression. The confirmed PSA response rate was 34% and the confirmed ORR (RECIST v1.1) was 23%. Median rPFS and OS were 8.5 mo and 20.2 mo, respectively. Treatment-related adverse events (TRAEs) occurred in 100 patients (96%). Grade 3–5 TRAEs occurred in 46 patients (44%). Seven AE-related deaths (6.7%) occurred (2 due to treatment-related pneumonitis). Limitations of the study include the single-arm design and small sample size.
Conclusions: Pembrolizumab plus docetaxel and prednisone demonstrated antitumor activity in chemotherapy-naïve naive patients with mCRPC treated with abiraterone or enzalutamide for mCRPC. Safety was consistent with profiles for the individual agents. Further investigation is warranted.
Patient summary: We evaluated the efficacy and safety of the anti-PD-1 antibody pembrolizumab combined with the chemotherapy drug docetaxel and the steroid prednisone for patients with metastatic prostate cancer resistant to androgen deprivation therapy, and who never received chemotherapy. The combination showed antitumor activity and manageable safety in this patient population.
This trial is registered on ClinicalTrials.gov as NCT02861573.
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1. Introduction

Despite significant advances in the treatment of prostate cancer, the primary systemic treatment for regional or metastatic prostate cancer is androgen deprivation therapy (ADT) [1]. Most patients with metastatic disease develop resistance to ADT within 1–2 yr and progress to metastatic castration-resistant prostate cancer (mCRPC) [2]. Several treatment options show a survival benefit after development of mCRPC—including abiraterone [3], enzalutamide [4], docetaxel [5], cabazitaxel [6], sipuleucel-T [7], and radium-223 [8]—but are not curative. Next-generation hormonal agents (NHAs) such as abiraterone and enzalutamide are often used following disease progression after ADT, but there is no consensus regarding the optimal sequence for therapy after progression. Docetaxel is a recommended treatment after initial progression on abiraterone or enzalutamide despite the lack of prospective data for docetaxel after NHA therapy [1]. To date, docetaxel combination regimens have not shown a survival benefit over sequential monotherapies with docetaxel [1]. With a 5-yr survival rate estimated at 30% for patients with distant metastases [9,10], there is a need for therapies that prolong survival.

The tumor microenvironment is immunosuppressive in patients with prostate cancer, and therefore restoring the T-cell antitumor response via programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) blockade is a promising treatment approach [11,12]. Elevated expression of PD-L1 on tumor-infiltrating T cells has been associated with disease progression in prostate cancer [13]. Furthermore, a recent immunohistochemical study showed that metastases from CRPC tumors in patients previously treated with NHAs had increased PD-L1 expression and immunoreactivity [14]. Pembrolizumab is a highly selective humanized monoclonal antibody that blocks interaction between PD-1 and its ligands, PD-L1 and PD-L2, and is approved for the treatment of multiple tumor types [15]. In the phase 2 KEYNOTE-199 trial, pembrolizumab monotherapy showed antitumor activity with manageable safety in patients with mCRPC previously treated with docetaxel and one or more targeted endocrine therapies [16]. Preclinical studies have shown that many chemotherapeutic agents, including taxanes such as docetaxel, can have immunostimulatory effects [17]. Combining immunotherapy and standard chemotherapy may therefore enhance antitumor activity.

The phase 1b/2 KEYNOTE-365 trial (NCT02861573) evaluated the safety, tolerability, and efficacy of pembrolizumab combination therapy in patients with mCRPC. We describe the results for cohort B, which included chemotherapy-naïve patients with mCRPC who experienced disease progression

on abiraterone or enzalutamide for mCRPC and who were treated with the combination of pembrolizumab, docetaxel, and prednisone.

2. Patients and methods

2.1. Study design and patients

KEYNOTE-365 is a multicohort, nonrandomized, multicenter, open-label, phase 1b/2 trial. Patients in eight countries (Australia, Canada, France, Germany, New Zealand, Spain, UK, and USA) were enrolled in cohort B. The trial was conducted in accordance with good clinical practice and the Declaration of Helsinki. The protocol and its amendments were approved by the appropriate ethics body at each participating institution. All patients provided written informed consent.

Key eligibility criteria included age ≥18 yr; histologically or cytologically confirmed adenocarcinoma of the prostate without small-cell histology; disease that progressed within 6 mo before screening (prostate-specific antigen [PSA] progression or radiologic bone/soft tissue progression); Eastern Cooperative Oncology Group performance status score of 0 or 1; received ≥4 wk of treatment with either abiraterone or enzalutamide (but not both) for mCRPC and with treatment failure or intolerance to the drug; no previous chemotherapy; and serum testosterone level <50 ng/dL. The full inclusion and exclusion criteria are listed in the Supplementary material.

Pembrolizumab 200 mg was administered intravenously (IV) every 3 wk (Q3W) with docetaxel 75 mg/m^2 IV Q3W and prednisone 5 mg orally twice daily. Pembrolizumab was administered for up to 35 cycles (~2 yr), and docetaxel was administered for up to ten cycles.

2.2. Assessments and endpoints

On-study computed tomography or magnetic resonance imaging and radionuclide bone imaging were performed every 9 wk from the date of allocation through week 54, and then every 12 wk thereafter. The response and radiographic progression for soft tissue lesions were assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), and radiographic progression for bone lesions was determined according to Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1. Imaging continued until confirmed disease progression, the start of a new anticancer treatment, withdrawal of consent, or death, whichever occurred first. PSA was assessed by a central laboratory at screening and every 3 wk after allocation. Follow-up time began at allocation. PD-L1 positivity was defined as a combined positive score (CPS) ≥1, where CPS is defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

Adverse events (AEs) were monitored throughout the study through 30 d after the last dose of trial treatment (90 d for serious AEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Immune-mediated AEs were determined by the sponsor on the basis of a list of terms specified by the sponsor as potentially associated with immunologic causes.

Primary efficacy endpoints included the PSA response (PSA reduction of ≥50% from baseline, measured twice ≥3 wk apart) and the objective response rate (ORR; complete response [CR] or partial response [PR]) according to RECIST v1.1 as assessed by blinded independent central review (BICR). The primary safety objective was to characterize the safety and tolerability. Secondary endpoints included time to PSA progression; ORR according to PCWG3-modified RECIST v1.1 by BICR; the disease control rate (DCR; CR, PR, stable disease [SD] or non-CR/non-progressive disease [PD] ≥6 mo) and the duration of response (DOR) according to RECIST v1.1 and PCWG3-modified RECIST v1.1 by BICR; radiographic progression-free survival (rPFS) according to PCWG3-modified RECIST v1.1 by BICR; and overall survival (OS).

2.3. Statistical considerations

Efficacy and safety populations included all patients who received at least one dose of study treatment (all patients as treated [APaT]). APaT for ORR included only patients with measurable disease at baseline; APaT for DOR included only patients with an objective response. The Clopper-Pearson method was used to provide point estimates and 95% confidence intervals (CIs) for the PSA response rate, ORR, and DCR. The Kaplan-Meier method was used to provide median point estimates and 95% CIs for DOR, time to PSA progression, rPFS, and OS.

Safety and tolerability were assessed via clinical review of all relevant parameters, including AEs, laboratory tests, and vital signs. Counts and percentages for AEs are provided.

Table 1 – Patient demographics and baseline characteristics for the 104 patients treated with pembrolizumab + docetaxel + prednisone

Parameter	Result
Median age, yr (interquartile range)	68 (64–74)
Age ≥65 yr, *n* (%)	77 (74)
Race, *n* (%)	
White	79 (76)
All others	9 (8.7)
Unknown	16 (15)
Geographic region of enrolling site, *n* (%)	
North America	41 (39)
Europe	54 (52)
Rest of the world	9 (8.7)
Eastern Cooperative Oncology Group performance status, *n* (%)	
0	56 (54)
1	48 (46)
Median prostate-specific antigen, ng/mL (interquartile range)	44.1 (17.1–131.4)
PD-L1 status, *n* (%)	
Positive[a]	24 (23)
Negative	76 (73)
Unknown	4 (3.8)
Disease measurable according to RECIST v1.1, *n* (%)	52 (50)
Median baseline tumor size, mm (interquartile range)[b]	49.9 (26.9–73.8)
Visceral disease, *n* (%)[c]	
With liver	8 (7.7)
Without liver	18 (17)
No visceral disease	78 (75)
Metastatic staging, *n* (%)	
M1	61 (59)
M1A	4 (3.8)
M1B	34 (33)
M1C	5 (4.8)
History of brain metastases, *n* (%)	
No	101 (97)
Unknown	3 (2.9)
Previous use of abiraterone/enzalutamide, *n* (%)	
Abiraterone only	51 (49)
Enzalutamide only	52 (50)
Abiraterone and enzalutamide	1 (1.0)

RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.
[a] PD-L1 positivity was defined as a combined positive score (CPS) ≥1. CPS was calculated as the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.
[b] Assessed by blinded independent central review according to RECIST v1.1.
[c] Soft tissue (not in brain, bone, or lymph nodes).

3. Results

3.1. Disposition, demographics, and exposure

As of July 9, 2020, cohort B enrolled 105 patients; 104 patients whose median age was 68.0 yr (interquartile range [IQR] 64–74) with median PSA of 44.1 ng/mL (IQR 17.1–131.4) were treated (Table 1). Median time from allocation to data cutoff was 32.4 mo (IQR 12.2–27.8). At data cutoff, 101 patients (97%) had discontinued treatment (Supplementary Fig. 1). Among those patients, 81 (78%) discontinued because of disease progression and 15 (14%) because of AEs. Patients received a median of 12 cycles (IQR 7.5–15) of pembrolizumab, and 8.5 cycles (IQR 6–10) of docetaxel. All treated patients received at least two cycles of both treatments; 65 (63%) received at least ten cycles of pembrolizumab and 86 (83%) received at least six cycles of docetaxel. The median duration on therapy, defined as the time between the first dose date and the last dose date, was 7.7 mo (IQR 4.8–9.7).

3.2. Efficacy

The confirmed PSA response rate in patients with a baseline PSA measurement was 34% (35/103) for the total population and 27% (14/51) for patients with RECIST-measurable disease. Seventy-six patients (74%) exhibited any reduction in PSA from baseline, and 45 patients (44%) experienced a PSA reduction of ≥50% from baseline (Fig. 1A). Of 24 patients with PD-L1–positive tumors, 16 (67%) experienced a reduction in PSA from baseline and nine (38%) experienced a reduction of ≥50%. Overall, 56/75 patients (75%) with PD-L1–negative tumors experienced a reduction in PSA from baseline, whereas 35 patients (47%) experienced a reduction of ≥50%. The median time to PSA progression was 29.3 wk (95% CI 21–32; Fig. 1B). PSA response rates were generally consistent across subgroups (Supplementary Fig. 2A).

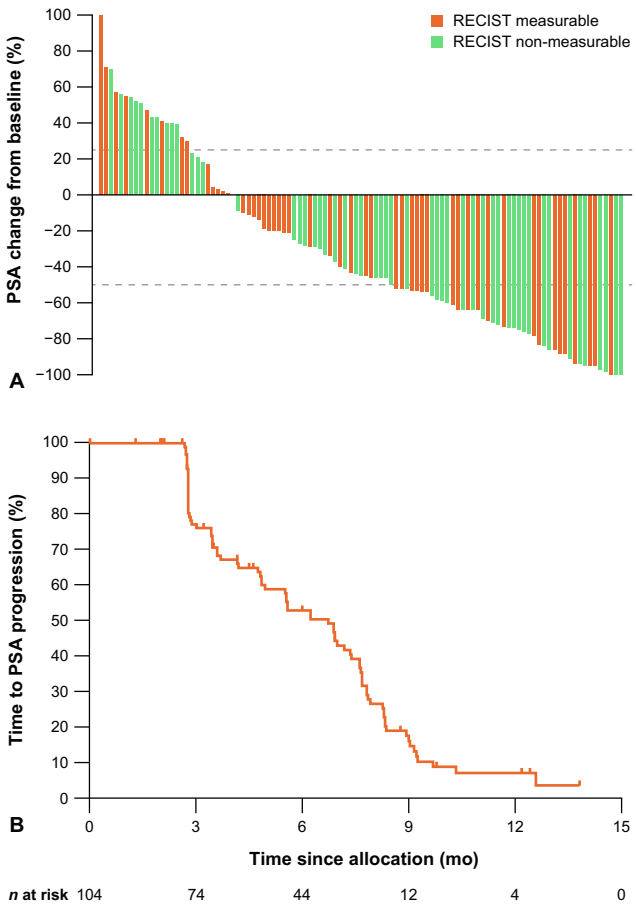

Fig. 1 – (A) Percentage PSA change from baseline (confirmed and unconfirmed; one patient did not have a baseline PSA measurement). (B) Kaplan-Meier estimate of time to PSA progression. PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

The confirmed ORR for patients with RECIST-measurable disease was 23% (CR, n = 0; PR, n = 12; Table 2). DCR was 54% for the total population by BICR according to RECIST v1.1. ORRs and DCRs were largely similar between subgroups (Supplementary Fig. 2B,C). Forty-seven of 52 patients (90%) experienced reductions in target lesion size from baseline, and 22 patients (42%) experienced reductions of >30% by BICR according to RECIST v1.1 (Fig. 2A). BICR assessment according to PCWG3-modified RECIST v1.1 revealed a DCR of 68% overall and a confirmed ORR of 33% for patients with measurable disease (Supplementary Table 1). For the 12 patients with a response, the estimated median DOR by BICR according to RECIST v1.1 was 6.3 mo (range 3.4–9.0+), and eight patients (67%) had a response duration ≥6 mo according to Kaplan-Meier estimates (Fig. 2B,C). BICR assessment according to PCWG3-modified RECIST v1.1 revealed a median DOR of 6.8 mo (range 3.4–10.4), and nine patients (62%) had a response duration ≥6 mo. Median rPFS was 8.5 mo (95% CI 8.3–10); the 6-mo rPFS rate was 77% and the 12-mo rPFS rate was 26% (Fig. 3A). Median OS was 20.2 mo (95% CI 17–24); the 6-mo OS rate was 96% and the 12-mo OS rate was 76% (Fig. 3B).

3.3. Safety

Treatment-related AEs (TRAEs) attributed by the investigator occurred in 100 patients (96%) (Supplementary Table 2).

Table 2 – Confirmed best response by blinded independent central review according to RECIST v1.1

Parameter	RECIST-MD (n = 52)	RECIST-NMD (n = 52)	Total (n = 104)
Objective response rate, % (95% CI)	23 (13–37)	NA	NA
Disease control rate, % (95% CI) [a]	52 (38–66)	56 (41–70)	54 (44–64)
Best response, n (%)			
CR	0 (0)	NA	NA
PR	12 (23)	NA	NA
SD of any duration	26 (50)	0 (0)	26 (25)
Non-CR/non-PD	0 (0)	41 (79)	41 (39)
SD or non-CR/non-PD ≥6 mo	15 (29)	29 (56)	44 (42)
PD	14 (27)	11 (21)	25 (24)

CI = confidence interval; CR = complete response; MD = measurable disease; NA = not applicable; NMD = non-measurable disease; PD = progressive disease; PR = partial response; SD = stable disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

[a] Disease control rate defined as CR + PR + SD or non-CR/non-PD ≥6 mo.

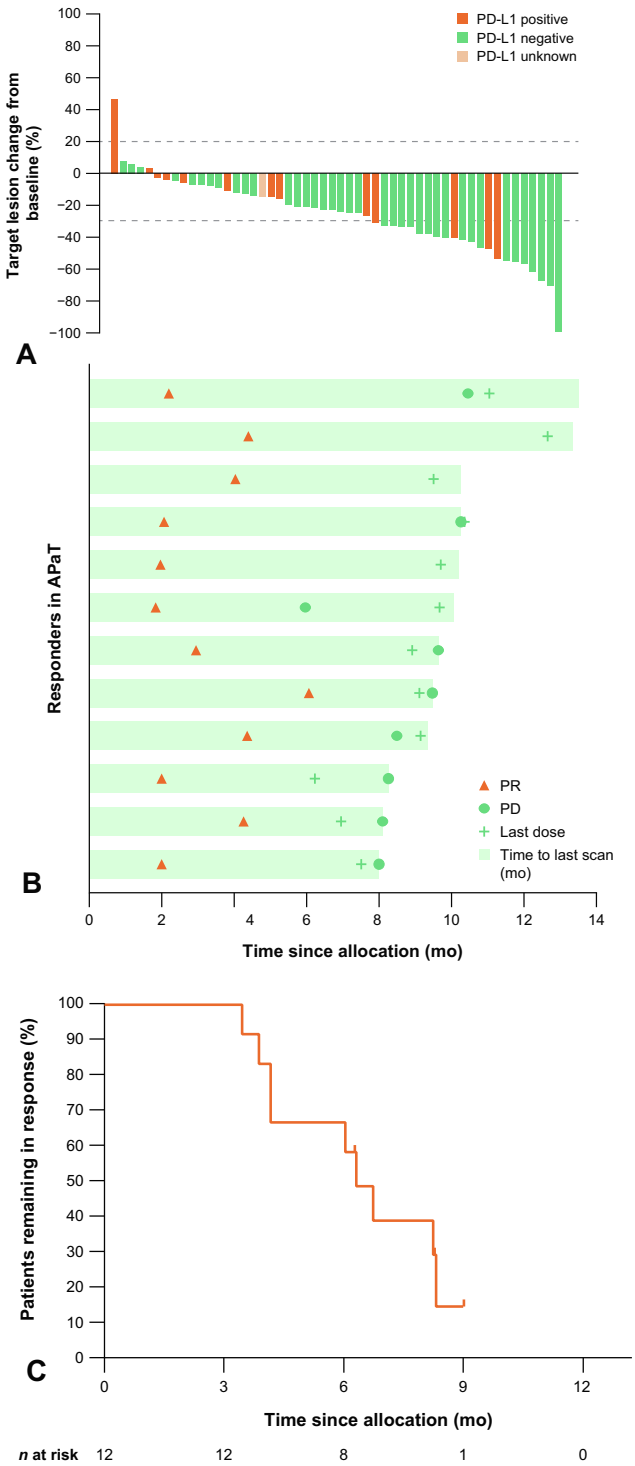

Fig. 2 – (A) Target lesion change from baseline (confirmed and unconfirmed), (B) time to response for responders by BICR according to RECIST version 1.1, and (C) Kaplan-Meier estimate of the duration of response for responders by BICR according to RECIST version 1.1. APaT = all patients as treated; BICR = blinded independent central review; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

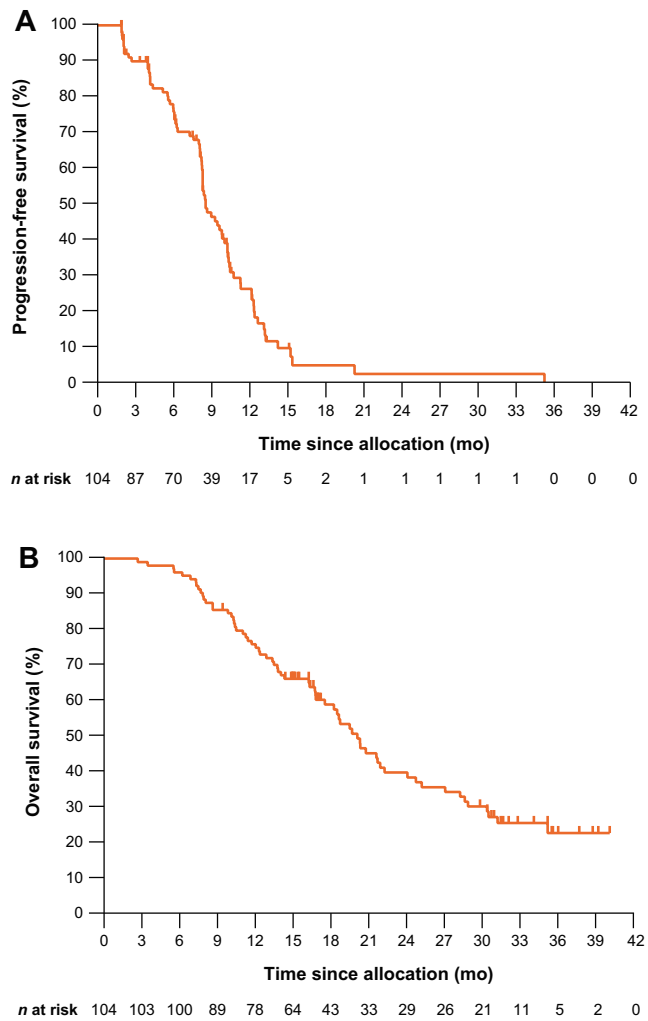

Fig. 3 – Kaplan-Meier estimates of (A) radiographic progression-free survival according to Prostate Cancer Working Group 3–modified Response Evaluation Criteria in Solid Tumors version 1.1 and (B) overall survival.

Grade 3–5 TRAEs occurred in 46 patients (44%). The most frequent TRAEs (incidence ≥20%) were diarrhea, fatigue, alopecia, dysgeusia, nausea, peripheral neuropathy, and asthenia (Table 3). The most frequent grade 3–5 TRAEs (incidence ≥2%) were febrile neutropenia, decreased neutrophil count, anemia, neutropenia, diarrhea, fatigue, pneumonitis, and decreased lymphocyte count. Serious TRAEs occurred in 24 patients (23%; Supplementary Table 3), and 28 (27%) discontinued because of TRAEs (pembrolizumab, n = 13 [13%]; docetaxel, n = 24 [23%]; prednisone, n = 10 [9.6%]).

Sponsor-defined immune-mediated AEs occurred in 34 patients (33%); nine (8.7%) experienced grade 3–5 events (pneumonitis, n = 4; colitis, n = 4; severe skin reaction, n = 1; Supplementary Table 4). The most common immune-mediated AEs (incidence ≥5%) were infusion reactions, hyperthyroidism, pneumonitis, colitis, and hypothyroidism. Of 46 immune-mediated AE episodes, ten (22%) necessitated concurrent systemic corticosteroids with a high starting dose (≥40 mg/d prednisone or equivalent).

Overall, seven patients (6.7%) died of AEs. Five deaths (4.8%) were unrelated to treatment (cerebrovascular accident, n = 1; pneumonia, n = 2; malignant neoplasm progression, n = 2). Two deaths (1.9%) from AEs (both pneumonitis, an immune-mediated AE) were related to treatment as

Table 3 – Treatment-related adverse events with ≥5% incidence among the 104 patients treated with pembrolizumab + docetaxel + prednisone

Treatment-related adverse event	Patients, *n* (%)	
	Any grade	Grade 3–5
Any	100 (96)	46 (44)
Diarrhea	43 (41)	3 (2.9)
Fatigue	43 (41)	3 (2.9)
Alopecia	42 (40)	0 (0)
Dysgeusia	28 (27)	0 (0)
Nausea	27 (26)	0 (0)
Peripheral neuropathy	23 (22)	0 (0)
Asthenia	22 (21)	2 (1.9)
Anemia	19 (18)	5 (4.8)
Decreased appetite	16 (15)	0 (0)
Peripheral edema	15 (14)	1 (1.0)
Mucosal inflammation	13 (13)	0 (0)
Febrile neutropenia	12 (12)	12 (12)
Dyspepsia	11 (11)	0 (0)
Paresthesia	11 (11)	0 (0)
Arthralgia	10 (9.6)	1 (1.0)
Dyspnea	10 (9.6)	0 (0)
Decreased neutrophil count	10 (9.6)	6 (5.8)
Peripheral sensory neuropathy	10 (9.6)	0 (0)
Hyperthyroidism	8 (7.7)	0 (0)
Nail discoloration	8 (7.7)	0 (0)
Nail disorder	8 (7.7)	0 (0)
Neutropenia	8 (7.7)	5 (4.8)
Pruritus	8 (7.7)	0 (0)
Pyrexia	8 (7.7)	0 (0)
Constipation	7 (6.7)	0 (0)
Cough	7 (6.7)	0 (0)
Dry skin	7 (6.7)	0 (0)
Infusion reaction	7 (6.7)	0 (0)
Insomnia	7 (6.7)	0 (0)
Pain in extremity	7 (6.7)	0 (0)
Pneumonitis	7 (6.7)	3 (2.9)
Exertional dyspnea	6 (5.8)	0 (0)
Flushing	6 (5.8)	0 (0)
Decreased lymphocyte count	6 (5.8)	3 (2.9)
Muscle spasms	6 (5.8)	0 (0)
Myalgia	6 (5.8)	0 (0)
Maculopapular rash	6 (5.8)	1 (1.0)

determined by the investigator. One death from pneumonitis occurred 40 d after the patient's last exposure to treatment (4 d after AE onset), and the other occurred 63 d after the patient's last exposure to treatment (13 d after AE onset).

4. Discussion

Combination therapy with pembrolizumab plus docetaxel and prednisone showed a clinical benefit for chemotherapy-naïve patients previously treated with abiraterone or enzalutamide for mCRPC in cohort B of the KEYNOTE-365 study. The confirmed PSA response rate was 34% for patients with baseline PSA measurements, with an ORR of 23% by BICR for those with measurable disease. Antitumor activity was noted in RECIST-measurable and bone-predominant disease, and in PD-L1–positive and PD-L1–negative tumors. The benefit was similar regardless of whether the previous NHA was abiraterone or enzalutamide. Among the patients with RECIST-measurable disease, none experienced CR, and 12 experienced PR as the best response. The target lesion size was reduced in 90% of patients in the current study, with 42% of patients experiencing reductions >30% by BICR. The safety profile of the combination was manageable and consistent with the profiles of the individual agents. The PSA response rate, ORR, and OS observed in the present study are higher than those observed in two cohorts of patients with RECIST-measurable mCRPC in the phase 2 KEYNOTE-199 study of pembrolizumab monotherapy (cohort 1 [PD-L1–positive]: PSA response, 6%; ORR, 6%; OS, 9.5 mo; cohort 2 [PD-L1–negative]: PSA response, 8%; ORR, 3%; OS, 7.9 mo) [18]. However, patients in KEYNOTE-199 previously received docetaxel, whereas patients in KEYNOTE-365 cohort B had chemotherapy-naïve mCRPC.

The efficacy of docetaxel was established in the phase 3 study of docetaxel and prednisone versus mitoxantrone and prednisone in patients with mCRPC who experienced progression during hormone therapy and subsequently received antiandrogen therapy [19]. Docetaxel Q3W led to a 2.4-mo improvement in OS versus mitoxantrone (18.9 vs 16.5 mo; hazard ratio [HR] 0.76, 95% CI 0.62–0.94; p = 0.009). Confirmed PSA levels decreased by ≥50% from baseline in 45% of patients receiving docetaxel and 32% receiving mitoxantrone. In the current study, the confirmed PSA response rate was 34%. The docetaxel versus mitoxantrone study took place before the development of abiraterone and enzalutamide; hence, the data are limited regarding the efficacy of docetaxel after NHA treatment, and the optimal order of therapies is not clear.

The phase 3 FIRSTANA trial compared OS after cabazitaxel (two dose schedules) versus docetaxel in 1168 patients with chemotherapy-naïve mCRPC [20]. For the docetaxel group, the median OS was 24.3 mo, the median time to tumor progression was 12.1 mo, and the tumor response rate (CR or PR) was 31%. However, few patients enrolled in FIRSTANA had previously received enzalutamide or abiraterone. In one retrospective study that included patients from a phase 1/2 abiraterone trial, median OS for patients who received docetaxel after abiraterone was 12.5 mo (95% CI 10.6–19.4), and 13 patients (37%) experienced a PSA decrease of ≥30% [21]. By contrast, the current study showed longer OS after pembrolizumab plus docetaxel and prednisone (20.2 mo, 95% CI 16.9–24.2) than previously reported. Cross-resistance between abiraterone and docetaxel could be the reason why patients receiving docetaxel after abiraterone are more likely to experience disease progression, but additional studies are needed to confirm this hypothesis [21,22]. Enzalutamide has also been used in patients with mCRPC with disease progression after abiraterone. Although the sample size was small (n = 61), a retrospective analysis compared docetaxel (n = 31) and enzalutamide (n = 30) in patients with mCRPC whose disease had progressed on abiraterone [23]. In a multivariable logistic model controlled for baseline and primary refractoriness to previous abiraterone therapy, there was no significant difference between the groups in the odds of a PSA decline of ≥30% (odds ratio 2.17, 95% CI 0.68–7.30; p = 0.20) or ≥50% (odds ratio 1.68, 95% CI 0.51–5.66; p = 0.40). Median PSA PFS was 4.1 mo for both the docetaxel and enzalutamide cohorts (HR 1.35, 95% CI 0.53–3.656); median PFS was 4.7 mo for the enzalutamide cohort and 4.4 mo for the docetaxel cohort (HR, 1.44, 95% CI 0.77–2.71; p = 0.257) [23]. A mouse model of CRPC showed lower

efficacy of docetaxel in mice with enzalutamide-resistant tumors compared with enzalutamide-naïve tumors, similar to the hypothesized cross-resistance between abiraterone and docetaxel [24]. These findings suggest that further study of the optimal sequencing of NHA and chemotherapy agents such as docetaxel may be warranted.

The current study is limited by its small sample size and single-arm design. However, the promising ORR (23%; n = 12 with PR) and OS (20.2 mo) served as a rationale to further investigate this treatment combination in KEYNOTE-921 (NCT03834506). KEYNOTE-921 is a randomized, global, parallel-group, double-blind, phase 3 trial to investigate pembrolizumab (200 mg IV Q3W) plus docetaxel (75 mg/m^2 IV Q3W) and prednisone (5 mg orally twice daily) versus placebo plus docetaxel and prednisone in patients with histologically or cytologically confirmed chemotherapy-naïve mCRPC with disease progression after NHA therapy [25].

The phase 2 CheckMate 9KD study examined the PD-L1 inhibitor nivolumab combined with docetaxel and prednisone. The ORR was 36.8%, with median rPFS of 8.2 mo after minimum follow-up of 28 wk for patients with chemotherapy-naïve mCRPC (65% previously received abiraterone or enzalutamide), similar to the rPFS in the current study (8.5 mo) with comparable safety results [26]. The subsequent phase 3 CheckMate 7DX trial will further investigate this combination.

Mismatch repair deficiency (dMMR), microsatellite instability, and/or hypermutation are believed to be potential enrichment biomarkers for response to immunotherapy in patients with solid tumor malignancies. However, the microsatellite instability-high/dMMR phenotype is rare in mCRPC, affecting only 3–4% of patients [27,28]. There is limited information about and there are no trial data for the response rate to pembrolizumab for this rare prostate cancer population. Therefore, we feel it is unlikely that our findings were significantly affected by these potential enrichment factors.

5. Conclusions

Pembrolizumab plus docetaxel and prednisone demonstrated antitumor activity in chemotherapy-naïve patients with mCRPC previously treated with abiraterone or enzalutamide for mCRPC. OS was longer than observed in previous studies in this population, and the ORR is similarly promising. The safety profile was manageable and consistent with the known profiles of each agent. Our results show activity for this combination, which will be confirmed in the phase 3 KEYNOTE-921 trial.

Author contributions: Evan Y. Yu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: None.
Obtaining funding: Massard.
Administrative, technical, or material support: Retz, Massard, Schloss.
Supervision: None.
Other (*provision of study materials/patients*): Appleman, Berry, de Bono, Emmenegger, Yu, Gravis, Gurney, Joshua, Linch, Massard, Mourey, Piulats.

Financial disclosures: Evan Y. Yu certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Evan Y. Yu has received personal fees from Bayer, Clovis, Janssen, Merck, SeaGen, Sanofi, AbbVie, Advanced Accelerator Applications, and Exelixis, and has received grants from SeaGen, Daiichi-Sankyo, Taiho, Blue Earth, and Lantheus. Michael P. Kolinsky has received personal consultancy fees from Astellas, AstraZeneca, Bayer, BMS, Eisai, Ipsen, Janssen, and Merck. William R. Berry has received personal advisory fees from Merck. Margitta Retz has nothing to disclose. Loic Mourey has received personal fees and nonfinancial support from Sanofi, Astellas, Janssen, Ipsen, AstraZeneca, Pfizer, BMS, and MSD. Josep M. Piulats has received research grants and personal fees from MSD. Leonard J. Appleman has received personal consultancy fees from AADi; has received institutional grants from Astellas Pharma, Amgen, AVEO, Bayer, BMS, Eisai, Epizyme, Exelexis, Genentech/Roche, Inovio Pharmaceuticals, Lilly, Merck, Novartis, Peleton Therapeutics, Pfizer, Surface Oncology, and Tokai; and has received institutional research contracts from Bayer, Calithera Biosciences, Seattle Genetics, and BioNTech. Emanuela Romano has nothing to disclose. Gwenaelle Gravis has received institutional research grants from Janssen, Astellas, MSD, BMS, Pfizer, Alliance Merck-Pfizer, Amgen, Sanofi, and AAA; has received personal speaker fees from Janssen, Astellas, BMS, MSD, Amgen, and Sanofi; and has received personal advisory fees from Janssen, Astellas, BMS, Pfizer, Alliance Merck-Pfizer, and AAA. Howard Gurney has received personal speaker fees from MSD and personal advisory fees from MSD, Roche, Merck, BMS, Pfizer, and Ipsen. Martin Bögemann has received personal fees from MSD, Janssen, Bayer, and Sanofi and has received a grant from Janssen. Urban Emmenegger has received personal advisory fees from Amgen, Astellas, AstraZeneca, Bayer, Ferring, Janssen, Merck, and Knight; has received institutional research grants from Astellas, AstraZeneca, Bayer, Endocyte (Novartis), Janssen, Merck, and Roche/Genentech; and has received personal research grants from Astellas, Bayer, and Janssen. Anthony M. Joshua has received institutional grants from Merck and Sanofi. Mark Linch has nothing to disclose. Srikala Sridhar has received grants from Pfizer, Bayer, and AstraZeneca; and has received personal fees from Astellas, Janssen, and Immunomedics. Henry J. Conter has received personal fees from Hoffmann La-Roche Canada. Brigitte Laguerre has received honoraria from MSD, BMS, AstraZeneca, Ipsen, and Roche; and has received personal speaker fees from Astellas, Janssen, and Pfizer. Christophe Massard has received personal consultancy fees from Amgen, Astellas, AstraZeneca, Bayer, BeiGene, BMS, Celgene, Debiopharm, Genentech, Ipsen, Janssen, Lilly, MedImmune, MSD, Novartis, Pfizer, Roche, Sanofi, and Orion; and has served as a principal investigator or subinvestigator of clinical trials for AbbVie, Aduro, Agios, Amgen, Argenx,

Astex, AstraZeneca, Aveo Pharmaceuticals, Bayer, BeiGene, Blueprint, BMS, Boehringer Ingelheim, Celgene, Chugai, Clovis, Daiichi Sankyo, Debiopharm, Eisai, Eos, Exelixis, Forma, GamaMabs, Genentech, Gortec, GSK, H3 Biomedicine, Incyte, Innate Pharma, Janssen, Kura Oncology, Kyowa, Lilly, Loxo, Lysarc, Lytix Biopharma, MedImmune, Menarini, Merus, MSD, Nanobiotix, Nektar Therapeutics, Novartis, Octimet, OncoEthix, Oncopeptides AB, Orion, Pfizer, PharmaMar, Pierre Fabre, Roche, Sanofi, Servier, Sierra Oncology, Taiho, Takeda, Tesaro, and Xencor. Xin Tong Li is an employee of MSD China. Charles Schloss and Christian H. Poehlein are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and own stock in Merck & Co., Inc., Kenilworth, NJ, USA. Johann S. de Bono has received personal fees and travel expenses for serving as an advisor for Amgen, Astellas, AstraZeneca, Bayer, BioXcel Therapeutics, Boehringer Ingelheim, CellCentric, Daiichi, Eisai, Roche/Genentech, Genmab, GlaxoSmithKline, Harpoon, Janssen, Menarini Silicon Biosystems, Merck Serono, Merck Sharp & Dohme, Orion Pharma, Pfizer, Qiagen, Sanofi Aventis, Sierra Oncology, Taiho, Terumo, and Vertex Pharmaceuticals; has received institutional grants from Astellas, AstraZeneca, Bayer, CellCentric, Daiichi, Roche/Genentech, Genmab, GlaxoSmithKline, Harpoon, Janssen, Merck Serono, Merck Sharp & Dohme, Orion Pharma, Pfizer, Sanofi Aventis, Sierra Oncology, Taiho, and Vertex Pharmaceuticals; and holds patents WO 2005 053662 licensed to AstraZeneca and US5604213 licensed to Janssen, for which he receives no personal income.

***Funding/Support and role of the sponsor*:** Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. The sponsor played a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript. Evan Y. Yu was also supported in part by the Department of Defense Prostate Cancer Clinical Trials Consortium grant W81XWH-16-PCRP-CCRSA.

Acknowledgments: The data used in this manuscript were presented in part at the American Society of Clinical Oncology 2021 Genitourinary Cancers (ASCO-GU) Virtual Symposium, February 11–13, 2021. Previous iterations of the study using earlier database cutoff dates were presented in part at the European Society for Medical Oncology (ESMO) Asia Virtual Meeting, November 20–22, 2020; the European Society of Urology Virtual Congress, July 17–21, 2020; the ESMO 2020 Virtual Congress, September 19–21, 2020; the ASCO 2020 Virtual Congress, May 29–31, 2020; the ASCO-GU Symposium, February 13–15, 2020; the ASCO 2019 Annual Meeting, May 31–June 4, 2019; and the ASCO-GU 2019 Meeting, February 14–16, 2019. We thank the patients and their families and caregivers for participating in the study. Michelle Carbuto and Adi Avidar, both from Merck & Co., Inc., Kenilworth, NJ, USA, under contract with ExecuPharm, provided study support. Medical writing and/or editorial assistance was provided by Shane Walton, PhD, and Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Data sharing statement: Merck Sharp & Dohme Corp. (MSD), a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

Appendix A. Supplementary data

Peer Review Summary and Supplementary Data associated with this article can be found online at https://doi.org/10.1016/j.eururo.2022.02.023.

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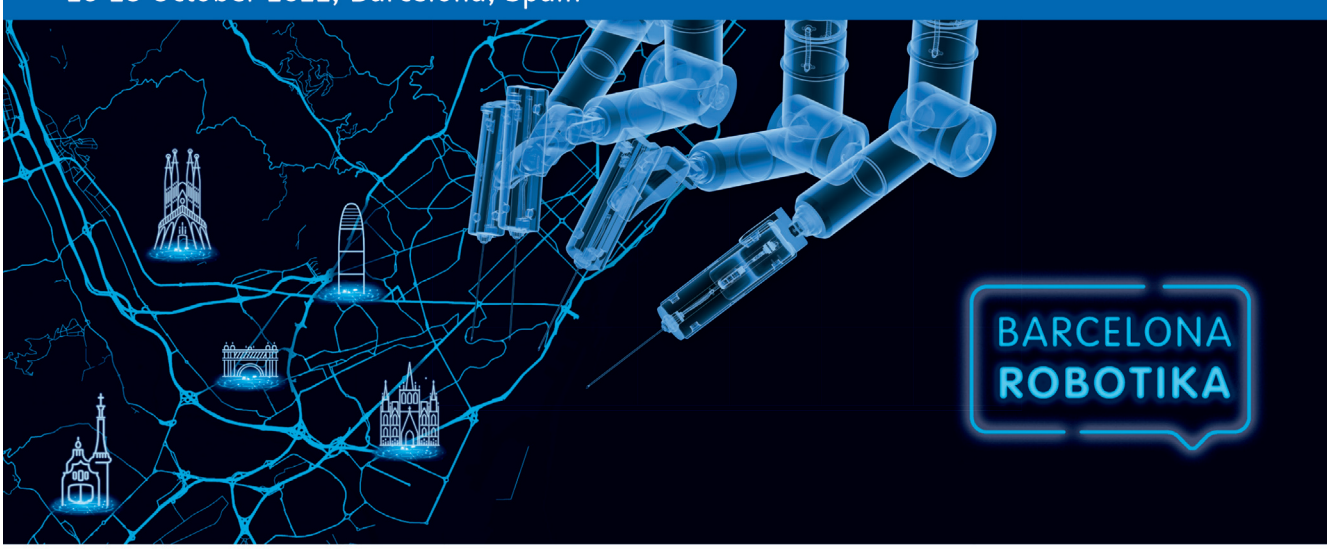

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Platinum Priority – Prostate Cancer

Editorial by Noel W. Clarke on pp. 27–28 of this issue

Pembrolizumab plus Olaparib in Patients with Metastatic Castration-resistant Prostate Cancer: Long-term Results from the Phase 1b/2 KEYNOTE-365 Cohort A Study

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Article info

Article history:
Accepted August 3, 2022

Associate Editor:
Todd M. Morgan

Statistical Editor:
Rodney Dunn

Keywords:
Metastatic castration-resistant prostate cancer
Olaparib
Pembrolizumab

Abstract

Background: Pembrolizumab and olaparib have shown single-agent activity in patients with previously treated metastatic castration-resistant prostate cancer (mCRPC).
Objective: To evaluate the efficacy and safety of pembrolizumab plus olaparib in mCRPC.
Design, setting, and participants: Cohort A of the phase 1b/2 KEYNOTE-365 study enrolled patients with molecularly unselected, docetaxel-pretreated mCRPC whose disease progressed within 6 mo of screening.
Intervention: Pembrolizumab 200 mg intravenously every 3 wk plus olaparib 400-mg capsule or 300-mg tablet orally twice daily.
Outcome measurements and statistical analysis: The primary endpoints were safety, confirmed prostate-specific antigen (PSA) response rate, and objective response rate (ORR) as per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, by blinded independent central review. The secondary endpoints included radiographic progression-free survival (rPFS) and overall survival (OS).
Results and limitations: Of 104 enrolled patients, 102 were treated. The median age was 70 yr (interquartile range [IQR], 65–76), and 59 patients (58%) had measurable disease as

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https://doi.org/10.1016/j.eururo.2022.08.005
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per RECIST v1.1. The median time from the first dose to database cutoff was 24 mo (IQR, 22–47). The confirmed PSA response rate was 15%. The confirmed ORR was 8.5% (five partial responses) for patients with measurable disease. The median rPFS was 4.5 mo (95% confidence interval [CI], 4.0–6.5) and median OS was 14 mo (95% CI, 10.4–18.2). Clinical activity was consistent across the programmed death ligand 1 (PD-L1)-positive and homologous recombination repair mutation subgroups. Treatment-related adverse events (TRAEs) occurred in 93 patients (91%). Grade 3–5 TRAEs occurred in 49 patients (48%). Six deaths (5.9%) were due to adverse events; two (myocardial infarction and unknown cause) were attributed to treatment. Limitations of the study include the single-arm design.

Conclusions: Pembrolizumab plus olaparib had a safety profile consistent with the profiles of the individual agents and demonstrated antitumor activity in previously treated patients with molecularly unselected, docetaxel-pretreated mCRPC.

Patient summary: Pembrolizumab plus olaparib showed antitumor activity and expected safety in patients with metastatic castration-resistant prostate cancer.

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1. Introduction

Standard-of-care treatment for metastatic prostate cancer is evolving rapidly, with multiple treatment options available for both hormone-sensitive and metastatic castration-resistant prostate cancer (mCRPC) [1,2]. Docetaxel in combination with prednisone was the only life-prolonging treatment for mCRPC until sipuleucel-T, an autologous cellular immunotherapy, was approved in 2010, which demonstrated that immunotherapy can improve outcomes in this disease setting [3–5]. Recent advances in drug development have produced new therapies for mCRPC, including the next-generation hormonal agents (NHAs) abiraterone acetate [6] and enzalutamide [7], poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors [8,9], radium 223 [10], lutetium-177–PSMA-617 [11], and cabazitaxel [12,13]. Despite these advances, mCRPC is incurable, and few treatment options are available to patients whose disease progresses on both docetaxel and NHAs. Therefore, a need exists for novel agents that improve clinical outcomes for patients with mCRPC.

Pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, has demonstrated preliminary activity as monotherapy for mCRPC in the open-label phase 1b KEYNOTE-028 and phase 2 KEYNOTE-199 clinical trials [14,15]. Olaparib, a PARP inhibitor, is approved by the US Food and Drug Administration for a subset of patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (*HRR*) gene-mutated mCRPC whose disease has progressed on abiraterone or enzalutamide treatment [16]. In the phase 2 TOPARP-A and TOPARP-B trials, olaparib monotherapy showed activity in patients with mCRPC and aberrations in DNA damage response genes [17,18]. In the phase 3 PROfound study of patients with mCRPC and *BRCA1*, *BRCA2*, or *ATM* gene alterations, olaparib monotherapy demonstrated longer overall (OS) and progression-free (PFS) survival and a higher objective response rate (ORR) than enzalutamide or abiraterone [8,19].

PARP inhibitors can upregulate programmed death ligand 1 (PD-L1) on the tumor cell surface, which could lead to immune activation of the tumor microenvironment and increased sensitivity to PD-1 inhibitors [20]. Even in cells that are homologous recombination proficient, PARP inhibitors amplify STING signaling and promote tumor-infiltrating lymphocytes and antitumor immunity, which can enhance anti–PD-L1 activity in vitro [21]. Therefore, addition of an anti–PD-1/PD-L1 immunotherapy with a PARP inhibitor might enhance antitumor response. Furthermore, pembrolizumab is approved by the US Food and Drug Administration for advanced microsatellite instability–high or mismatch repair–deficient cancer [22]. The phase 1b or 2 KEYNOTE-365 trial (NCT02861573) examined the safety, tolerability, and efficacy of pembrolizumab combination therapies in men with mCRPC, irrespective of *HRR* status. We describe the results from cohort A of KEYNOTE-365, which included patients with molecularly unselected, docetaxel-pretreated mCRPC who were treated with the combination of pembrolizumab and olaparib.

2. Patients and methods

2.1. Study design and patients

KEYNOTE-365 is a multicohort nonrandomized, multicenter, open-label phase 1b or 2 trial. Patients in eight countries (Australia, Canada, France, Germany, New Zealand, Spain, UK, and USA) were enrolled in cohort A. The trial was conducted in accordance with the Good Clinical Practice guidelines, and the protocol and its amendments were approved by the appropriate ethics body at each participating institution. All patients provided written informed consent.

Male patients aged 18 yr or older with molecularly unselected mCRPC were enrolled. The key eligibility criteria for cohort A were histologically or cytologically confirmed adenocarcinoma of the prostate without small cell histology, disease progression within 6 mo before screening (by prostate-specific antigen [PSA] progression as per the Prostate Cancer Working Group 3 [PCWG3] criteria or radiologic bone/soft tissue progression), Eastern Cooperative Oncology Group performance status of 0–2, and previous use of docetaxel for mCRPC.

2.2. Treatment

Patients received pembrolizumab 200 mg intravenously every 3 wk (Q3W) for up to 35 cycles (approximately 24 mo) plus olaparib 400-mg capsules (first 40 patients enrolled) or 300-mg tablets orally twice daily until confirmed disease progression, unacceptable toxicity, or withdrawal of consent. The capsule formulation of olaparib necessitated patients to take a total of 16 capsules per day, whereas the tablet formulation of olaparib is clinically equivalent to the capsule formulation, and provides a reduced pill burden and a more convenient dosing regimen of a total of four tablets per day [23]. If one of the drugs was discontinued because of toxicity, the other drug could be continued at the investigator's discretion.

2.3. Assessments and endpoints

On-study imaging assessments were performed by computed tomography or magnetic resonance imaging and radionuclide bone imaging at baseline and every 9 wk (Q9W) from the date of patient allocation to cohort A through week 54, and every 12 wk (Q12W) thereafter until documented confirmed disease progression, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurred first. PSA was assessed by a central laboratory at screening and Q3W until disease progression. Follow-up time began at the date of patient allocation to cohort A. PD-L1 positivity was defined as a combined positive score (CPS) of $\geq$1 by PD-L1 IHC 22C3 pharmDx (Agilent), in which CPS is defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

Adverse events (AEs) were monitored throughout the study and for 30 d after the last dose of study drug (90 d for serious AEs). AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Immune-mediated AEs were based on a list of terms specified by the sponsor regardless of attribution to study treatment or immune relatedness by the investigator.

The primary efficacy endpoints were confirmed PSA response (PSA decrease of $\geq$50% from baseline measured twice $\geq$3 wk apart), and ORR (complete response [CR] + partial response [PR]) as per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, by blinded independent central review (BICR). Secondary efficacy endpoints were time to PSA progression, ORR as per PCWG3-modified RECIST v1.1 by BICR, duration of response (DOR), disease control rate (DCR; CR or PR + stable disease or non-CR/non–progressive disease [PD] $\geq$6 mo) as per RECIST v1.1 and PCWG3-modified RECIST v1.1 by BICR, radiographic PFS (rPFS) as per PCWG3-modified RECIST v1.1 by BICR, and OS. Based on the TOPARP-A study [17], a composite response rate was also a secondary endpoint. The primary safety objective was to characterize the safety and tolerability of pembrolizumab plus olaparib.

Blood for circulating tumor DNA (ctDNA) was collected before the dose on day 1 of cycles 1–3. After cycle 3, ctDNA was collected before the dose Q9W through week 54 and Q12W thereafter, and at treatment discontinuation. Germline status was not specifically tested. Circulating tumor cells were measured using the CELLSEARCH circulating tumor cell test (Veridex LLC, Raritan, NJ, USA). The Guardant360 assay was initially used as it was the only validated ctDNA assay available at that time; the GuardantOMNI assay (Guardant Health, Inc., Redwood City, CA, USA) became available in 2017 and was used for patients subsequently enrolled in cohort A. *BRCA1*, *BRCA2*, and *ATM* mutations were detected using Guardant360. Formalin-fixed, paraffin-embedded tissue was analyzed by FoundationOne CDx assay (Foundation Medicine, Inc., Cambridge, MA, USA). Most tissues were archival and biopsied within 1 yr of screening and after diagnosis of mCRPC, although some patients provided older archival tissue. *BRCA1*, *BRCA2*, and *ATM* mutations were detected using Guardant360 (Guardant Health, Inc.). The *HRR* genes evaluated for mutational status using GuardantOMNI (Guardant Health, Inc.) or FoundationOne CDx (Foundation Medicine, Inc.) were *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. Both Guardant360 and GuardantOMNI have a 96–100% positive predictive value for single nucleotide variants, copy number variations, fusions, and indels [24,25]. Based on American College of Medical Genetics guidelines, only known pathogenic mutations were classified as mutations, and variants of uncertain significance were not classified as mutations [26]. Mutational status classified as unknown included cases in which there were no available samples (tissue or plasma), there was insufficient DNA, or assay results did not meet quality control. The Guardant360 test is a 73-gene panel validated for the detection of single nucleotide variations, insertion and deletion alterations, copy number alterations (CNAs), and fusions in all guideline-recommended indications for advanced solid tumors [27]. The GuardantOMNI comprehensive genomic profiling tool is a 500-gene panel that incorporates the majority of genes being evaluated in cancer drug development pipelines and biomarkers for immuno-oncology applications, including tumor mutational burden. FoundationOne CDx is a next-generation sequencing-based in vitro diagnostic device for the detection of substitutions, indels, and CNAs in 309 cancer-related genes, one promoter region, one noncoding RNA, and select intronic regions from 36 commonly rearranged genes [28].

2.4. Statistical considerations

Efficacy and safety were assessed in all patients who received at least one dose of study treatment. For ORR, patients must have had measurable disease as per RECIST v1.1 at baseline. DOR was evaluated only for patients with an objective response. The point estimates and 95% confidence intervals (CIs) for PSA response rate, ORR, DCR, and composite response rate were evaluated using the Clopper-Pearson method. The Kaplan-Meier method was used to estimate DOR, time to PSA progression, rPFS, and OS.

3. Results

3.1. Disposition, demographics, and exposure

Between January 17, 2017, and December 2, 2019, 165 patients were screened for enrollment into cohort A. Of these 165 patients, 61 were excluded and 104 were enrolled (Supplementary Fig. 1). Two patients were not treated because of a screening failure (n = 1) and physician decision (n = 1). The median age was 70 yr (interquartile range [IQR], 65–76), 29 patients (28%) had PD-L1–positive tumors, and 59 patients (58%) had measurable disease per RECIST v1.1 (Table 1). All patients received prior docetaxel, and 40 patients (39%) received prior cabazitaxel. Most patients (92%) received prior abiraterone and/or enzalutamide treatment; 45% of patients received both abiraterone and enzalutamide. The median time from allocation to data cutoff was 24 mo (IQR, 22–47). As of March 29, 2021, 95 patients (93%) had discontinued treatment, primarily because of clinical or radiographic PD (72%; Supplementary Fig. 1). Patients received a median of 7.5 administrations (IQR, 4–14) of pembrolizumab and a median olaparib daily dose of 600 mg (IQR, 590–778). The median duration of therapy was 4.9 mo (IQR, 2.6–9.7) for pembrolizumab and 5.4 mo (IQR, 2.8–10.1) for olaparib.

Table 1 – Patient demographics and baseline characteristics

Characteristic	Pembrolizumab + olaparib (*N* = 102)
Age (yr), median (IQR)	70 (65–76)
≥65 yr, *n* (%)	79 (77)
Race, *n* (%)	
White	84 (82)
Black or African American	3 (2.9)
American Indian or Alaska native	1 (1.0)
Asian	1 (1.0)
Multiple	1 (1.0)
Native Hawaiian or other Pacific Islander	1 (1.0)
Missing	11 (11)
Geographic region of enrolling site, *n* (%)	
North America	27 (26)
Western Europe	62 (61)
Rest of the world	13 (13)
ECOG PS, *n* (%)	
0	48 (47)
1	48 (47)
2	6 (5.9)
Baseline ALP value (IU/l), median (range)	101 (23–865)
Baseline HgB value (g/dl), median (range)	12 (9.6–15)
Baseline LDH value (IU/l), median (range)	222 (120–1857)
PSA value (ng/ml), median (IQR)	109 (30–480)
PD-L1 status, *n*(%)	
Positive[a]	29 (28)
Negative	28 (27)
Unknown	45 (44)[b]
Disease measurable as per RECIST v1.1, *n* (%)	59 (58)
Baseline tumor size (mm)[c], median (IQR)	75 (41–124)
Visceral disease[d], *n* (%)	34 (33)
Metastatic staging[e], *n* (%)	
M1	66 (65)
M1A	2 (2.0)
M1B	24 (23)
M1C	10 (9.8)
History of brain metastases, *n* (%)	0 (0.0)
Prior use of docetaxel, *n* (%)	102 (100)
Prior use of cabazitaxel, *n* (%)	40 (39)
Prior use of abiraterone/enzalutamide, *n* (%)	
Abiraterone only	24 (24)
Enzalutamide only	24 (24)
Abiraterone and enzalutamide	46 (45)
Neither	8 (7.8)

ALP = alkaline phosphatase; BICR = blinded independent central review; CPS = combined positive score; ECOG PS = Eastern Cooperative Oncology Group performance status; HgB = hemoglobin; IQR = interquartile range; LDH = lactate dehydrogenase; PD-L1 = programmed death ligand 1; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] PD-L1 positive was defined as CPS ≥1. CPS was defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells, multiplied by 100.

[b] Thirty-two patients had bone-only disease.

[c] Assessed by BICR as per RECIST v1.1.

[d] Soft tissue (not in brain, bone, or lymph nodes).

[e] Patients with M1 designation may not have been subdivided into A, B, or C categories.

3.2. *Genomic analysis*

The Guardant360 assay was used for the first 42 patients enrolled in the study, and the GuardantOMNI assay was used for 60 subsequently enrolled patients. By a ctDNA analysis, three patients had a *BRCA* gene mutation (n = 2 *BRCA2*; n = 1 *BRCA1*) and 14 had an *HRR* gene mutation. Notably, no *HRR* mutations were detected using the Guardant360 assay (first 42 patients), and plasma-negative results were classified as unknown because mutational status was uncertain. Of 76 patient samples with soft tissue available for FoundationOne CDx analysis, 41 passed quality control successfully. Twelve patients had *HRR* mutations, four had a *BRCA* mutation, and no microsatellite instability alterations were detected. The overall percentage agreement between Guardant Health and FoundationOne CDx assays was 98% for *BRCA* mutation status and 87% for *HRR* status (Supplementary Table 1). In at least one assay, 18 of 102 patients (18%) had tumors identified as having an *HRR* mutation, and four (3.9%) had a *BRCA* mutation.

3.3. *Efficacy*

The confirmed PSA response rates in patients with a baseline PSA measurement were 15% (15/102) for the total population and 19% (11/59) for patients with RECIST-measurable disease. Overall, of 102 patients, 51 (50%) had any reduction in PSA from baseline (confirmed and unconfirmed) and 19 (19%) had ≥50% PSA reduction from baseline (confirmed and unconfirmed; Fig. 1A). The median time to confirmed PSA progression was 4.0 mo (95% CI, 3.0–4.9; Fig. 1B). PSA response rates were generally consistent across subgroups, including in the PD-L1 and *HRR* mutation subgroups, although the analysis is limited by a low patient population in certain subgroups (Supplementary Fig. 2A and Supplementary Table 2).

By BICR as per RECIST v1.1, ORR was 8.5% (five PRs) in patients with RECIST-measurable disease (Table 2). For all 102 treated patients, the DCR was 26%. Similar to PSA response rate, ORR and DCR were generally consistent between subgroups, including the PD-L1 and *HRR* mutation subgroups (Supplementary Fig. 2B and 2C, and Supplementary Table 2). Thirty-four patients (58%) with RECIST-measurable disease experienced a reduction in target lesion size from baseline (confirmed and unconfirmed); 11 (19%) experienced a >30% reduction (Fig. 2A). The median time to response was 8.3 mo (IQR, 2.1–8.8; Fig. 2B). The median DOR was 24 mo (IQR, 8.3–12.3), and 75% of responses were ongoing at 12 mo by the Kaplan-Meier estimate. The composite response rate (confirmed objective response, confirmed PSA response, or a circulating tumor cell response reduction of circulating tumor cells from five or more cells per 7.5 ml blood at baseline to fewer than five cells per 7.5 ml blood during treatment) was 18% in the total population, 24% in patients with RECIST-measurable disease, and 9.3% in patients without measurable disease.

By BICR as per PCWG3-modified RECIST v1.1, ORR was 12% (seven PRs) in patients with measurable disease. DCR was 36% in all treated patients (Supplementary Table 3). The median time to response was 8.3 mo (IQR, 2.1–8.8), and the median DOR was not reached; 83% of responses were ongoing at 12 mo by the Kaplan-Meier estimate.

In all 102 treated patients, the median rPFS was 4.5 mo (95% CI, 4.0–6.5), the 6-mo rPFS rate was 47%, and the 12-mo rPFS rate was 27% (Fig. 3A). The median OS was 14 mo (95% CI, 10.4–18.2; Fig. 3B). The 6-mo OS rate was 80%, and the 12-mo OS rate was 56%. The median rPFS was 4.1mo (95% CI, 2.1–13) in the PD-L1–positive subgroup and 5.2 mo (95% CI, 4.0–11) in the PD-L1–negative subgroup (Supplementary Fig. 3A). The median OS was 10 mo (95% CI,

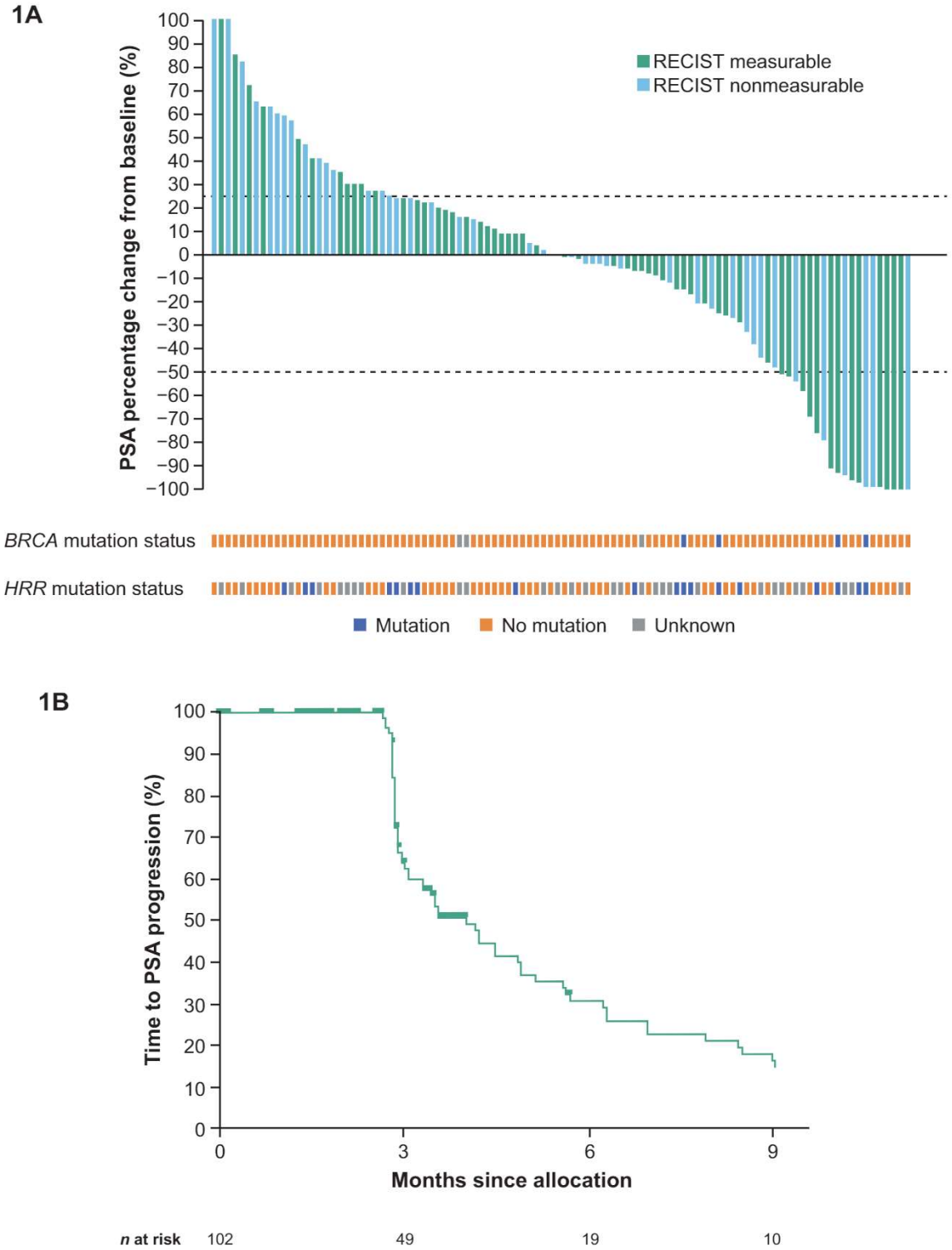

Fig. 1 – (A) PSA percentage change from baseline (confirmed and unconfirmed) and (B) Kaplan-Meier estimate of time to PSA progression. CI = confidence interval; HRR = homologous recombination repair; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

6.5–20) in the PD-L1–positive subgroup and 18 mo (95% CI, 7.7–31) in the PD-L1–negative subgroup (Supplementary Fig. 3B). By *HRR* status, the median rPFS was 6.5 mo (95% CI, 2.1–14.1) and the median OS was 8.9 mo (95% CI, 6.5–18) in patients with an *HRR* mutation (Supplementary Fig. 4A and 4B). In patients with no *HRR* mutation, the median rPFS was 4.5 mo (95% CI, 4.0–11) and the median OS was 17 mo (95% CI, 10–31; Supplementary Fig. 4A and 4B).

Table 2 – Confirmed best response by BICR assessment as per RECIST v1.1

Characteristic	RECIST-measurable disease (n = 59)	RECIST-nonmeasurable disease (n = 43)	Total (N = 102)
ORR, % (95% CI)	8.5 (2.8–19)	NA	NA
DCR[a], % (95% CI)	25 (15–38)	28 (15–44)	26 (18–36)
Best response, n (%)			
CR	0 (0.0)	NA	0 (0.0)
PR	5 (8.5)	NA	5 (4.9)
SD of any duration	20 (34)	0 (0.0)	20 (20)
Non-CR/non-PD	0 (0.0)	23 (53)	23 (23)
SD or non-CR/non-PD ≥6 mo	10 (17)	12 (28)	22 (22)
PD	30 (51)	17 (40)	47 (46)
Nonevaluable	0 (0.0)	2 (4.7)	2 (2.0)
No assessment	4 (6.8)	1 (2.3)	5 (4.9)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; DCR = disease control rate; NA = not applicable; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Defined as the proportion of patients who had an objective response (CR or PR) or who had SD or non-CR/non-PD for at least 6 mo.

3.4. *Safety*

All 102 treated patients (100%) experienced at least one all-cause AE, and grade 3–5 AEs occurred in 74 patients (73%; Supplementary Table 4). Treatment-related AEs occurred in 93 patients (91%; Table 3). Grade 1 treatment-related AEs occurred in 17 patients (17%), grade 2 treatment-related AEs occurred in 27 patients (26%), and grade 3–5 treatment-related AEs occurred in 49 patients (48%). Nineteen patients (19%) discontinued treatment because of treatment-related AEs. Olaparib-related AEs occurred in 89 patients (87%); 45 patients (44%) experienced grade 3–5 olaparib-related AEs (Table 3). Pembrolizumab-related AEs occurred in 75 patients (74%); 20 patients (20%) experienced grade 3–5 pembrolizumab-related AEs (Table 3). Twenty patients (20%) had a serious treatment-related AE (Supplementary Table 4).

Immune-mediated AEs occurred in 12 patients (12%), with four (3.9%) experiencing events with a toxicity grade 3–5 (pneumonitis [n = 2], adrenal insufficiency [n = 1], and severe skin reaction [n = 1]; Supplementary Table 5). Six patients (5.8%) received corticosteroids to manage immune-mediated AEs. Three of 15 episodes (20%) of immune-mediated AEs were treated with high-dose corticosteroids (≥40 mg/d prednisone or equivalent).

Overall, six patients (5.9%) died of AEs. Four deaths (3.9%) occurred from AEs considered unrelated to treatment by the investigator (colorectal cancer [n = 1], general health deterioration [n = 1], *Pneumocystis jirovecii* pneumonia [n = 1], and unknown cause [n = 1]); two deaths (1.9%) from AEs were determined by the investigator to be treatment related (myocardial infarction [n = 1] and unknown cause [n = 1]).

4. Discussion

Advances in therapy over the past decade have improved survival and quality of life for patients with mCRPC. However, the median OS for patients with metastatic disease treated with newer therapies is approximately 2.8 yr, indicating a need for novel agents that may improve patient outcomes [29]. In the present study, pembrolizumab plus olaparib demonstrated durable antitumor activity in a limited number of men with molecularly unselected docetaxel-pretreated mCRPC in cohort A of the KEYNOTE-365 study. The confirmed PSA response rate was 15%, with an ORR of 8.5% and a DCR of 26% by BICR as per RECIST v1.1. The ORR was generally consistent across subgroups in this study.

This was a heavily pretreated population; 92% of patients had previously received both docetaxel and enzalutamide and/or abiraterone treatment, 39% had previously received cabazitaxel, and 45% had previously received both abiraterone and enzalutamide. Interim results from the COSMIC-021 study of cabozantinib in combination with atezolizumab showed an ORR of 15% in patients with mCRPC who had previously received enzalutamide and/or abiraterone treatment; however, only 25% of patients had previously received docetaxel for metastatic hormone-sensitive prostate cancer [30]. Other studies have reported limited success in this heavily pretreated patient population. In the phase 3 COMET-1 study, cabozantinib did not improve OS compared with prednisone (11 vs 9.8 mo, p = 0.213) in patients with progressive mCRPC who had previously received docetaxel [31]. A lack of success has also been reported in a heavily pretreated mCRPC population that received radium-223 [32]. An increase in PSA level was observed in 20 of 29 patients (69%) in a retrospective study of patients with mCRPC treated with radium-223; 52% (15/29) of patients had a >50% increase in PSA [32]. Satraplatin, a fourth-generation oral platinum compound, plus prednisone was compared with placebo plus prednisone for chemotherapy-refractory mCRPC [33]. Compared with placebo (n = 315), satraplatin plus prednisone (n = 635) was associated with a benefit in PFS (median, 11 vs 9.7 wk; hazard ratio [HR], 0.67; 95% CI, 0.57–0.77; p < 0.001) but not in OS (median, 61 vs 61 wk; HR, 0.98; 95% CI, 0.84–1.2; p = 0.80).

Patients in this study were not preselected by biomarker status. In a biomarker-defined subgroup of patients with mCRPC who had DNA-repair defects in the phase 2 TOPARP-A trial, a composite response rate of 88% was observed with olaparib monotherapy [17]. These results were confirmed in the phase 2 TOPARP-B trial of patients with mCRPC and aberrations in DNA damage response genes, including *BRCA1/2*, *ATM*, *CDK12*, and *PALB2*; the greatest antitumor activity was observed in patients with *BRCA1/2* mutations (ORR, 52%) [18]. Patients with mCRPC enrolled in the phase 3 PROfound study whose tumors were *HRR* mutation positive had longer median OS when treated with olaparib than patients treated with an NHA (19 vs 15mo) [8].

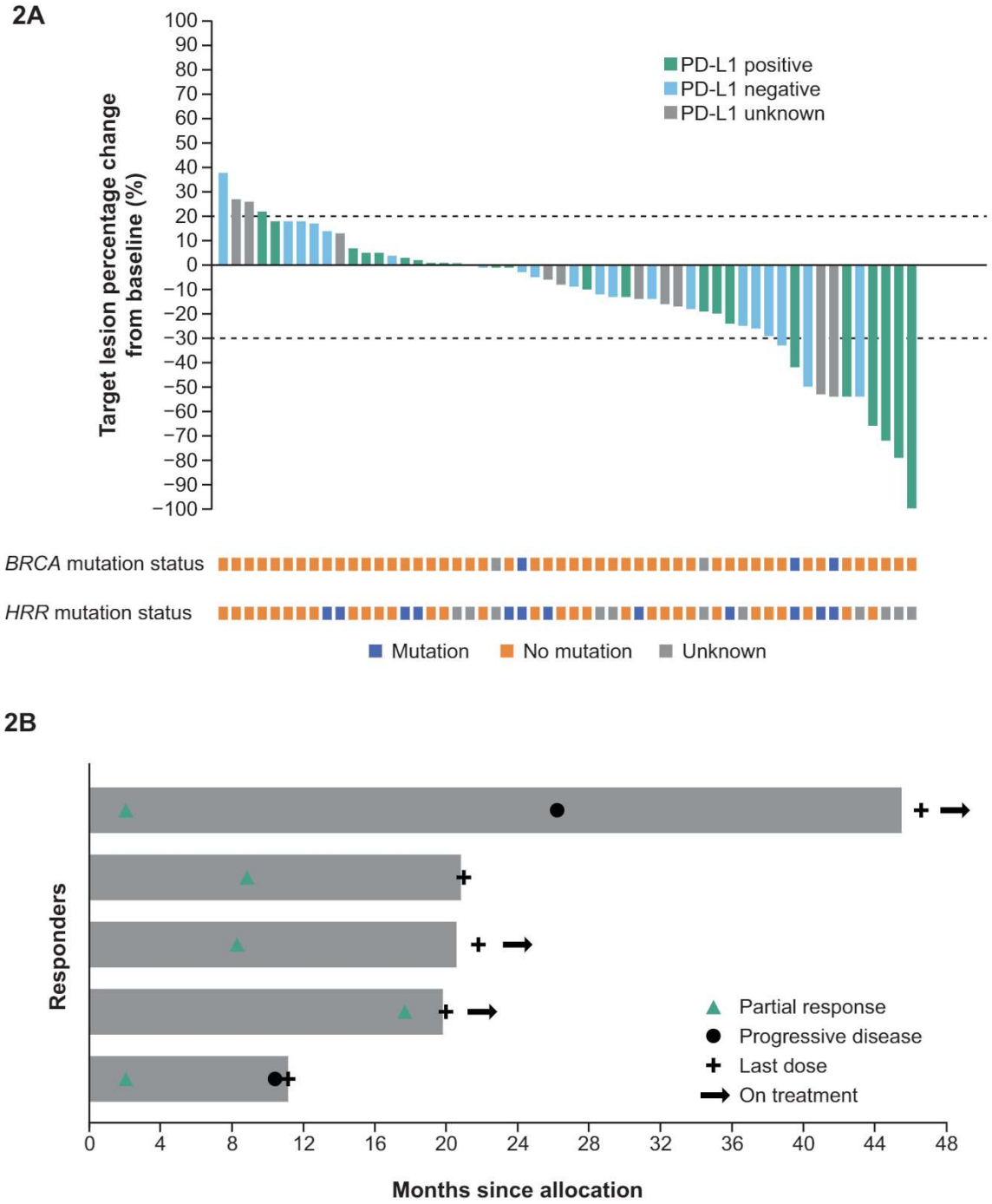

Fig. 2 – (A) Best target lesion percentage change from baseline (confirmed and unconfirmed) and (B) time to response by BICR as per RECIST v1.1. BICR = blinded independent central review; HRR = homologous recombination repair; NE = nonevaluable; NR = not reached; PD = progressive disease; PD-L1 = programmed death ligand 1; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

Previous studies have also shown antitumor activity of pembrolizumab monotherapy in prostate cancer. In the phase 1b KEYNOTE-028 study, pembrolizumab monotherapy demonstrated antitumor activity in heavily pretreated patients with mCRPC with PD-L1–positive prostate cancer with an ORR of 17% and a median DOR of 14 mo [14]. Pembrolizumab monotherapy also demonstrated antitumor activity and disease control in the phase 2 KEYNOTE-199 study; an ORR of 3.9%, a DCR of 26%, and median OS of 9.6mo were observed among all patients with either RECIST-measurable or bone-predominant mCRPC who previously received docetaxel and NHA therapy (eg, enzalutamide or abiraterone) [14,15]. In patients with solid tumors with mismatch repair gene mutations, an ORR of 53%, which included 18 CRs, was observed with pembrolizumab monotherapy; these results led to a regulatory

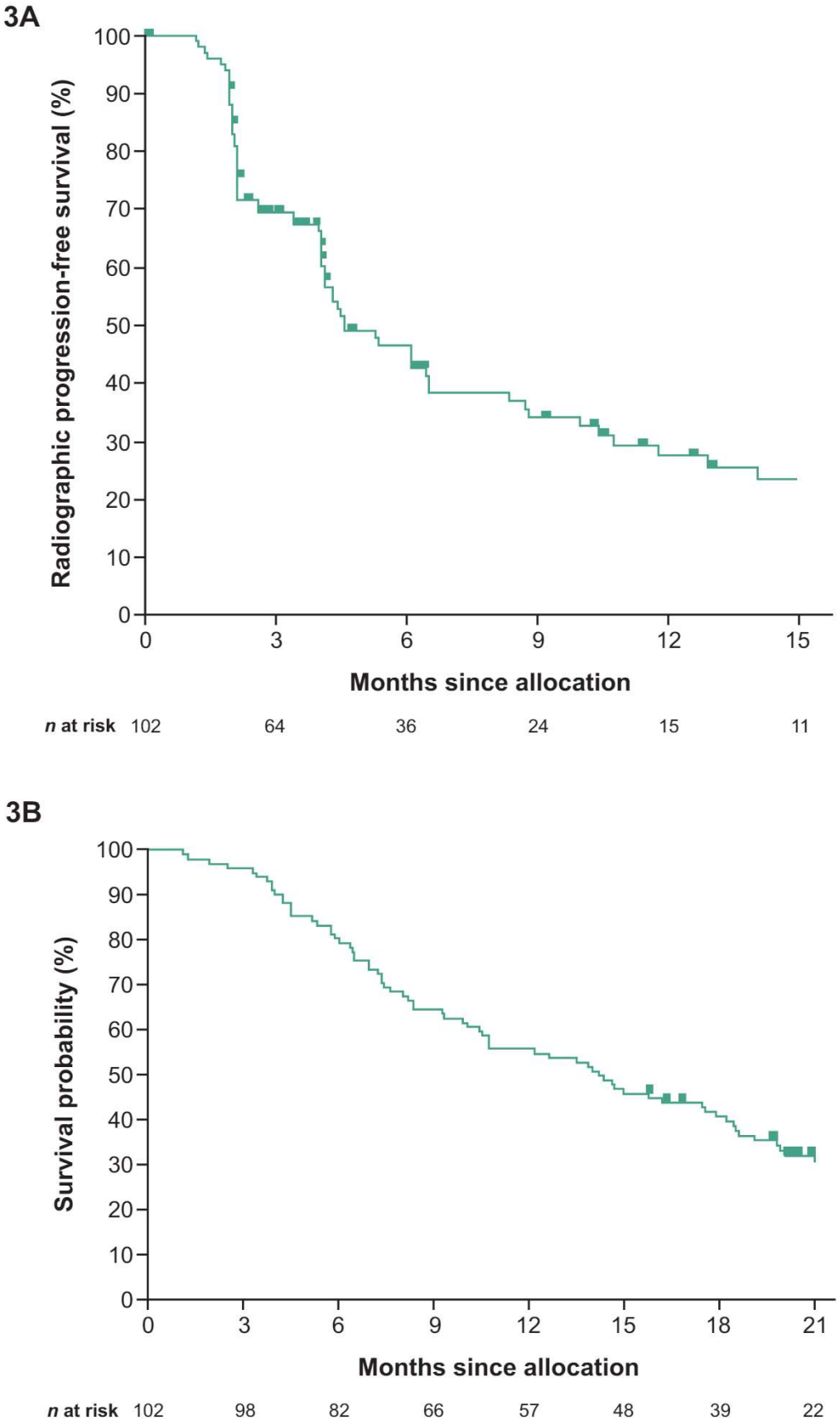

Fig. 3 – Kaplan-Meier estimates of (A) radiographic progression-free survival as per PCWG3-modified RECIST v1.1 and (B) overall survival. CI = confidence interval; PCWG3 = Prostate Cancer Working Group 3; RECIST = Response Evaluation Criteria in Solid Tumors.

Table 3 – Pembrolizumab- and/or olaparib-related adverse events with ≥3% incidence

Treatment-related adverse event, *n* (%)	Pembrolizumab + olaparib (*N* = 102)		Olaparib-related (*N* = 102)		Pembrolizumab-related (*N* = 102)	
	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5
Any	93 (91)	49 (48)	89 (87)	45 (44)	75 (74)	20 (20)
Anemia	42 (41)	28 (27)	42 (41)	28 (27)	6 (5.9)	3 (2.9)
Nausea	42 (41)	2 (2.0)	41 (40)	2 (2.0)	15 (15)	1 (1.0)
Decreased appetite	31 (30)	0 (0.0)	31 (30)	0 (0.0)	15 (15)	0 (0.0)
Fatigue	31 (30)	6 (5.9)	29 (28)	6 (5.9)	22 (22)	3 (2.9)
Asthenia	29 (28)	4 (3.9)	28 (27)	4 (3.9)	24 (24)	2 (2.0)
Vomiting	27 (26)	1 (1.0)	27 (26)	1 (1.0)	11 (11)	0 (0.0)
Diarrhea	23 (23)	0 (0.0)	18 (18)	0 (0.0)	17 (17)	0 (0.0)
Neutropenia	12 (12)	5 (4.9)	12 (12)	5 (4.9)	1 (1.0)	0 (0.0)
Pruritus	11 (11)	0 (0.0)	4 (3.9)	0 (0.0)	11 (10.8)	0 (0.0)
Rash	10 (9.8)	1 (1.0)	4 (3.9)	1 (1.0)	9 (8.8)	1 (1.0)
Blood creatinine increased	9 (8.8)	0 (0.0)	7 (6.9)	0 (0.0)	4 (3.9)	0 (0.0)
Weight decreased	9 (8.8)	0 (0.0)	9 (8.8)	0 (0.0)	3 (2.9)	0 (0.0)
Thrombocytopenia	7 (6.9)	2 (2.0)	7 (6.9)	2 (2.0)	1 (1.0)	0 (0.0)
Arthralgia	5 (4.9)	0 (0.0)	4 (3.9)	0 (0.0)	3 (2.9)	0 (0.0)
Dysgeusia	5 (4.9)	0 (0.0)	5 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism	5 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.9)	0 (0.0)
Constipation	4 (3.9)	0 (0.0)	4 (3.9)	0 (0.0)	3 (2.9)	0 (0.0)
Cough	4 (3.9)	0 (0.0)	3 (2.9)	0 (0.0)	3 (2.9)	0 (0.0)
Dizziness	4 (3.9)	0 (0.0)	4 (3.9)	0 (0.0)	2 (2.0)	0 (0.0)
Dyspnea	4 (3.9)	1 (1.0)	3 (2.9)	1 (1.0)	3 (2.9)	1 (1.0)
Platelet count decreased	4 (3.9)	1 (1.0)	4 (3.9)	1 (1.0)	1 (1.0)	0 (0.0)

approval through the US Food and Drug Administration in patients with microsatellite instability–high or mismatch repair–deficient cancer [22,34]. Although olaparib monotherapy is approved for patients with an *HRR* gene mutation [16], the combination of pembrolizumab and olaparib demonstrates activity regardless of *HRR* mutation status. Notably, olaparib plus abiraterone has shown significant improvement in rPFS compared with abiraterone alone in patients with mCRPC regardless of mutational status [35].

Pembrolizumab plus olaparib had an expected safety profile, which was consistent with the profiles of the individual agents [8,36]. The most common treatment-related AEs of any grade were anemia (41%) and nausea (41%). A greater percentage of patients had grade 3–5 AEs related to olaparib (44%) than related to pembrolizumab (20%).

The current study is limited by its open-label design and lack of comparator group. Although clinical outcomes were largely consistent across subgroups, PD-L1 status was unknown in 44% of patients, and results should be interpreted with caution. There were also a limited number of patients with an *HRR* mutation, determined from the heterogeneity of testing assays. The observed activity in this study, independent of PD-L1 or *HRR* mutation status, served as a rationale to further investigate this treatment combination in the ongoing phase 3 KEYLYNK-010 trial (NCT03834519). KEYLYNK-010 was a randomized, global, parallel-group, open-label phase 3 trial investigating the combination of pembrolizumab plus olaparib versus abiraterone or enzalutamide in abiraterone- or enzalutamide-pretreated patients with docetaxel-pretreated mCRPC. Although the median OS of 14 mo observed in this analysis was considered comparable with the existing literature in patients previously treated with docetaxel, no survival benefit was observed between pembrolizumab plus olaparib versus abiraterone acetate or enzalutamide in the KEYLYNK-010 trial [31,33,37–40].

5. Conclusions

The combination of pembrolizumab plus olaparib demonstrated limited antitumor activity and had an expected safety profile in patients with molecularly unselected docetaxel-pretreated mCRPC. Biomarker data suggest that antitumor activity with this treatment combination is independent of PD-L1 or *HRR* mutation status.

***Author contributions*:** Evan Y. Yu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Carles, de Bono, Fong, Gravis, Gurney, Heinzelbecker, Kolinsky, Laguerre, Massard, Nordquist, Oudard, Piulats, Qiu, Poehlein, Schloss, Tafreshi, Todenhöfer, Yu.
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Critical revision of the manuscript for important intellectual content: Arranz, Augustin, Carles, de Bono, Fong, Gravis, Gurney, Heinzelbecker, Kolinsky, Laguerre, Li, Massard, Nordquist, Oudard, Piulats, Qiu, Poehlein, Schloss, Tafreshi, Todenhöfer, Yu.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: None.
Other: None.

***Financial disclosures*:** Evan Y. Yu certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed,

received, or pending), are the following: Evan Y. Yu has received personal fees from AbbVie, Advanced Accelerator Applications, Amgen, AstraZeneca, Bayer, Clovis, Dendreon, Exelixis, Janssen, Merck, Pharmacyclics, SeaGen, Inc., QED, and Sanofi, and has received grants paid to his institution from Blue Earth, Daiichi Sankyo, Lantheus, SeaGen, Inc., Merck, and Taiho. Josep M. Piulats has received research grants and personal fees from MSD. Gwenaelle Gravis has received research grants paid to her institution from AAA, Alliance Merck-Pfizer, Amgen, Astellas, BMS, Janssen, MSD, Pfizer Inc., and Sanofi; has received personal fees for serving as a speaker for Amgen, Astellas, BMS, Janssen, MSD, and Sanofi; and has received personal fees for serving as an advisor for AAA, Alliance Merck-Pfizer, Astellas, BMS, Janssen, and Pfizer Inc. Peter C.C. Fong has received personal fees for serving as an advisor for MSD and has received travel/accommodations expenses from Pfizer. Tilman Todenhöfer has received personal fees for serving as an advisor for Amgen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen-Cilag, Merck, MSD, Pfizer, Roche, and Sanofi. Brigitte Laguerre has received honoraria from AstraZeneca, BMS, Ipsen, MSD, and Roche, and has received personal fees for serving as a speaker for Astellas, Janssen, and Pfizer Inc. Jose A. Arranz has received honoraria from Astellas, Pfizer, and BMS; has received personal fees for serving as an advisor for Astellas, Pfizer, BMS, Janssen Cilag, MSD, BMS, Astra Zeneca, and Eisai; and has received research funding paid to his institution from BMS. Stephane Oudard has received research grants paid to her institution from Alliance Merck-Pfizer, Astellas, BMS, Janssen, Pfizer Inc., and Sanofi; has received personal fees for serving as a speaker for AAA, Astellas, Bayer, BMS, Ipsen, Janssen, MSD, Novartis, Pfizer Inc., Roche, and Sanofi; and has received personal fees for serving as an advisor for Amgen, AAA, Alliance Merck-Pfizer, Astellas, BMS, Janssen, and Sanofi. Christophe Massard has received personal fees for serving as a consultant for Amgen, Astellas, AstraZeneca, Bayer, BeiGene, BMS, Celgene, Debiopharm, Genentech, Ipsen, Janssen, Lilly, MedImmune, MSD, Novartis, Pfizer Inc., Roche, Sanofi, and Orion; and has served as a principal investigator or subinvestigator of clinical trials for AbbVie, Aduro, Agios, Amgen, Argenx, Astex, AstraZeneca, Aveo Pharmaceuticals, Bayer, BeiGene, Blueprint, BMS, Boehringer Ingelheim, Celgene, Chugai, Clovis, Daiichi Sankyo, Debiopharm, Eisai, Eos, Exelixis, Forma, GamaMabs, Genentech, Gortec, GSK, H3 Biomedicine, Incyte, Innate Pharma, Janssen, Kura Oncology, Kyowa, Lilly, Loxo, Lysarc, Lytix Biopharma, MedImmune, Menarini, Merus, MSD, Nanobiotix, Nektar Therapeutics, Novartis, Octimet, OncoEthix, Oncopeptides AB, Orion, Pfizer Inc., PharmaMar, Pierre Fabre, Roche, Sanofi, Servier, Sierra Oncology, Taiho, Takeda, Tesaro, and Xencor. Julia Heinzelbecker has served on advisory boards from Eisai, has received honoraria/personal fees from Janssen, BMS, Merck, Boston Scientific, and Roche and has received travel/accommodation expenses from Ipsen, Pfizer, Bayer, and Janssen. Luke T. Nordquist has no conflicts to declare. Joan Carles has received person fees for serving as a consultant to Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Johnson & Johnson, MSD Oncology, Novartis (AAA), Pfizer, Roche, and Sanofi; has participated in speakers' bureau for Astellas Pharma, Bayer, and Johnson & Johnson; has received research funding for her institution from AB Science, Aragon Pharmaceuticals, Arog Pharmaceuticals, Inc., Astellas Pharma, AstraZeneca AB, Aveo Pharmaceuticals, Inc., Bayer AG, Blueprint Medicines Corporation, BN Immunotherapeutics, Boehringer Ingelheim España, S.A., Bristol Myers Squibb International Corporation (BMS), Clovis Oncology, Inc., Cougar Biotechnology Inc., Deciphera Pharmaceuticals LLC, Exelixis, Inc., F. Hoffmann-La Roche LTD, Genentech Inc., GlaxoSmithKline, SA, Incyte Corporation, Janssen-Cilag International NV, Karyopharm Therapeutics, Inc., Laboratoires Leurquin Mediolanum SAS, Lilly, S.A., MedImmune, Millennium Pharmaceuticals, Inc., Nanobiotix SA, Novartis Farmacéutica, S.A., Pfizer, S.L.U, Puma Biotechnology, Inc., Sanofi-Aventis, S.A., SFJ Pharma LTD. II, Teva Pharama S.L.U.; and has received travel/accommodations expenses from BMS, Ipsen, Roche, and AstraZeneca. Michael P. Kolinsky has received personal fees for serving as a consultant for Merck. Marinela Augustin has received personal fees for serving as a consultant to Bristol Myers Squib, MSD, Pfizer, Merck, PharmaMar, Ipsen, AstraZeneca, Novartis, Bayer, and Roche; has received research funding for her institution from Bristol Myers Squibb, MSD, Morphosys, AstraZeneca, Pfizer, PharmaMar, Ipsen, and Exelixis; and has received travel/accommodation expenses from Lilly, Novartis, Bristol Myers Squibb, PharmaMar, Ipsen, and Pfizer. Howard Gurney has received personal fees for serving as a speaker for MSD and as an advisor for BMS, Ipsen, Merck, MSD, Pfizer Inc., and Roche. Ali Tafreshi has no conflicts to disclose. Xin Tong Li is an employee of MSD China. Ping Qiu is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and owns stock in Merck & Co., Inc., Rahway, NJ, USA. Christian H. Poehlein is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and owns stock in Merck & Co., Inc., Rahway, NJ, USA. Charles Schloss is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and owns stock in Merck & Co., Inc., Rahway, NJ, USA. Johann S. de Bono has received personal fees and travel expenses for serving as an advisor for Amgen, Astellas, AstraZeneca, Bayer, BioXcel Therapeutics, Boehringer Ingelheim, CellCentric, Daiichi, Eisai, Roche/Genentech, Genmab, GlaxoSmithKline, Harpoon, Janssen, Menarini Silicon Biosystems, Merck Serono, Merck Sharp & Dohme, Orion Pharma, Pfizer Inc., Qiagen, Sanofi Aventis, Sierra Oncology, Taiho, Terumo, and Vertex Pharmaceuticals; has received grants paid to his institution from Astellas, AstraZeneca, Bayer, CellCentric, Daiichi, Roche/Genentech, Genmab, GlaxoSmithKline, Harpoon, Janssen, Merck Serono, Merck Sharp & Dohme, Orion Pharma, Pfizer Inc., Sanofi Aventis, Sierra Oncology, Taiho, and Vertex Pharmaceuticals; and holds patents WO 2005 053662 licensed to AstraZeneca and US5604213 licensed to Janssen, for which he receives no personal income.

***Funding/Support and role of the sponsor*:** This work was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Evan Y. Yu was also supported in part by the Department of Defense Prostate Cancer Clinical Trials Consortium grant W81XWH-16-PCRP-CCRSA.

***Acknowledgments*:** The data featured in this manuscript were presented in part at the American Urological Association Virtual Congress, September 10–13, 2021, and the European Society for Medical Oncology (ESMO) Virtual Congress, September 16–21, 2021. Previous iterations of the study using earlier database cutoff dates were presented in part at the ESMO Asia Virtual Meeting, November 20–22, 2020; European Association of Urology Virtual Congress, July 17–21, 2020; ESMO 2020 Virtual Congress, September 19–21, 2020; ASCO Virtual Congress, May 29–31, 2020; ASCO-GU, February 13–15, 2020, San Francisco, CA; ASCO Annual Meeting, May 31–June 4, 2019, Chicago, IL; and ASCO-GU, February 14–16, 2019, San Francisco, CA. We thank the patients and their families and caregivers for participating in the study. Medical writing and/or editorial assistance was provided by Robert Steger, PhD, and Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

***Data sharing*:** Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants, and as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the

process and requirements for submitting a data request. Applications will be assessed promptly for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the USA and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor, or construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

Peer Review Summary and Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2022.08.005.

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UNIVERSITY OF WASHINGTON
SCHOOL OF MEDICINE

September 12, 2022

Heather H. Cheng

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Date: 2022.10.10 09:36:50 -07'00'

CURRICULUM VITAE

HEATHER H. CHENG, MD, PhD

1. Personal Data:

Place of birth: Taipei, Taiwan
Citizenship: USA

2. Education:

1994-1998 — Bachelor of Arts, Molecular Biology
Princeton University, Princeton, NJ

2000-2005 — Doctor of Philosophy, Molecular and Cellular Biology
University of Washington, Seattle, WA

1998-2007 — Doctor of Medicine (NIH Medical Scientist Training Program)
University of Washington School of Medicine, Seattle, WA

3. Postgraduate Training:

06/2007-06/2009 — Internship and Residency, Internal Medicine
University of Washington, Seattle, WA

07/2009-08/2014 — Fellowship, Hematology-Oncology (ABIM Research Pathway)
University of Washington, Seattle, WA

4. Faculty Positions Held:

03/2014-06/2019 — Assistant Professor, Division of Medical Oncology, Department of Medicine,
University of Washington, Seattle, WA

03/2014-06/2019 — Assistant Professor, Clinical Research Division, Fred Hutchinson Cancer
Research Center, Seattle, WA

07/2019-present — Associate Professor, Division of Medical Oncology, Department of Medicine
University of Washington, Seattle, WA

07/2019-present — Associate Professor, Clinical Research Division, Fred Hutchinson Cancer
Research Center, Seattle, WA

04/2021-present — Adjunct Associate Professor, Department of Laboratory Medicine and Pathology,
University of Washington, Seattle, WA

5. Hospital Positions Held:

03/2014-present — Attending Physician, Genitourinary Medical Oncology Clinics
Seattle Cancer Care Alliance, Seattle, WA

03/2014-present — Attending Physician, Inpatient Oncology Service, Oncology Consult Service,
University of Washington Medical Center, Seattle, WA

09/2016-present — Director, Prostate Cancer Genetics Clinic
Seattle Cancer Care Alliance, Seattle, WA

02/2019-present — Attending Physician, Genitourinary Cancer Risk Management (GU/GICP)
Seattle Cancer Care Alliance, Seattle, WA

6. Current (non-UW) Employment: n/a

7. Honors:

1998 Sigma Xi Society, Princeton, NJ
1998 New Jersey Cancer Commission Research Fellowship
2000 Paul Allen Research Fellowship
2009 University of Washington School of Medicine: Resident Teaching Award
2010 University of Washington: Honor Your Physician Award (patient-nominated)
2012 American Society of Clinical Oncology/National Cancer Institute Markers in Cancer Meeting, Merit Award
2014 American Society of Clinical Oncology Genitourinary Oncology Symposium, Merit Award
2014 American Society of Clinical Oncology Annual Meeting, Merit Award
2015 Prostate Cancer Foundation Young Investigator Award
2015 SWOG Integrated Translational Science Workshop, Cold Spring Harbor
2017 Becker's Healthcare, Rising Stars: Healthcare Leaders Under 40
2020 National Cancer Institute, Cancer Clinical Investigator Team Leadership Award

8. Board Certification:

2010 American Board of Internal Medicine, Certification in Internal Medicine
2013 American Board of Internal Medicine, Certification in Medical Oncology

9. Current License(s) to Practice:

Washington State Medical License #MD60095549 expires 11/03/2024
DEA #FC2472328 expires 08/31/2025

10. Diversity, Equity and Inclusion Activities:

2020-present Prostate Cancer Clinical Trials Consortium Diversity and Outreach Committee

11. Professional Organizations:

2022-present American Urological Association
2009-present American Society of Clinical Oncology
2005-present American Association of Cancer Research
2013-present Southwest Oncology Group (SWOG)
2005-2009 American College of Physicians
1998-2009 Physicians for Social Responsibility

12. Teaching Responsibilities:

Courses:

University of Washington School of Medicine:

2012-2013 ***HUBIO 513, 522 and 535****, Intro to Clinical Medicine,* Small Group Leader
2014 ***MEDECK 614****, Medical Oncology Clerkship*, Richard Stein, MS4 (Fall 2014).
2014 ***HUBIO 550***, *Introduction to Clinical Medicine*, panelist
2014-2016 ***MED 505****, Dept of Medicine Preceptorship,* clinical preceptor: Dilip Nagakar, MS1 (Fall 2014); Caroline Jackson, MS1 (Fall 2015); J.D. Neumeister, MS2 (Fall 2016)
2016-2017 ***MEDSCI 540A****, Blood and Cancer*, small group leader

Teaching/Committees:

A. Internal Medicine Residents, Graduate & Medical Students (*primary mentor)

2017	Paul Katangole, MD, MS, (Uganda Cancer Institute), mentor for NCI Fogarty International Center Fellow Candidate
2018-2019	*Darren Pouv, University of Washington School of Medicine: MS1, primary research mentor, Independent Investigative Inquiry
2020	Emiko M. Oshima, University of Washington School of Medicine: MPH candidate, research mentoring committee member

2022-present	Sunny Ren, University of Washington Genetic Counseling Program, Masters candidate, research project co-mentor

B. Subspecialty Fellows (*primary/co-primary mentor)

2014-2015	Faculty advisor for UW/FHCRC Heme/Onc Fellows' Solid Tumor Conference, biweekly
2014-present	Teaching Faculty for Heme/Onc fellows and Internal Medicine residents in Genitourinary Oncology and Bladder Multi-disciplinary Clinics and Inpatient Oncology service.
2018-2021	***Alexandra Sokolova, MD,** University of Washington/Fred Hutch Hematology/Oncology fellow, primary research mentor, current position: **Assistant Professor at Oregon Health Sciences University**
2019-present	**Heme/Onc Fellowship Faculty Champion for Outpatient Genitourinary Oncology Block**
2019-2022	**Risa Wong, MD**, University of Washington/Fred Hutch Hematology/Oncology fellow, research co-mentor, **current position: Assistant Professor at University of Pittsburg**
2021-present	***Hiba Khan, MD, MPH,** University of Washington/Fred Hutch Hematology/Oncology fellow, primary research co-mentor
2022-present	**Ruben Raychaudry, MD,** University of Washington/Fred Hutch Hematology/Oncology fellow, research project co-mentor

13. Editorial Responsibilities: n/a

14. Special National Responsibilities:

June 2017	Organizing Chair, Coffey-Holden Prostate Cancer Academy*, Carlsbad, CA (*prestigious, invitation-only annual meeting for ~75 prostate cancer researchers)
June 2017-	Chair, Prostate Cancer Clinical Trials Consortium/PCF Genetics Working Group
2017-2018	Co-Leader, Prostate Cancer Foundation DNA Repair Working Group
October 2017	Session Chair, DNA Repair, Prostate Cancer Foundation 24th Scientific Retreat, Washington D.C.
February 2018	Prostate Cancer Foundation Delegation on Prostate Cancer Genetics, Tel Aviv, Israel
April 2018-	Healthcare and Scientific Advisory Board, FORCE: Facing Hereditary Cancer Empowered Organization
June 2018	Education Session Chair, American Society for Clinical Oncology, 2018 Annual Meeting, Practical Methods for Integrating Genetic Testing into Clinical Practice for Advanced Prostate Cancer, Chicago, IL
August 2019-	Member, **Prostate Cancer Guidelines Panel, National Comprehensive Cancer Network, (NCCN)**
2020-2021	Board of Directors, Us-TOO International Prostate Cancer Education and Support Network (private, non-profit 501(c)3)
October 2020-	**Member, Prostate Cancer Task Force, National Cancer Institute Genitourinary Steering Committee**
June 2021-	**Member, American Society for Clinical Oncology, Annual Meeting Education Committee**: Genitourinary Cancer—Prostate, Testicular, and Penile Track (3-year term)
August 2021-	Member, Germline and Somatic Genomic Testing for Advanced and Metastatic Prostate Cancer Guideline Panel, American Society for Clinical Oncology
March 2022-	Member, American Urological Association Salvage Therapy for Prostate Cancer Panel
May 2022-	Member, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Panel **Guidelines Panel, National Comprehensive Cancer Network, (NCCN)**
June 2022-	Member, Scientific Advisory Committee, BRCA Research & Cure Alliance (CureBRCA)

15. Special Local Responsibilities:

2011	University of Washington Hematology-Oncology Fellowship, fellow representative
2010-2011	University of Washington Hematology-Oncology Fellows Orientation Handbook, first editor and author
2011-2012	University of Washington Hematology-Oncology Solid Tumor Conference, fellow organizer
2014-2019	Genitourinary Cancer Clinical Research Database, faculty lead
2015-2016	Seattle Cancer Care Alliance Schwartz Center Rounds Planning Committee
2016-present	**Fred Hutch/University of Washington Cancer Consortium Data Safety Monitoring Committee**
2018-2021	Fred Hutch/Clinical Research Division, Appointments and Promotions Committee
2019-2020	Fred Hutch/Human Biology Division, Prostate Program Faculty Search Committee
2020-present	**Associate Program Director, University of Washington/Fred Hutch Medical Scientist Training Program**
2021	Fred Hutch/UW Cancer Consortium Pilot Award Review Committee
2020-2021	SCCA Genitourinary Medical Oncology Community Research Working Group lead

16. Research Funding

CURRENT RESEARCH SUPPORT

Title: A ph I/II trial of concurrent chemohormonal therapy using enzalutamide (MDV-3100) and cabazitaxel in patients with metastatic castration resistant prostate cancer.
Major Goals: To determine safe dosing level. To collect correlative biospecimens to understand the biological effects of the treatment and to evaluate for potential prognostic biomarkers. The major goal of this project is to test the safety and efficacy of combination treatment with enzalutamide (MDV3100) and cabazitaxel chemotherapy of prostate cancer.
Status of Support: Active
Project Number: MDV3100
Name of PD/PI: Heather Cheng
Source of Support: PCCTC, LLC (Medivation and Sanofi)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 07/14/16 to 11/30/22
Total Award Amount: [redacted]
Overlap: None

Title: PROSTATE CANCER CLINICAL TRIALS CONSORTIUM, W81XWH-17-2-0043 (Cheng)
Major Goals: The Department of Defense provides funding for infrastructure to support participation as a clinical site in the Prostate Cancer Clinical Trials Consortium.
Status of Support: Active
Project Number: W81XWH-17-2-0043
Name of PD/PI: Heather Cheng
Source of Support: US Department of Defense (DOD)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 09/30/2017 to 09/29/2022
Total Award Amount: [redacted]
Overlap: None

Title: Clinical qualification of DNA repair defects as biomarkers in metastatic prostate cancer using integrated genomics and tissue-based functional assays.
Major Goals: We aim to evaluate tissue-based tests of HR proficiency to stratify patients to receive DNA repair targeting agents. In a two-step approach, we will optimize the test and study the correlation with genomic data in a cohort of mCRPC biopsies, to then implement the assay into a clinical trial to stratify patients for receiving treatment with carboplatin, a DNA damaging chemotherapy.

Status of Support: Active
Project Number: W81XWH-15-1-0430
Name of PD/PI: Colin Pritchard
Source of Support: US Department of Defense (DOD)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 09/30/18 to 09/29/22
Total Award Amount: [redacted]
Overlap: None

Title: A phase 1b study of enzalutamide plus CC-115 in men with castration-resistant prostate cancer.
Major Goals: The major goal of this study is to determine the safety, pharmacokinetics, and the Maximum Tolerated Dose and/or Recommended Phase 2 Dose of the combination of CC-115 plus enzalutamide.
Status of Support: Active
Project Number: CC-115
Name of PD/PI: Heather Cheng
Source of Support: PCCTC, LLC (Celgene)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 10/01/17 to 12/31/22
Total Award Amount: [redacted]
Overlap: None

Title: PLATI-PARP: A phase 2 study of induction docetaxel and carboplatin followed by maintenance rucaparib in treatment of patients with metastatic castration resistant prostate cancer with homologous recombination DNA repair deficiency
Status of Support: Active
Project Number: 338-IIT-071
Name of PD/PI: Heather Cheng
Source of Support: Clovis Oncology, Inc
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 07/26/2018 to 08/30/2022
Total Award Amount: [redacted]
Overlap: None

Title: Pacific Northwest (PNW) Prostate Cancer Sponsored Program of Research Excellence (SPORE) Project 1: Molecular Predictors of Prostate Cancer Progression and Mortality
Major Goals: The proposed study will ascertain and recruit germline cancer risk mutation carriers from: 1) population- and clinic-based incident cases of metastatic PC to find index cases with germline cancer risk mutations; 2) to conduct a PC early detection study incorporating novel biomarkers for unaffected, male germline mutation carriers (including first degree relatives of those with metastatic PC who are mutation carriers); and 3) to understand the cascade genetic testing process what will facilitate an innovative recruitment strategy for recruiting men at highest genetic risk of aggressive prostate cancer.
Status of Support: Active
Project Number: 5 P50 CA097186-16
Name of PD/PI: Peter Nelson
Source of Support: NIH/NCI
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 09/01/18 to 08/31/23
Total Award Amount: [redacted]
Overlap: None

Title: ACT PROMISE (Cheng)
Major Goals: The major goal of this study, in collaboration with Dr. Channing Paller, is to design, implement, recruit patients, and identify prostate cancer patients who carry germline pathogenic variants, assessing frequency, family history, outcomes, longitudinal treatment response, treatment sequences and therapy combinations.

Status of Support: Active
Project Number: ACT c19-235-Promise Registry
Name of PD/PI: Heather Cheng
Source of Support: DOD PROSTATE CANCER CLINICAL TRIALS CONSORTIUM
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 06/19/2020 to 06/30/2022
Total Award Amount: [redacted]
Overlap: None

Title: Enhanced Genetic Awareness and Genetic Evaluation for Men Through Technology - The ENGAGEMENT Study
Major Goals: The project will 1) Develop and implement a web-based virtual PCA genetics board across academic, community, and VA settings. Perceived usefulness, acceptability, self-efficacy for genetically-based recommendations, and genetics knowledge from dynamic case-based learning will be assessed. 2) Establish a web-based, national, patient-driven registry for any male who has undergone PCA genetic testing to assess men's experience with the genetic evaluation process and inform patient centered genetics practice and resource development. 3) Utilize digital media to share updated information on genetic testing and precision management of PCA through a public-facing podcast series.
Status of Support: Active
Project Number: W81XWH2010310
Name of PD/PI: Heather Cheng
Source of Support: US Department of Defense (DOD)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 09/30/2020-09/29/2023
Total Award Amount: [redacted]
Overlap: None

Title: CO-338-063
Major Goals: The major goal of this study is to assess the efficacy of rucaparib versus physician's choice of treatment based on radiographic progression free survival (rPFS) in mCRPC patients with HRD who progressed on prior AR-directed therapy and have not yet received chemotherapy in the castration-resistant setting.
Status of Support: Active
Project Number: CO-338-063
Name of PD/PI: Celestia Higano (2018-2021) Heather Cheng (2021 – Present)
Source of Support: Clovis Oncology
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 8/21/2018 – 4/30/2023
Total Award Amount: [redacted]
Overlap: None

Title: 67652000PCR3002
Major Goals: The major goal of this study is to assess the primary endpoint, rPFS, and defined as the time from the date of the randomization to the date of radiographic progression, or death.
Status of Support: Active
Project Number: 67652000PCR3002
Name of PD/PI: Heather Cheng
Source of Support: Janssen Research & Development, LLC
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 8/16/2021 – 1/31/2026
Total Award Amount: [redacted]
Overlap: None

Title: Long-read DNA-sequencing and targeted RNA-Seq to identify previously undetectable classes of mutations in families with lethal prostate cancer.

Major Goals: We intend our approach to improve genetic testing for inherited predisposition to prostate cancer, particularly in families with a severe history of the disease but no genetic diagnosis. We will Inform all patients with positive test results and integrate new genetic information into their care following NCCN guidelines for mutation carriers and offer genetic testing to their family members. As such, our proposal specifically addresses the overarching challenge of reducing lethal prostate cancer in high risk populations.
Status of Support: Active
Project Number: W81XWH-21-1-0343
Name of PD/PI: Tomas D. Walsh
Source of Support: US Department of Defense (DOD)
Primary Place of Performance: University of Washington Medical Center – Seattle, WA
Project/Proposal Start and End Date: 06/01/2021 – 05/31/2024
Total Award Amount: [redacted]
Overlap: None

Title: A Phase 1, open label study evaluating the safety, pharmacokinetics and clinical effects of intravenously administered PT-112 injecting in patients with advanced solid tumors and subsequent expansion cohorts
Major Goals: Define the recommended dose level for PT-112, administered on Days 1 and 15 of each 28-day cycle, for pivotal studies based on the risk/benefit ratio of 360 mg/m2 (Arm 1) and 250 mg/m2 (Arm 2) dose levels.
Status of Support: Active
Project Number: PT-112-101
Name of PD/PI: Heather Cheng
Source of Support: Phosplatin Therapeutics LLC
Supporting Agency: Phosplatin Therapeutics LLC
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 9/28/21 – 7/31/2026
Total Award Amount: [redacted]
Overlap: None

Title: Technology-Enhanced Acceleration of Germline Evaluation for Therapy - The TARGET Study
Major Goals: The proposed study will 1) evaluate understanding of providers around genetic testing in prostate cancer patients and uncover barriers to identifying patients who meet the NCCN guidelines for genetic testing. 2) develop a mobile app to assist providers in educating patients and identifying candidates for genetic testing. 3) devise a randomized clinical trial comparing mobile-assisted app to traditional, in-person genetic counseling for men with metastatic prostate cancer in different practice settings.
Status of Support: Active
Project Number: 080-27000-U23201
Name of PD/PI: Heather Cheng
Source of Support: Prostate Cancer Foundation
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 08/06/20 – 12/31/2022
Total Award Amount: [redacted]
Overlap: None

PENDING RESEARCH SUPPORT

Title: IRONMAN: An International Registry and/or the PMC Sub-Study for Men with Advanced Prostate Cancer
Major Goals: The primary objective of this substudy is to describe the response and DOR to olaparib among subjects with mCRPC whose disease has progressed following prior treatment with an NHA. Subjects with a mutation in one of the nine HRR genes (BARD1, BRIP1, CHEK1, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L) that were evaluated in five or fewer subjects within cohort B of the PROfound study will be included in the study.

Status of Support: Pending
Project Number: C16-170
Name of PD/PI: Heather Cheng
Source of Support: AstraZeneca Pharmaceuticals, LP (via PCCTC, LLC)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 08/18/17 – 01/31/2029
Total Award Amount: [redacted]
Overlap: None

Title: Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men with Advanced Prostate Cancer (IRONMAN)
Major Goals: The major goal of this study is to create an international, population-based, prospective registry of at least 5,000 men with advanced prostate cancer.
Status of Support: Pending
Project Number: C15-160
Name of PD/PI: Heather Cheng
Source of Support: Movember (via PCCTC, LLC)
Primary Place of Performance: Fred Hutch Cancer Center – Seattle, WA
Project/Proposal Start and End Date: 08/18/17 – 01/31/2029
Total Award Amount: [redacted]
Overlap: None

COMPLETED RESEARCH SUPPORT

1998	New Jersey Cancer Commission Research Fellowship
1998-2000	NIH Medical Scientist Training Program Fellowship
2000-2004	Paul Allen Research Fellowship
2010-2013	NIH T32 Training in Cancer Biology and Transplantation Fellowship

Title: SWOG 1216: A phase III randomized trial comparing androgen deprivation therapy + TAK-700 with androgen deprivation therapy + bicalutamide in patients with newly diagnosed metastatic hormone sensitive prostate cancer
Supporting Agency: NIH/NCI (U10 CA180828)
Performance Period: 05/20/14 – 02/28/18
Level of Funding: [redacted]
Project Goals: Compare overall survival in newly diagnosed metastatic prostate cancer patients randomly assigned to androgen deprivation therapy (ADT) (LHRHa or orchiectomy) + TAK-700 versus ADT (LHRHa or orchiectomy) + bicalutamide.

Title: Genitourinary Cancer Clinical Research Database Support
Supporting Agency: Institute for Prostate Cancer Research (IPCR)
Performance Period: 09/01/14 – 12/31/19
Level of Funding: [redacted]
Project Goals: The GU Cancer Clinical Research Database (GUCCRD) is designed to inventory, display, aggregate, and integrate comprehensive clinical information derived from patients with prostate cancer (and potentially other GU malignancies).

Title: Cancer Center Support Grant: New Investigator Award
Supporting Agency: NIH/NCI (P30 CA015704)
Performance Period: 12/15/14 – 12/31/19
Level of Funding: [redacted]
Project Goals: The major goal of this project is to recruit new investigators who will further the strategic objectives of the University of Washington/Fred Hutchinson Cancer Consortium. Specifically, this project will develop infrastructure to study the underlying genetic causes of early onset prostate cancer and familial prostate cancer.

Title: Defining the role of cancer risk genes in early-onset, lethal prostate cancer
Supporting Agency: NIH/NCI (P50 CA097186)
Performance Period: 01/01/15 – 12/31/15
Level of Funding: [redacted]
Project Goals: The major goal of this project is to examine the role of germline cancer risk genes in early-onset, lethal prostate cancer and parlay the resulting data into future research projects.

Title: Identifying germline cancer risk genes in advanced prostate cancer
Supporting Agency: NIH/NCI (P50 CA097186)
Performance Period: 01/01/15 – 08/31/16
Level of Funding: [redacted]
Project Goals: The major goal of this project is to identify the underlying genetic cause in some hereditary prostate cancer families--especially those with early-onset, aggressive prostate cancer--by examining tumor suppressor genes known to be involved in other familial cancer syndromes.

Title: A precision clinical trial targeting DNA repair defects
Supporting Agency: Institute for Prostate Cancer Research (IPCR)
Performance Period: 07/01/15 – 12/31/19
Level of Funding: [redacted]
Project Goals: The major goal of this project is to determine if men with tumors that harbor DNA repair defects will exhibit the hypothesized enhanced sensitivity to platinum-based chemotherapy.

Title: 2016 Challenge Award: Exploiting DNA repair vulnerabilities as a precision oncology target in metastatic prostate cancer
Supporting Agency: Movember Foundation & Prostate Cancer Foundation
Performance Period: 07/31/15 – 07/31/18
Level of Funding: [redacted]
Project Goals: The major goal of this project is to test the hypothesis that aberrations in key genes that repair DNA strand breaks by homologous repair are predictive of meaningful clinical responses to FDA-approved genotoxic therapeutics.

Title: 2015 PCF Young Investigator Award: Identifying high-penetrance prostate cancer risk genes: leveraging families for next generation discovery and prevention
Supporting Agency: Prostate Cancer Foundation
Performance Period: 10/01/15 – 09/30/18
Level of Funding: [redacted]
Project Goals: The major goals of this project are to collect families affected by prostate cancer and discover new prostate cancer risk genes, to collect men with prostate cancer who are found via tumor testing to carry high-penetrance germline cancer risk mutations, and to provide both groups of men and their family members with access to better educational materials, genetic counseling resources, and research opportunities.

Title: PCa-001: Phase I, open-label trial to evaluate the safety and immugenicity of INO-5150 alone or in combination with INO-9012 in men with biochemically relapsed (PSA) prostate cancer
Supporting Agency: Inovio Pharmaceuticals
Performance Period: 11/12/15 – 11/11/18
Level of Funding: [redacted]
Project Goals: The major goal of this study is to test the study drug INO-5150 (plasmid DNA vaccine) for prostate specific proteins alone or in combination with INO-9012 (plasmid DNA vaccine for human interleukin 12) to see how safe they are and if they cause any side effects or generate an immune response against prostate cancer cells when given by intramuscular injection followed by electroporation.

Title: Pharmacogenetic dissection of protein synthesis control across the spectrum of PI3K pathway mutations in prostate cancer

Supporting Agency: Movember Foundation & Prostate Cancer Foundation (2016CHAL1523)
Performance Period: 10/01/16 – 09/30/18
Level of Funding: [redacted]
Project Goals: The major goal of this project is to delineate the biology of various PI3K pathway mutations that occur in CRPC and develop strategies to effectively target tumors harboring these mutations.

Title: CRISPR-excision and long-read sequencing of BRCA1, BRCA2, PALB2 and ATM to identify previously undetectable classes of mutations in families severely affected with advanced prostate cancer (PIs Tom Walsh, Heather Cheng)
Level (%) of effort: 10%
Funding Agency: Brotman Baty Institute
Performance period: 02/01/2020 to 01/31/2021
Total level of Funding: [redacted]
Goals of the project: The goal is to identify complex structural mutations in advanced prostate cancer families that have been missed by current sequencing approaches.

Title: Telehealth to Reduce Prostate Cancer Burden in Rural Underserved Communities
Effort: 0.30 calendar
Supporting Agency: Fred Hutchinson Cancer Research Center CCSG (NIH)
Contracting/Grants Officer: Heidi Tham, hharbach@fredhutch.org, (206) 667-7245
Performance Period: 07/01/18 to 12/31/21
Level of Funding: [redacted]
Project Goals: The major goal of this study is to provide prostate cancer patients in rural areas with access to treatment options and resources they may not otherwise receive from a general practitioner.
Specific Aims: 1) Evaluate the telehealth program through patient-reported outcomes, 2) assess some clinician-directed and health system-responsiveness outcomes, and 3) specifically assess the outcomes in the prostate cancer Genetics Clinic, with an eye toward developing a model on which to base other niche clinics in genitourinary oncology.

Title: A phase 1b study of enzalutamide plus CC-115 in men with castration-resistant prostate cancer
Effort: 0.60 calendar
Supporting Agency: PCCTC, LLC (Celgene)
Performance Period: 10/01/17 to 12/31/21
Level of Funding: [redacted]
Project Goals: The major goal of this study is to determine the safety, pharmacokinetics, and the Maximum Tolerated Dose and/or Recommended Phase 2 Dose of the combination of CC-115 plus enzalutamide.

Title: A ph I/II trial of concurrent chemohormonal therapy using enzalutamide (MDV-3100) and cabazitaxel in patients with metastatic castration resistant prostate cancer
Effort: 0.60 calendar
Supporting Agency: PCCTC, LLC (Medivation and Sanofi)
Performance Period: 07/14/16 to 11/30/21
Level of Funding: [redacted]
Project Goals: The major goal of this project is to test the safety and efficacy of combination treatment with enzalutamide (MDV3100) and cabazitaxel chemotherapy of prostate cancer.
Specific Aims: To determine safe dosing level. To collect correlative biospecimens to understand the biological effects of the treatment and to evaluate for potential prognostic biomarkers.

Title: The Galahad Study: A phase 2 efficacy and safety study of niraparib in men with metastatic castration-resistant prostate cancer and DNA-repair anomalies
Effort: 0.60 calendar
Supporting Agency: Janssen Research & Development, LLC
Performance Period: 12/28/16 to 12/27/21
Level of Funding: [redacted]

Project Goals: The major goal of this project is to assess the efficacy of niraparib in men with mCRPC and DNA-repair anomalies who have measurable disease by looking at the objective response rate.
Specific Aims: To assess the efficacy of niraparib in subjects with mCRPC and DNA-repair anomalies.

17. Bibliography:

Scopus Index (08/25/2022)
h-index: 26
Cumulative citations: 6,921

Google Scholar, All (08/25/2022)
h-index: 28
Cumulative citations: 9325

a) Publications in Refereed Journals

1. Pöpperl H, Rikhof H, **Cheng H.**, Haffter P, Kimmel CB, Moens CB. lazarus is a novel pbx gene that globally mediates hox gene function in zebrafish. Molecular Cell. 2000 Aug; 6(2): 255-267. [**original work**]

2. Lauring, A.S., **Cheng, H.H.**, Eiden, M.V., and Overbaugh, J. Genetic and biochemical analyses of receptor and cofactor determinants for T-cell-tropic feline leukemia virus infection. Journal of Virology. 2002 Aug; 76(16): 8069-8078. [**original work**]

3. **Cheng, H.H**., Anderson, M.M., Hankenson, F.C., Johnston, L., Kotwaliwale, C.V., Overbaugh, J. Envelope determinants for dual-receptor specificity in feline leukemia virus subgroup A and T variants. Journal of Virology. 2006 Feb; 80(4): 1619-1628. [**original work**]

4. **Cheng, H.H.**, Anderson, M.M., Overbaugh, J. Feline Leukemia Virus T entry is dependent on both expression levels and specific interactions between cofactor and receptor. Virology. 2007 Mar; 359(1): 170-178. [**original work**]

5. Pritchard, C.C., **Cheng, H.H.**, Tewari, M. MicroRNA Profiling: approaches and considerations. Nature Reviews Genetics. 2012 Apr 18; 13(5): 358-69. **[review]**

6. **Cheng, H.H.,** Lin, D., Yu, E.Y. Advanced Clinical States in Prostate Cancer. Urologic Clinics of North America. 2012 Nov;39 (4):561-71. **[review]**

7. **Cheng, H.H.,** Yi, H.S., Kim, Y., Kroh, E., Goodman, M., Chien, J., Tait, J.F., Tewari, M., Pritchard, C.C. Plasma processing conditions substantially influence circulating microRNA biomarker levels. PLoS ONE 2013 Jun 7;8(6). [**original work**] ***One of the top 1% of most highly cited articles in PLoS ONE.***

8. **Cheng, H.H.,** Mitchell, P.S., Kroh, E., Dowell, A.E., Chéry, L., Siddique J., Nelson, P.S., Vessella, R., Knudsen, B.S., Chinnaiyan, A.M., Pienta, K.J., Morrissey, C., Tewari, M. Circulating microRNA Profiling Identifies a Subset of Metastatic Prostate Cancer Patients with Evidence of Cancer-Associated Hypoxia, PLoS ONE, 2013 Jul 30;8(7). [**original work**]

9. Lee, F., Harris, W.P., **Cheng, H.H.**, Shenoi, J., Zhao, S., Wang, J., Champion, T., Izard, J., Gore, J.L., Porter, M.P., Yu, E.Y., Wright, J.L. Pathologic Response Rates of Gemcitabine/Cisplatin VS. Methotrexate/Vinblastine/Adriamycin/Cisplatin Neoadjuvant Chemotherapy for Muscle Invasive Urothelial Bladder Cancer. Advances in Urology, 2013; 2013:317190. [**original work**]

10. Mossanen, M., Lee, F., **Cheng, H.H.**, Harris, W., Shenoi, J., Zhao, S., Wang, J., Champion, T., Izard, J., Gore, J.L., Porter, M.P., Yu, E.Y., Wright, J.L. Non-Response to Neoadjuvant Chemotherapy for Muscle

Invasive Urothelial Cell Carcinoma of the Bladder. Clinical Genitourinary Cancer, 2013 Nov 12. [**original work**]

11. James, A.C., Lee, F.C., Izard, J.P., Harris, W.P., **Cheng, H.H.,** Zhao, S., Gore, J.L., Lin, D.W., Porter, M.P., Yu, E.Y., Wright, J.L. Role of maximal endoscopic resection prior to cystectomy for invasive urothelial bladder cancer. Clinical Genitourinary Cancer, 2014 Jan 23. [**original work**]

12. Montgomery, R.B., **Cheng, H.H.,** Drechsler, J., Mostaghel, E.A. Glucocorticoids and prostate cancer treatment: Friend or foe? Asian Journal of Andrology, 2014 Mar 7. **[review]**

13. **Cheng, H.H.** and Higano. C.S. Targeting the AR signaling axis: how low to go? Oncology, 2014 Aug 15. **[editorial]**

14. Ramos, J.D., **Cheng, H.H.,** Yu, E.Y. Long-term survival in bone-predominant metastatic urothelial carcinoma. Clinical Genitourinary Cancer, 2014 Jul 23. **[case report]**

15. Chevillet, J.R., Kang, Q., Ruf, I.K., Briggs, H.A., Vojtech, L.N., Hughes, S.M., **Cheng, H.H.**, Arroyo, J.D., Knouf, E.C., Gallichotte, E.N., Pogosova-Agadjanyan, E.L., Vessella, R.L., Stirewalt, D.L., Hladik, F., Yu, E.Y., Higano, C.S., Tewari, M. Quantitative and stoichiometric analysis of the microRNA content of exosomes, PNAS, 2014 Oct 14. **[original work]**

16. **Cheng, H.H.,** Gulati, R., Azad, A.A., Nadal, R., Twardowski, P., Vaishampayan, U.N., Agarwal, N., Heath, E.I., Pal, S.K., Rehman, H., Leiter, A., Batten, J.A., Montgomery, R.B., Galsky, M.D., Antonarakis, E.S., Chi, K.N., Yu, E.Y. Activity of enzalutamide in men with metastatic castration resistant prostate cancer depends on prior treatment with abiraterone and/or chemotherapy. Prostate Cancer and Prostatic Diseases, 2015 Jan 20. **[original work]**

17. Yu, E.Y., Li, H., Higano, C.S., Agarwal, N., Pal, S.K., Alva, A., Heath, E.I., Lam, E.T., Gupta, S., Lilly, M.B., Inoue, Y., Chi, K.N., Vogelzang, N.J., Quinn, D.I., Li, H., **Cheng, H.H.,** Plymate, S.R., Hussain, M.H., Thompson, I.M. SWOG S0925: A randomized phase 2 study of androgen deprivation combined with cixutumumab (IMC-A12) versus androgen deprivation alone for patients with new metastatic castration-sensitive prostate cancer. Journal of Clinical Oncology, 2015 Apr 6. **[original work]**

18. **Cheng, H.H.**, Soleau, C., Yu, E.Y. Improved disease markers suggest dual response in a patient with metastatic castration resistant prostate cancer and chronic lymphocytic leukemia following active cellular immunotherapy. Journal of Hematology and Oncology, Journal of Hematology and Oncology, 2015 May 14**. [case report]**

19. **Robinson, D, Van Allen, E.M., Wu, Y, Schultz, N., Lonigro, R.J., Mosquera, J., Montgomery, R., Taplin, M.E., Pritchard, C.C., Attard, G., Beltran, H., Abida, W.M., Bradley, R.K., Vinson, J., Cao, X., Vats, P., Kunju, L.P., Hussain, M., Feng, F.Y., Tomlins, S.A., Cooney, K.A., Smith, D.C., Brennan, C., Siddiqui, J., Mehra, R., Scher, H.I., Chen, Y., Rathkopf, D.E., Morris, M.J., Solomon, S.B.,Durack, J.C., Reuter, V.E., Gopalan, A., Gao, J., Loda, M., Lis, R.T., Bowden, M., Balk, S.P., Gaviola, G., Sougnez, C., Gupta, M., Yu, E.Y., Mostaghel, E.A., **Cheng, H.H.,** Chew, F.S., True, L.D., Plymate, S.R., Dvinge, H., Ferraldeschi, R., Flohr, P., Miranda, S., Zafeiriou, Z., Tunariu, N., Mateo, J., Demichelis, F., Elemento, O., Robinson, B.D., Sboner, A., Schiffman, M.A., Nanus, D.M., Tagawa, S.T., Sigaras, A., Eng, K.W., Heath, E., Pienta, K.J., Kantoff, P., de Bono, J.S., Rubin, M.A., Nelson, P.S., Garraway, L.A., Sawyers, C.L., Chinnaiyan, A.M. Integrative clinical sequencing analysis of metastatic castration resistant prostate cancer reveals a high frequency of clinical actionability. Cell, 2015 May 21. **[original work]**

20. ****Cheng, H.H.,** Pritchard, C.C., Boyd, T., Nelson, P.S., Montgomery, R.B. Biallelic inactivation of *BRCA2* in metastatic castration resistant prostate cancer and platinum sensitivity*;* European Urology, 2016, *Epub.* **[original work]** ***Selected as one of the Highlights of June 2016 issue.***

21. **Cheng, H.H.*,** Klemfuss, N., Montgomery, B., Higano, C.S., Schweizer, M.T., Mostaghel, E.H., McFerrin, L.G., Yu, E.Y., Nelson, P.S., Pritchard, C.C. Pilot study of clinical targeted next generation sequencing for prostate cancer: consequences for treatment and genetic counseling. The Prostate, 2016 Jun 21. [**original work]** *(*HHC corresponding author*)

22. Schweizer, M.T., Gulati, R., Mostaghel, E.M., Nelson, P.S., Montgomery, B., Yu, E.Y., **Cheng, H.H.** Docetaxel-Related Toxicity in Metastatic Hormone-Sensitive Versus Castration-Resistant Prostate Cancer; Medical Oncology, 2016 Jul. **[original work]**

23. **Pritchard, C.C., Mateo, J., Walsh, M.F., De Sarkar, N., Abida, W., Beltran, H., Garofalo, A., Gulati, R., Carreira, S., Eeles, R., Elemento, O., Rubin, M.A., Robinson, D., Lonigro, R., Hussain, M., Chinnaiyan, A.M., Vinson, J., Filipenko, J., Garraway, L.A., Taplin, M-E, AlDubayan, S., Celine Han, G., Beightol, M., Morrissey, C., Ngheim, B., **Cheng, H.H**., Montgomery, B., Walsh, T., Casadei, S., Berger, M., Zhang, L., Zehir, A., Vijai, J., Scher, H.I., Sawyers, C., Schultz, N., Kantoff, P., Solit, D., Robson, M., Van Allen, E.M., Offitt, K., De Bono, J.S., Nelson, P.S. Inherited DNA Repair Gene Mutations in Men with Metastatic Prostate Cancer; New England Journal of Medicine, 2016 Jul 6. **[original work]**

24. Schweizer, M.T.*, **Cheng, H.H**.*, Tretiakova, M.S., Vakar-Lopez, F., Klemfuss, N., Mostaghel, E.A., Morrissey, C., Nelson, P.S., Yu, E.Y., Montgomery, R.B., True, L.D., Pritchard, C.C., Mismatch Repair Deficiency is Common in Ductal Prostatic Adenocarcinoma. Oncotarget, 2016, Oct. **[original work]** *(*co-first authorship*)

25. Gulati, R., **Cheng, H.H.**, Lange, P.H., Nelson, P.S., Etzioni, R. Screening men at increased risk for prostate cancer diagnosis: Model estimates of benefits and harms. Cancer Epidemiology Biomarkers and Prevention, 2016, Oct. **[original work]**

26. **Cheng, H.H.*,** Pritchard, C.C., Montgomery, B., Lin, D.W., Nelson, P.S. Prostate Cancer Screening in a New Era of Genetics. Clinical Genitourinary Cancer, 2017, May 31. **[editorial]** *(*HHC corresponding author*)

27. Miyahira, A.K., **Cheng, H.H.,** Abida, W., Ellis, L., Harshman, L., Spratt, D., Simons, J.W., Pienta, K.J., and Soule, H.R. Beyond the Androgen Receptor II: New Approaches to Understanding and Treating Metastatic Prostate Cancer; Report from the 2017 Coffey-Holden Prostate Cancer Academy Meeting. The Prostate, 2017, Sept 18. [**review**]

28. Ly, A., **Cheng, H.H.**, Alwan, L. Hepatitis C infection and chemotherapy toxicity. Journal of Oncology Pharmacy Practice, 2018, Jan 1. [**case series**]

29. **Cheng, H.H.,** Plets, M., Li, H., Higano, C.S., Agarwal, N., Vogelzang, N.J., Hussain, M., Thompson, I.M., Tewari, M., Yu, E.Y. Circulating microRNAs and treatment response in the Phase II SWOG S0925 study for patients with new metastatic hormone-sensitive prostate cancer. The Prostate, 2018, Feb. **[original work]**

30. ****Cheng, H.H.**, Salipante, S., Nelson, P.S., Montgomery, B., Pritchard, C.C. Polyclonal *BRCA2* reversion mutations detected in circulating tumor DNA after platinum chemotherapy in a patient with metastatic prostate cancer. JCO Precision Oncology, 2018 Feb 14. **[case report]**

31. Mateo, J.*, **Cheng, H.H.*,** Beltran, H.*, Dolling, D., Xu, W., Pritchard, C.C., Mossop, H., Rescigno, P., Perez-Lopez, R., Kolinsky, M., Balasapoulou, A., Carreira, S., Thorne, H., Montgomery, B., Sandhu, S., Rubin, M.A., Nelson, P., de Bono, J.S. Clinical Outcomes of Prostate Cancer Patients with Germline DNA Repair Mutations: Follow-up from an International Study, European Urology, 2018 Jan 29. *(*co-first authorship)* **[original work]**

32. **Cheng, H.H.,** The Resounding Impact of DNA Repair Deficiency in Prostate Cancer. Urologic Oncology, 2018 Mar 16 **[editorial]**

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b) Collaborative Authorship: n/a

c) MedEDPortal or other peer reviewed curricula: n/a

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6. Schweizer MT, Gulati R, Yezefski T, **Cheng HH**, Mostaghel E, Haffner MC, Patel RA, de Sarkar N, Ha G, Dumpit R, Woo B, Lin A, Panlasigui P, McDonald N, Lai M, Nega K, Hammond J, Grivas P, Hsieh A, Montgomery B, Nelson PS, Yu EY. Bipolar Androgen Therapy plus Olaparib in Men with Metastatic Castration-resistant Prostate Cancer (*submitted)* **[original work]**

7. Sekar, R.R., Diamantopoulos, L.N., Bakaloudi, D.R., Khaki, A.R., Grivas, P., Winters, B.R., Vakar-Lopez, F., Tretiakova, M.S., Psutka, S.P., Holt, S.K., Gore, J.L., Lin, D.W., Schade, G.R., Hsieh, A.C., Lee, J.K., Yezefski, T., Schweizer, M.T., Cheng, H.H., Yu, E.Y., True, L.D., Montgomery, R.B.,

Wright, J.L. Sarcomatoid Urothelial Carcinoma is Associated with Limited Response to Neoadjuvant Chemotherapy and Poor Oncologic Outcomes after Radical Cystectomy (*submitted)* **[original work]**

8. Makrakis, D., Wright, J.L., Roudier, M.P., Garcia, J., Vakar-Lopez, F., Porter, M.P., Wang, Y., Dash, A., Lin, D.W., Schade, G., Winters, B., Zhang, X., Nelson, P.S., Mostaghel, E., **Cheng, H.H.,** Schweizer, M.T., Holt, S.K., Gore, J.L., Yu, E.Y., Lam, H.M., Montgomery, B. A Phase 1/2 Study of Rapamycin and Cisplatin/Gemcitabine for Treatment of Patients With Muscle-Invasive Bladder Cancer (*submitted)* **[original work]**

9. Graff, J.N., Sokolova, A.O., Smith, C.E., Beer, T.M., Latour, E., Chen, Y., Bailey, S., Kreitner, D., Petreaca, D., Grivas, P., Schweizer, M.T., Higano, C.S., Alumkal, J.J., Vuky, J., Yu, E.Y., **Cheng, H.H.** A Phase I/II Trial of Concurrent Chemo-hormonal Therapy Using Enzalutamide and Cabazitaxel in Patients with Metastatic Castration Resistant Prostate Cancer. (*in preparation)* **[original work]**

10. Zhao, J.L., Antonarakis, E.S., **Cheng, H.H.,** George, D., Aggarwal, R., Riedel, E., Sumiyoshi, T., Schonhoft, J., Mao, N., Haywood, S., Decker, B., Curley, T., Abida, A., Feng, F.Y., Knudsen, K., Carber, B., Lacouture, M.E., Wyatt, A., Rathkopf, D., Phase 1b Study of Enzalutamide plus CC-115, a dual mTORC1/2 and DNA-PK inhibitor, in Men with Metastatic Castration-Resistant Prostate Cancer. (*in preparation)* [original work]

11. Gillessen S, Antonarakis E, Aparicio AM**,** Armstrong A, Attard G, Beer TM, Beltran H, Bjartell A, Blanchard P, Bossi A, Briganti A, Bristow RG, Bulbul M, Caffo O, Castellano D, Castro E, **Cheng HH**, Chi KN, Chowdhury S, Clarke CS, Clarke N, Daugaard G, Davis ID, de Bono J, de Santis M, Duran I, Eeles R, Efstathiou E, Efstathiou J, Ekeke ON, Evans CP, Fanti S, Feng FY, Fizazi K, Fonteyne V, Fossati N, Frydenberg M, George D, Gleave M, Gravis G, Halabi S, Heinrich D, Herrmann K, Higano C, Hofman MS, Horvath LG, Hussain M, James ND, Jereczek-Fossa BA, Jones R, Kanesvaran R, Kellokumpu-Lehtinen PL, Khauli RB, Klotz L, Kramer G, Leibowitz R, Logothetis C, Mahal B, Maluf F, Mateo J, Matheson D, Mehra N, Merseburger A, Morgans AK, Morris MJ, Mottet N, Mrabti H, Mukherji D, Murphy DG, Murthy V, Nguyen PL, Oh WK, Ost P, O'Sullivan JM, Padhani AR, Pezaro CJ, Poon DMC, Pritchard CC, Rabah DM, Rathkopf D, Reiter RE, Rubin M, Ryan CJ, Saad F, Sade JP, Sartor O, Scher HI, Sharifi N, Shore N, Skoneczna I, Small E, Smith M, Soule H, Spratt DE, Srinivas S, Sternberg CN, Steuber T, Suzuki H, Sweeney C, Sydes MR, Taplin ME, Tilki D, Tombal B, Türkeri L, Turco F, Uemura H, Uemura H, Ürün Y, Vale CL, van Oort I, Vapiwala N, Yamoah K, Ye D, Yu EY, Zapatero A , Zilli T, Omlin A. Management of patients with advanced prostate cancer: Report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022 (*in preparation)* **[original work]**

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h) Abstracts (last 5 years, 2017 to present**)**

1. True, L., Gulati, R., Lange, J., Tretiakov, M., Vakar-Lopez, F., Humphrey, P., Egevad, L., Hes, O., Antic, T., **Cheng, H.H.,** Montgomery, B., Nelson, P., Konnick, E., Schweizer, M., Pritchard, C.C. *Histological Patterns of Ductal Adenocarcinoma of Prostate Correlates with Mutations in DNA Repair Genes and May Aid in Selecting the Type of Systemic Therapy for Castration-Resistant Prostate Carcinoma.* 2017 United States & Canadian Academy of Pathology Annual Meeting (2017). Abstract #5047.

2. Schweizer, M.T., Haugk, K., **Cheng, H.H.,** Dumpit, R., Nelson, P.S., Montgomery, B., Plymate, S.R., Yu, E.Y. *Challenges in Enrolling to Metastatic Castration-Resistant Prostate Cancer (mCRPC) Studies that Require Androgen Receptor Splice Variant (AR-V) Positivity*. Genitourinary Cancers Symposium (2017). J Clin Oncol 35, 2017 (suppl 6S; abstract 264)

3. Shore, N.D., Heath, E.I., Whang, Y.E., Nordquist, L.T., **Cheng, H.H.**, Bhatt, K., Carroll, N., Mangrolia, D., Clasen, B., Kraynyak, K., Tagawa, S.T., Lin, J., Tutrone, R.F., Garcia, J.A., Lee, J., Yang, Z., Bagarazzi, M.L. *A clinical trial for the safety and immunogenicity of a DNA-based immunotherapy in men with biochemically (PSA) relapsed prostate cancer.* Genitourinary Cancers Symposium (2017). Abstract

4. Gill, D., Stenehjem, D., Hahn, A., **Cheng, H.**, Gupta, S., Alex, A., Patel, S., Kessler, E., Twardowski, P., Agarwal, N., *Association of time from definitive therapy (DT) to start of androgen deprivation therapy (ADT) for metastatic disease and survival outcomes in men with new metastatic hormone-sensitive prostate cancer (mHSPC).* Genitourinary Cancers Symposium (2017). J Clin Oncol 35, 2017 (suppl 6S; abstract 265)

5. Shore, N.D., Heath, E.I., Whang, Y.E., Nordquist, L.T., **Cheng, H.H.**, Bhatt, K., Carroll, N., Mangrolia, D., Clasen, B., Kraynyak, K., Tagawa, S.T., Lin, J., Tutrone, R.F., Garcia, J.A., Lee, J., Yang, Z., Bagarazzi, M.L. *Safety and Immunogenicity of a DNA-vaccine Immunotherapy in Men with Biochemically (PSA) Relapsed Prostate Cancer*. European Society of Medical Oncology Annual Meeting (2017) [Abstract 790PD, selected for oral poster discussion].

6. Schweizer, M.T., Gulati, R., **Cheng, H.H.,** de Sarkar, N., Yu, E.Y., Montgomery, B., Nelson, P.S., Pritchard, C.C. *Cell-free circulating tumor DNA is a reliable specimen for mutation profiling in prostate cancer patients with high-burden disease*. 24th Annual Prostate Cancer Foundation Scientific Retreat, Washington, D.C. (2017). [Abstract]

7. Mateo, J., **Cheng, H.H.,** Beltran, H., Dolling, D., Xu, W., Pritchard, C.C., Mossop, H., Rescigno, P., Perez-Lopez, R., Kolinsky, M., Balasapoulou, A., Carreira, S., Thorne, H., Montgomery, B., Sandhu, S., Rubin, M.A., Nelson, P., de Bono, J.S. *Clinical Outcomes of Prostate Cancer Patients with Germline DNA Repair Mutations: Follow-up From an International Study,* Genitourinary Cancers Symposium, San Francisco, CA (2018). [Abstract]

8. Montgomery, B., Russell, K., Liao, J.J., Ellis, W.J., **Cheng, H.H.**, Yu, E.Y., Mostaghel, E.M. *A Phase II Study of Neoadjuvant Degarelix on Prostatic Tissue Androgens Before Definitive Radiation,* Genitourinary Cancers Symposium, San Francisco, CA (2018). [Abstract]

9. Lim, D.M., Gulati, R., Aleshin-Guendel, S., **Cheng, H.H.,** Gawne, A., Wingate, J.T., Ruth, R., Etzioni, Yu, E.Y. *Prostate-Specific Antigen Recurrence Rates After Short Course Androgen Deprivation for Biochemical Recurrence of Prostate Cancer,* Genitourinary Cancers Symposium, San Francisco, CA (2018). [Abstract]

10. Lam, H., Vakar-Lopez, F., Hsieh, A.C., Winters, B., **Cheng, H.**, Schweizer, M., Yu, E.Y., Montgomery, B., Corey, E., Wright, J.L. *Bladder Cancer Rapid Autopsy: A mechanism for collecting metastatic tumor tissue and establishing xenograft models of metastatic disease,* Genitourinary Cancers Symposium, San Francisco, CA (2018). [Abstract]

11. **Cheng, H.H.,** Bowen, D., Klemfuss, N., Sievers, C.M., Kang, S.H., Zhou, A., Pritchard, C.C., Nelson, P.S., Montgomery, B., *The GENTleMEN Study: Genetic Testing for Men with Metastatic Prostate Cancer in Washington State and Beyond*, ASCO Annual Meeting, Chicago, IL (2018) [Abstract, poster]

12. Chae, Y.K., Vaklavas, C., **Cheng, H.H.,** Hong, F., Harris, L., Mitchell, E., Zwiebel, J., Rubinstein, L., McShane, L., Gray, R., Li, S., Ivy, P., Ansher, S., Hamilton, S., Williams, M., Patton, D., Tricoli, J., Arteaga, C., Conley. B., O'Dwyer, P., Chen, A., Flaherty, K., *Molecular Analysis for Therapy Choice (MATCH) Arm W: Phase II Study of AZD4547 in Patients with Tumors with Aberrations in the FGFR Pathway*, ASCO Annual Meeting, Chicago, IL (2018) [Abstract, oral presentation]

13. Yu, E.Y., Gulati, R., Aleshin-Guendel, S., **Cheng, H.H.,** Gawne, A., Wingate, J.T., Etzioni, R.,. Lim, D.M., *Undetectable PSA after short-course androgen deprivation therapy for biochemically-recurrent*

prostate cancer patients correlates with time to metastasis and prostate cancer-specific survival, ASCO Annual Meeting, Chicago, IL (2018) [Abstract]

14. Shore, N.D., Heath, E.I., Nordquist, L., **Cheng, H.H.,** Bhatt, K., Morrow, M., McMullan, T., Kraynyak, K., Lee, J., Sacchetta, B., Liu, L., Rosencranz, S., Tagawa, S.T., Parikh, R.A., Tutrone, R., Garcia, J., Y.Whang, Kelly, W., Csiki, I., Bagarazzi, M., *Safety and Immunogenicity of a DNA-vaccine for Immunotherapy in Biochemically Relapsed Prostate Cancer*, ASCO Annual Meeting, Chicago, IL (2018) [Abstract]

15. Rathkopf, D., Autio, K., Antonarakis, E., **Cheng, H.,** Arauz, G., Slack, A., Hullings, M., Scher, H.I., Feng, F., Knudsen, K. *Enzalutamide (ENZA) Plus CC-115 in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC): A Phase 1b Prostate Cancer Clinical Trials Consortium Study*, ASCO Annual Meeting, Chicago, IL (2018) [Abstract]

16. Schweizer, M.T., Antonarakis, E., Bismar, T.A., Guedes, L., **Cheng, H.H.,** Tretiakova, M.S., Vakar-Lopez, F., Klemfuss, N., Konnick, E.Q., Mostaghel, E.A., Hsieh, A.C., Nelson, P.S., Yu, E.Y., Montgomery, B., True, L.D., Epstein, J.I., Lotan, T.L., Pritchard, C.C. *Genomic Characterization of Ductal Adenocarcinoma of the Prostate*, ASCO Annual Meeting, Chicago, IL (2018) [Abstract, poster]

17. Naylor, L., Laurino, M., Sjoding, B., **Cheng, H.H.** *Prostate Cancer Genetics Clinic: First 16 Month Report of Establishing a Multidisciplinary Service*, European Society of Human Genetics, Milan, Italy (2018) [Abstract, poster]

18. Winters, B.R., De Sarkar, N., Arora, S., Bolouri, H., Lam, H., Vakar-Lopez, F., **Cheng, H.H.,** Schweizer, M.T., Yu, E.Y., Montgomery, B., Kollath, L., Grivas, P., Wright, J.L., Hsieh, A.C., *Metastatic upper tract urothelial carcinoma possesses a distinct genomic signature from lower tract urothelial carcinoma: Initial results from the University of Washington rapid autopsy program for urothelial carcinoma,* Western Section American Urological Association, Hawaii (2018) [Abstract]

19. Schweizer, M.T., Gulati, R., **Cheng, H.H.,** de Sarkar, N., Yu, E.Y., Montgomery, R.B., Nelson, P.S., Pritchard, C.C. *Cell-free Circulating Tumor DNA is a Reliable Specimen for Mutation Profiling in Prostate Cancer Patients with High-Burden Disease*. Fred Hutch Solid Tumor Translational Research Symposium (2018) [Abstract]

20. Shore, N.D., Heath, E.I., Nordquist, L., **Cheng, H.H.,** Bhatt, K., Morrow, M., McMullan, T., Kraynyak, K., Lee, J., Sacchetta, B., Liu, L., Rosencranz, S., Tagawa, S.T., Parikh, R.A., Tutrone, R., Garcia, J., Whang, Y., Kelly, W., Csiki, I., Bagarazzi, M., *Synthetic DNA Immunotherapy in Biochemically Relapsed Prostate Cancer*, European Society for Medical Oncology Annual Meeting (2018) [Abstract]

21. Labrecque, M.P., Brown, L.G., Coleman, I.M., True, L.D., Kollath, L., Lakely, B., Yang, Y.C.**,** Nguyen, H.M., Higano, C.S., Yu, E., **Cheng, H.H.,** Mostaghel, E., Montgomery, B., Schweizer, M., Hsieh, A., Corey, E., Nelson, P.S.**,** Morrissey, C. *Defining the molecular phenotypes of metastatic castration-resistant prostate cancer and their sensitivity to FGF pathway inhibition,* Prostate Cancer Foundation Scientific Retreat (2018) [Abstract]

22. Lam, H., Vakar-Lopez, F., **Cheng, H.H.,** Schweizer, M.T., Grivas, P., Yu, E.Y., Montgomery, B., Hsieh, A., Corey, E., Wright, J.L. *Bladder Cancer Rapid Autopsy: Emerging patient-derived xenograft models for metastatic diseases,* Society for Basic Urologic Research, Rancho, Mirage, CA (2018). [Abstract]

23. Sonpavde G., Agarwal N., Maughan B., Wei X., McGregor B., Kilbridge K., Lee R.J., Yu E.Y., Schweizer M.T., Montgomery B., **Cheng H.H.**, Hsieh A., Birhiray R., Gabrail N., Nemunaitis J., Rezazadeh A., Vanveldhuizen P., Vogelzang N., Heery C., Grivas P. *A Phase 2, Multicenter, Single-Arm Trial of CV301 plus Atezolizumab in Locally Advanced or Metastatic Urothelial Cancer*, Genitourinary Cancers Symposium, San Francisco, CA (2019). [Abstract]

24. Winters, B., De Sarkar, N., Arora, S., Bolouri, H., Vakar-Lopez, F., **Cheng, H.H.,** Yu, E.Y., Kollath, L., Grivas, P., McFerrin, L., Montgomery, B., Wright, J.L., Lam, H., Hsieh, A.C., *Distinct Genomic Hallmarks Exist Between Metastatic Upper and Lower Tract Urothelial Carcinoma*, Genitourinary Cancers Symposium, San Francisco, CA (2019). [Abstract]

25. Sokolova, A., **Cheng, H.H.**, Hintze, B., Kelley, M., Spector, N., Duffy, J., Lynch, J., Rettig, M., Montgomery, B., *The Veterans Health Administration Precision (VHA) Oncology Program for Advanced Prostate Cancer Patients: expanding tumor NGS opportunities to a broader patient population*, Genitourinary Cancers Symposium, San Francisco, CA (2019). [Abstract]

26. Winters, B., Ngo, S., Vakar-Lopez, F., Tretriakova, M., True, L., Dighe, M., Lee, J., Russell, K., Zeng, J., Liao, J.J., **Cheng, H.,** Montgomery, B., Schweizer, M., Hsieh, A., Yu, E., Schade, G., Gore, J., Lin, D., Wright, J. *Multi-specialty bladder cancer clinics can be associated with significant radiologic and pathologic diagnostic changes resulting in updated treatment recommendations: Results from a tertiary referral center*. American Urological Association Annual Meeting, Chicago, IL (2019). [Abstract]

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28. Lynch, J., Lee, K.M., Pritchard, C., **Cheng, H**., Chantreau, C., Stoll, K., Meeks, J., Ball, D., Montgomery, B. *Clinically validating and returning MVP results to participants with mutation-positive metastatic prostate cancer*. Million Veteran Program Science Meeting, Philadelphia, PA (2019). [Abstract and oral presentation]

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30. Mucci, L., Villanti, P., Vinson, J., Gold, T., Rathkopf, D., Chi, K., Zhang, T., Barata, P., **Cheng, H.,** Pomerantz, M., Dreicer, R., Alva, A., Ong, M., Heath, E., Enting, D., Whang, Y., Hotte, S., Bjartell, A., Fay, A., Morgans, A., Paich, K., McReynolds, J., George, D., Kantoff, P., *Patient Reported Outcomes among Men with Advanced Prostate Cancer: Results from the IRONMAN registry.* Prostate Cancer Foundation Annual Meeting, Carlsbad, CA (2019) [Abstract]

31. Ha, G., Doebley, A., Reichel, J., Hoge, A., **Cheng, H.H.,** Schweizer, M., Pritchard, C., Nelson, P. *Multi-omic profiling of circulating tumor DNA in patients with CRPC.* Prostate Cancer Foundation Annual Meeting, Carlsbad, CA (2019) [Abstract]

32. **Cheng, H.H.,** DeJong, M., Yu, E.Y., Rettig, M.B., Higano, C.S., Nelson, P.S., Pritchard, C.C., Montgomery, B. *A Pilot Study of Docetaxel and Carboplatin for treatment of patients with mCRPC containing biallelic inactivation of genes in the BRCA1/2 pathway*. Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]

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34. Graham, L.S., Montgomery, R.B., **Cheng, H.H.,** Yu, E.Y., Alva, A., Schweizer, M.T., *Mismatch Repair Deficiency in Metastatic Prostate Cancer (PC): Response to PD-1 Blockade and Standard Therapies.* Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]

35. Wong, R.L., Duong, M.T., Tangen, C.M., Agarwal, N., **Cheng, H.H.,** Vogelzang, N.J., Hussain, M., Thompson, I.M., Quinn, D.I., Yu, E.Y. *Final overall and progression-free survival outcomes from SWOG S0925, a randomized phase II study of androgen deprivation with cixutumumab versus androgen deprivation alone in patients with new metastatic hormone-sensitive prostate cancer.* Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]

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38. Sokolova, A.O., Marshall, C.H., Lozano, R., Grivas, P., Higano, C.S., Montgomery, B., Nelson, P.S., Schweizer, M.T., Yezefski, T.A., Yu, E.Y., Paller, C.J., Castro, E., Antonarakis, E.A., **Cheng, H.H.,** *Clinical characteristics and treatment response of prostate cancer patients with germline ATM mutations.* Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]

39. Psutka, S.P., Ngo, S., Diamantopoulos, L., Maldonado, R., O'Malley, R., Laidlaw, G.L., Fintelmann, F., Holt, H., Gore, J.L., Schade, G.R., Lin, D.W., Grivas, P., Montgomery, B., Hsieh, A.C., **Cheng, H.H.,** Yezefski, T.A., Schweizer, M.T., Yu, E.Y., Wright, J.L. *Associations between baseline Skeletal Muscle Index, Neoadjuvant Chemotherapy-Associated Severe Adverse Events and 90-day Post-Radical Cystectomy Complication.* American Urological Associate, Washington, DC (2020). [Abstract]

40. Psutka, S.P., Ngo, S., Diamantopoulos, L., Maldonado, R., O'Malley, R., Laidlaw, G.L., Fintelmann, F., Holt, H., Gore, J.L., Schade, G.R., Lin, D.W., Grivas, P., Montgomery, B., Hsieh, A.C., **Cheng, H.H.,** Yezefski, T.A., Schweizer, M.T., Yu, E.Y., Wright, J.L. *Associations between baseline Skeletal Muscle Index, Fat Mass Index, and Cancer-Specific Mortality following Neoadjuvant Chemotherapy and Radical Cystectomy for Bladder Cancer.* American Urological Associate, Washington, DC (2020). [Abstract]

41. Pouv, D.L., Sokolova, A.O., **Cheng., H.H**. Seattle Cancer Care Alliance Prostate Cancer Genetics Clinic: Germline Genetic Testing in Practice and its Implications for Precision Therapy. Western Medical Research Conference, Carmel, CA (2020). [Abstract]

42. Facchini, L., Naylor, L., Sjoding, B., Laurino, M., Handford. C., Lally, E., **Cheng, H.H.,** *Seattle Cancer Care Alliance's Prostate Cancer Genetics Clinic: A report of 125 patients between 2017-2019*. Hereditary Breast and Ovarian Cancer Symposium, Montreal, Ontario. (2020) [Abstract]

43. Diamantopoulos, L.N., Sekar, R.R., Khaki, A.R., Winters, B.R., Vakar-Lopez, F., Tretiakova, M., Gore, J.L., Schade, G.R., Psutka, S.P., Hsieh, A., Lee, J.K., Yezefski, T., Schweizer, M.T., **Cheng, H.H.,** Yu, E.Y., Lin, D.W., Montgomery, B., Grivas, P., Wright, J.L. *Association of Perioperative Blood Transfusion (PBT) With Post-Operative Outcomes In Patients (Pts) Undergoing Radical Cystectomy (RC) For Bladder Cancer (BC).* American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Abstract]

44. Diamantopoulos, L.N., Ngo, S., Maldonado, R., O'Malley, R., Laidlaw, G., Fintelmann, F.J., Holt, S.K., Gore, J.L, Schade, G., Lin, D.W., Grivas, P., Montgomery, B., Hsieh, A.C., **Cheng, H.H.,** Yezefski, T , Schweizer, M.T., Yu, E.Y., Wright, J.L., Psutka, S.P. *Associations between Baseline Body Composition and Cancer-Specific Mortality following Neoadjuvant Chemotherapy and Radical Cystectomy for*

Bladder Cancer. American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Abstract]

45. Ledet, E.M., Jaeger, E., Hatton, W., Moses, M.W., Sokolova, A.O., Nakazawa, M., Zhu, J., Dellinger, B., Elrefai, S., McKay, R.R., **Cheng, H.H.,** Burgess, E.F., Antonarakis, E.S., Sartor, A.O. *Comparison of germline mutations in African American and Caucasian men with metastatic prostate cancer*. American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Abstract]

46. Geisler, A., Barrios, D.M., Lacouture, M.E., Antonarakis, E.S., George, D.J., **Cheng, H.H**., Aggarwal, R.R., Rathkopf, D.E., *CC-115 Treatment-Related Rash in Castration-Resistant Prostate Cancer*. American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Abstract]

47. Ngo, S. Diamantopoulos, L.N., Maldonado, R., O'Malley, R.B., Laidlaw, G., Fintelmann, F.J., Holt, S.K., Gore, J.L., Schade, G.R., Lin, D.W., Grivas, P., Montgomery, R.B., Hsieh, A.C., **Cheng, H.H**., Yezefski, T., Schweizer, M.T., Yu, E.Y., Wright, J.L., Psutka, S.P., *Skeletal Muscle Index and Adverse Events during a Bladder Cancer Treatment Episode*. American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Abstract]

48. Sekar, R.R., Diamantopoulos, L.N., Khaki, A.R., Vakar-Lopez, F., Tretiakova, M., Psutka, S.P., Hold, S.K., Gore, J.L., Schade, G.R., Lin, D.W., Hsieh, A., Lee, J.K., Yezefski, T., Schweizer, M.T., **Cheng, H.H.,** Yu, E.Y., True, L.D., Montgomery, B., Grivas, P., Wright, J.L. *Sarcomatoid Urothelial Carcinoma: Oncologic Outcomes From A Tertiary Center And SEER-Medicare Data.* American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Abstract]

49. Sokolova, A.O., Miyamoto, A.N., Pouv, D.L., **Cheng, H.H.,** Montgomery, R.B. *Implementation of Systematic Germline Genetic Testing (GT) for Metastatic Prostate Cancer (mPC) Patients at the Puget Sound VA Prostate Oncology Clinic.* American Society for Clinical Oncology Annual Meeting, Chicago, CA (2020). [Poster abstract]

50. Wong, R.L., Lin, D.W., Pritchard, C.C., Nelson, P.S., Stanford, J.L., **Cheng, H.H.** *Genetic Information to Inform Treatment and Screening (GIFTS) Study for Prostate Cancer: Characterizing Germline DNA Alterations in Men with Metastatic Prostate Cancer and their First-Degree Male Relatives.* European Society for Medical Oncology, virtual (2020). [Poster abstract]

51. Loeb, S., Thakker, S., Falge, E., Taneja, S., Byrne, N., Walter, D., Katz, M., Wong, R., Leader, A., Selvan, P., Rose, M., Joy, M., **Cheng, H.H.,** Massey, P., and Giri, V.N. *Twitter Discussions about Genetic Testing and BRCA Awareness in the Context of Prostate Cancer and Breast Cancer.* Prostate Cancer Foundation Annual Retreat, virtual (2020). [Poster abstract]

52. Rathkopf, D., Chi, K.N., Olmos, D., **Cheng, H.H.,** Agarwal, N., Graff, J , Sandhu, S , Hayreh, V , Lopez-Gitlitz, A. , Francis, P. , Attard, G. *AMPLITUDE: A Study of Niraparib (Nira) in Combination With Abiraterone Acetate and Prednisone (AAP) Versus AAP for the Treatment of Patients With Deleterious Germline or Somatic Homologous Recombination Repair (HRR) Gene-mutated Metastatic Castration-sensitive Prostate Cancer*. Genitourinary Cancers Symposium, San Francisco, CA (2021). [Abstract]

53. Wong, R.L., **Cheng, H.H.,** Holt, S.K., Conrad, N., Fernandez, S., Sahoo, R., Bauer, Z., Toulouse, A.E., Grivas, P., Yezefski, T., Russell, K.J., Wright, J.L, Schweizer, M.T., Montgomery, R.B., Lee, J.H., Chen, D.L., Zeng, J., Lin, D.W., Yu, E.Y. *Use of Fluciclovine PET/CT (FluPET) for Prostate Cancer: Initial Results from a Prospective Registry at the University of Washington/Seattle Cancer Care Alliance.* Genitourinary Cancers Symposium, San Francisco, CA (2021). [Abstract]

54. Loeb, S., Li, R., Sanchez Nolasco, T., Byrne, N., **Cheng, H.H.,** Leader, A., Giri, V., *Barriers and Facilitators of Germline Genetic Evaluation for Prostate Cancer*. Genitourinary Cancers Symposium, San Francisco, CA (2021). [Abstract]

55. Taza, F., Holler, A., Adra, N., Albany, C., Ashkar, R., **Cheng, H.H.,** Sokolova, A.O., Agarwal, N., Nussenzveig, R., Bryce, A., Nafissi, N., Barata, P., Sartor, O., Bastos, D., Smaletz, O., Berchuck, J., Taplin, M., Aggarwal, R., Sternberg, C., Vlachostergios, P.J., Alva, A.S., Su, C., Marshall, C.H., Antonarakis, E.S. *Differential activity of PARP inhibitors in BRCA1- vs BRCA2-altered metastatic castration-resistant prostate cancer (mCRPC).* Genitourinary Cancers Symposium, San Francisco, CA (2021). [Abstract]

56. Karzai, F., Couvillon, A., McKinney, Y., Lee-Wisdom, K., Choyke, P.L., Giri, V.N., Morgan, T.M., **Cheng, H.H**., Merino, M.J., Pinto, P.A., Turkbey, B., Dahut, W.L., *A Natural History Study of Men with High-Risk Genetics for Prostate Cancer (PCa) Using Multiparametric MRI (mpMRI).* American Association for Cancer Research Annual Meeting, Washington, D.C. (2021). [Abstract]

57. Rathkopf, D.E., Chi, K.N., Olmos, D., **Cheng, H.H.,** Agarwal, N., Graff, J.N., Sandhu, S.K., Hayreh, V., Lopez-Gitlitz, A., St. John, P., Attard, G., *AMPLITUDE: A Study of Niraparib in Combination With Abiraterone Acetate Plus Prednisone (AAP) vs AAP Alone for the Treatment of Metastatic Castration-Sensitive Prostate Cancer (mCSPC) in Patients With Deleterious Germline orSomatic Homologous Recombination Repair (HRR) Gene Alterations.* American Society for Clinical Oncology Annual Meeting, Chicago, CA (2021). [Abstract]

58. Zhao, J.L., Antonarakis, E.S., **Cheng, H.H.,** George, D.G., Aggarwal, R.A., Abida, W., Decker, B., Curley, T., Schonhoft, J., Haywood, S., Riedel, E., Carver, B., Wyatt, A., Feng, F.Y., Knudsen, K., Rathkopf, D. *A Phase 1b Study of Enzalutamide (Enza) plus CC-115 in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC).* American Society for Clinical Oncology Annual Meeting, Chicago, CA (2021). [Abstract]

59. Wong, R.L., Holt, S.K., Zeng, J., Graham, L., Kang, R., Conrad, N., Toulouse, A.E., Fernandez, S., Bauer, Z., Lai, M.Y., Yezefski, T., Wright, J.L, Weg, E.S., Hsieh, A.C., **Cheng, H.H.,** Lee, J.H., Chen, D.L., Lin, D.W., Yu, E.Y. *The fluciclovine (FACBC) PET/CT site-directed therapy of oligometastatic prostate cancer (Flu-BLAST-PC) trial.* American Society for Clinical Oncology Annual Meeting, Chicago, CA (2021). [Abstract]

60. Su, C.T., Nizialak, E., Berchuck, J.E., Vlachostergios, P., Ashkar, R., Sokolova, A.O., Barata, P., Aggarwal, R., McClure, H., Sartor, O., **Cheng, H.H.,** Adra, N., Sternberg, C.N., Taplin, M.E., Cieslik, M., Antonarakis, E., Alva, A. *Differential responses to taxanes and PARP inhibitors (PARPi) in ATM- versus BRCA2-mutated metastatic castrate-resistant prostate cancer (mCRPC) patients (pts)*. American Society for Clinical Oncology Annual Meeting, Chicago, CA (2021). [Abstract]

61. Giri, V.N., Walker, A., Gross, L., Fisher, C., **Cheng, H.H.,** Loeb, S. *HELIX: Development and Testing of New Digital Tool to Facilitate Guideline-Concordant Prostate Cancer Genetic Testing in Clinical Practice.* American Urological Association (2021). [Abstract]

62. Maldonado, R., Jan Marquardt, J., Fintelmann, F., O'Malley, R., Holt, S., Ngo, S., Diamantopoulos, L., Laidlaw, G., Schade, G., Lin, D.W., Wright, J.L., Gore, J.L., Nyame, Y., Grivas, P., Yu, E.Y., Montgomery, B., Hsieh, A., Yezefski, T., Schweizer, M., **Cheng, H.H.**, Psutka, S.P. *Change in Skeletal Muscle (SMI), Subcutaneous (SFI) and Visceral Fat Indices (SFI) with Neoadjuvant Chemotherapy (NAC) in patients with Muscle Invasive Bladder Cancer (MIBC): Associations with Adverse Events (AEs) and Oncologic Outcomes.* American Urological Association (2021). [Abstract]

63. Szymaniak, B.M., Facchini, L.A., **Cheng, H.H.,** Morgans, A.K., *Integrating Genetic Counseling and Testing into Genitourinary (GU) Oncology & Urology Clinics.* BRCA Conference (2021). [Abstract]

64. Couvillon, A., Karzai, F., Choyke, P.L., Giri, V.N., Morgan, T.M., **Cheng, H.H.,** Kesserwan, C., Merino, M.J., Pinto, P.A., Turkbey, B., Dahut, W.L., *Inherited Risk for Prostate Cancer: How to Follow and Image the Natural History of Men with High-Risk Genetics*. BRCA Conference (2021). [Abstract]

65. Schweizer, M.T., Roman Gulati, R., Yezefski, T., **Cheng, H.H.,** Sievers, C., Ruth Dumpit, Alexander, K., McDonald, N., Lai, M., Nega, K., Hammond, J., Grivas, P., Hsieh, A., Montgomery, B., Nelson, P.S., Yu, E.Y. Bipolar Androgen Therapy (BAT) plus Olaparib in Men with Metastatic Castration-resistant Prostate Cancer (mCRPC). European Society of Medical Oncology (2021). [Abstract]

66. **Cheng, H.H.**, Powers, J., Gulati, R., Le, A., Ledet, E., Van Allen, E., Vijai, J., Nicolosi, P., Nussbaum, R.L., Garber, J.E., Offit, K., Schiffman, J., Sartor, O., Nelson, P.S., Walsh, M.F., Pritchard, C.C., Maxwell, K.N. *TP53* variants are associated with an increased risk of prostate cancer. American Society of Human Genetics (2021). [Poster Abstract]

67. Maldonado, R., Marquardt, J.P., Fintelmann, F.J., O'Malley, R., Holt, S.K., Ngo, S., Diamantopoulos, L., Laidlaw, G., Schade, G.R., Lin, D.W., Wright, J.L., Gore, J.L., Nyame, Y., Grivas, P., Yu, E.Y., Montgomery, B., Hsieh, A.C., Yezefski, T.A., Schweizer, M., **Cheng, H.H.,** Psutka, S.P. Changes in Body Composition During Platinum-based Neoadjuvant Chemotherapy (NAC) Prior to Radical Cystectomy (RC and Association with Outcomes. Society for Urologic Oncology (2021). [Abstract]

68. Zhao, J.L., Antonarakis, E.S., **Cheng, H.H.,** George, D.G., Aggarwal, R.A., Abida, W., Decker B., Curley, T., Schonhoft, J., Anderson, A., Haywood, S., Riedel, E., Carver, B., Wyatt, A., Feng, F.Y., Knudsen, K., Rathkopf, D. *A Phase 1b Study of Enzalutamide (Enza) plus CC-115 in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC).* European Society of Medical Oncology (2021). [Abstract]

69. Mita, A.C., Mayer, I., Conley, B., Harris, L., Arteago, C., Maican, T., **Cheng.,H.H.** *Erdafitinib in patients with tumors harboring FGFR gene mutations or fusions: results from the NCI-MATCH arm K2 trial.* AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Virtual Conference (2021). [Abstract]

70. Selvan, P., Leader, A., Hunter, A., Massey, P., **Cheng, H.H.,** Loeb, S., Giri, V.N., *Assessing the Impact of Messaging about Prostate Cancer and Genetics on Facebook*. Prostate Cancer Foundation Annual Retreat, virtual (2021). [Poster abstract]

71. Sokolova, A.O., Gulati, R., **Cheng, H.H.,** Beer, T., Graff, J.N., Vuky, J., Yezefski, T., Grivas, P., Yu, E.Y., Schweizer, M.T. *Trial in progress: Durvalumab and Olaparib for the Treatment of Prostate Cancer in Men Predicted to Have a High Neoantigen Load.* Genitourinary Cancers Symposium, San Francisco, CA (2022). [Abstract]

72. Giri, V.N., **Cheng, H.H.,** Paller, C., Weg, E., Johnson, J., Gross, L., Russo, J., Loeb, S., *Virtual Genetics Board for Enhancing Knowledge and Practice of Prostate Cancer Genetic Testing: The ENGAGEMENT Study.* Genitourinary Cancers Symposium, San Francisco, CA (2022). [Poster Abstract]

73. Paller, C.J., Lorentz, J., DeMarco, T.A., Stadler, W.M., Armstrong, A.J., Taplin, M., Hussain, M.H., Pili, R., Mao, S., Elrod, J.B., Sokolova, A.O., Heath, E.I., McKay, R.M., Vinson, J., Tran, C., Macario, N., Cook, A., Chiang, J., **Cheng, H.H.** *PROMISE Registry: A Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness.* Genitourinary Cancers Symposium, San Francisco, CA (2022). [Abstract]

74. Clark, N.M., Roberts, E.A., Fedorenko, C., Sun, Q., Dubard-Gault, M., Handford, C., Yung, R., **Cheng, H.**, Norquist, B., Flanagan, M.R. *Guideline concordant genetic testing in patients with breast, ovarian, pancreatic and prostate cancer.* International Conference on Surgical Cancer Care, Dallas, TX (2022) [e-poster, Abstract]

75. Makrakis, D., Roudier, M.P., Wang, Y., Vakar-Lopez, F., Garcia, J., Dash, A., Lin, D., Schade, G., Mostaghel, E.M., **Cheng, H.H.,** Schweizer, M.T., Gore, J.L., Yu, E.Y., Lam, H.M., Wright, J.L., Montgomery, B. *A Phase 1/2 Study of Rapamycin and Cisplatin/Gemcitabine for Treatment of Patients With Bladder Cancer (NCT01938573).* American Urological Association (2022). [Abstract]

76. Garcia, J., Vakar-Lopez, F., Roudier, M., Grivas, P., Yu, E.Y., **Cheng, H.H.,** Schweizer, M.T., Haffner, M., Lee, J.K., Corey, E., Montgomery, B., Hsieh, A.C., Wright, J.L., Lam, H. *An update on the Urothelial Cancer Rapid Autopsy Program: Biospecimens and Patient-derived Preclinical Models.* American Urological Association (2022). [Abstract]

77. Noonavath, M., Muney, K., Marquandt, J.P., Fintelmann, F.J., O'Malley, R., Holt, S.K., Dwyer, E., Maldonado, R., Diamantopoulos, L., Makrakis, D., Laidlaw, G., Schade, G.R., Lin, D.E., Wright, J.L., Nyame, Y., Grivas, P., Yu, E.Y., Montgomery, B., Hsieh, A.C., Yezefski, T.A., Schweizer, M.T., **Cheng, H.H.,** Psutka, S.P. *Skeletal Muscle Gauge: A Novel Assessment of Muscle Mass and Quality: Associations with Outcomes Following Radical Cystectomy for Bladder Cancer.* American Urological Association (2022). [Abstract]

78. Gulhane, A. Lin, D., Dash, A., Nyame, Y., Schade, G., Wright, J., Chen, J., Liao, J., Wallner, K., Weg, E., **Cheng, H.H**., Hawley, J., Montgomery, B., Nelson, P.S., Schweizer, M.T., Yu, E.Y., Chen, D.L. *[^{68}Ga]-PSMA-11 clarifies equivocal lesions on conventional imaging and affects management for men with prostate cancer*. Society of Nuclear Medicine and Molecular Imaging Annual Meeting (2022). [Abstract]

79. Wong, R.L., **Cheng, H.H.,** Fann, J.R., Hnida, J., Chakoian, M., Schenker, Y., Yu, E.Y., Gore, J.L. *Longitudinal Screening for Depression and Anxiety in Prostate Cancer and Association with Disease and Treatment Factors*. American Society of Clinical Oncology Annual Meeting (2022). [Abstract]

80. Khan, H.M., Wong, R.L., Darst, B.F., Pritchard, C.C., Nelson, P.S., Stanford, J.L., Lin, D.W., **Cheng, H.H.** *Cancer Registry-Based Recruitment of Men with Incident Metastatic Prostate Cancer and their First-Degree Male Relatives for Germline Genetic Testing: Genetic Information to Inform Treatment and Screening (GIFTS) Study*. American Society of Clinical Oncology Annual Meeting (2022). [Oral Abstract Presentation] *(*HHC senior author)*

81. Gulhane, A., Talukder, R., Dash, A., Ellis, W., Nyame, Y.A., Schade, G., Wright, J.L., Apisarnthanarax, S., Chen, J., Liao, J.J., Wallner, K., Weg, E.S., **Cheng, H.H.,** Grivas, P., Hawley, J., Hsieh, A.C., Lee, J.K., Montgomery, B., Nelson, P.S., Schweizer, M.T., Yezefski, Y., Yu, E.Y., Lin, D.W., Chen, D.L. *Clinical Impact of PSMA PET in patients with biochemical recurrence of prostate cancer after local definitive therapy.* American Society of Clinical Oncology Annual Meeting (2022). [Abstract]

82. Liao, J.J., Mostaghel, E.A., Russell, K.J., Dalkin, B.L., Ellis, W.J., Lin, D., Wright, J., Schade, G., Nyame, Y., Yu, E.Y., Nelson, P., Grivas, P., Schweizer, M.T., **Cheng, H.H.,** Yezefski, T., Hawley, J.E.., Chen, J.J., Weg, E., Nguyen, M., Montgomery, B., *Abiraterone, Androgen Deprivation Therapy, and Radiotherapy for Localized High Risk and Intermediate Risk Prostate Cancer: Long-term follow up of the RAD1 Phase 2 trial.* American Society of Radiation Oncology, Annual Meeting (2022). [Abstract]

83. Garcia, J., Vakar-Lopez, F., Roudier, M., Grivas, P., Yu, E.Y., **Cheng, H.H.,** Schweizer, M.T., Haffner, M., Lee, J.K., Corey, E., Montgomery, B., Hsieh, A.C., Wright, J.L., Lam, H. *Bladder Cancer Rapid Autopsy Program provides a critical resource for the biological study of advanced bladder cancer.* American Urological Association (2022). [Abstract]

84. Gulhane, A., Talukder, R., Dash, A., Ellis, W., Nyame, Y.A., Schade, G., Wright, J.L., Apisarnthanarax, S., Chen, J., Liao, J.J., Wallner, K., Weg, E.S., **Cheng, H.H.,** Grivas, P., Hawley, J., Hsieh, A.C., Lee, J.K., Montgomery, B., Nelson, P.S., Schweizer, M.T., Yezefski, Y., Yu, E.Y., Lin, D.W., Chen, D.L. *Utility of PSMA PET for Initial Staging of Prostate Cancer.* Radiological Society of North America (2022). [Abstract]

85. Lorentz, J., Appleman, L., Armstrong, A.J., Barata, P., DeMarco, T.A., Dreicer, R., Elrod, J.B., Fleming, M., George, C., Heath, E.I., Hussain, M.A., Mao, S., McKay, R.R., Metwalli, A., Morgans, A., Orton, M., Pili, R., Saraiya, B., Sigmond, J., Sokolova, A.O., Stadler, W.M., Tran, C., Macario, N., Vinson, J., Green, R., Paller, C.J., **Cheng, H.H.** *Utilization of a decentralized national genetic registry to address*

informational needs caused by expanded testing recommendations and recently approved treatments for prostate cancer: the PROMISE Registry. National Society for Genetic Counseling (2022) [Abstract]

86. Wong, R.L., **Cheng, H.H.,** Fann, J.R., Hnida, J., Chakoian, M., Schenker, Y., Yu, E.Y., Gore, J.L. *Depression Screening in Prostate Cancer and Use of Supportive Care Services.* ASCO Quality Care Symposium (2022) [Abstract]

87. Rathkopf, D.E., Chi, K.N., Olmos, D., **Cheng, H.H.,** Agarwal, N., Graff, J.N., Sandu, S.K., Kim, W., Lopez-Gitlitz, Francis, P.S., Attard, G., *AMPLITUDE: Niraparib and Abiraterone Acetate Plus Prednisone to Treat Patients with Metastatic Castration Sensitive Prostate Cancer and Deleterious Germline or Somatic Homologous Recombination Repair Gene Alterations*. Society for Urology Oncology (2022) [Abstract]

88. Paller, C.J.*, Barata, P.C., Lorentz, J., Appleman, L.J., Armstrong, A.J., DeMarco, T.A., Dreicer, R., Elrod, J.B., Fleming, M., George, C., Heath, E.I., Hussain, M.H., Mao, S., McKay, R.M., Metwalli, A.R., Morgans, A., Stadler, W.M., Tran, C., Macario, N., Vinson, J., Green, R., **Cheng, H.H.*** *PROMISE Registry: A Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness*. Prostate Cancer Foundation Annual Retreat (2022). [Poster abstract]

18. Invited Talks, including CME presentations

a. National/International Invited Lectures

1. 12/2002: *Identifying the Requirements and Mechanisms of FeLV-T Entry*. **2002 International Workshop on Retroviral Pathogenesis**, Indian Wells, CA [invited lecture]

2. 05/2003: *Determinants of Receptor Specificity for Feline Leukemia Virus Variants.* **Cold Spring Harbor Meeting on Retroviruses**, Cold Spring Harbor, NY [invited lecture]

3. 06/25/2016: *Germline DNA Repair Gene Mutations in Metastatic Prostate Cancer.* **2016 Prostate Cancer Foundation Coffey-Holden Academy**, Coronado, CA [invited lecture]

4. 11/30/2016: *Clinical Implications for Prostate Cancer Screening and Treatment of Men with Germline Mutations in BRCA and other DNA Repair Genes.* The 17th Annual Meeting of the **Society of Urologic Oncology**, San Antonio, TX [invited lecture]

5. 06/05/2017: *Clinical Implications of Genomic Sequencing in Prostate Cancer.* **American Society for Clinical Oncology Annual Meeting**, Chicago, IL [invited abstract discussant]

6. 10/06/2017: *Beyond the Androgen Receptor II: New Approaches to Understanding and Treating Metastatic Prostate Cancer; Report from the 2017 Coffey-Holden Prostate Cancer Academy Meeting*. 24th Annual Prostate Cancer Foundation Scientific Retreat, Washington, D.C. [invited oral presentation]

7. 10/06/2017: *Implementing Germline Genetics into Prostate Cancer Clinical Care*. **24th Annual Prostate Cancer Foundation Scientific Retreat**, Washington, D.C. [invited oral presentation]

8. 02/09/2018: *A New Era in Prostate Cancer Treatment? Understanding DNA Repair Deficiencies and the Therapeutic Rationale for PARP Inhibition.* Genitourinary Cancers Symposium CME, San Francisco, CA. [invited CME faculty]

9. 02/11/2018: *The Changing Landscape of Prostate Cancer Genetics Care and the GENTleMEN Study*, **Morris Kahn and Maccabi Research and Innovation Institute, Tel Aviv, Israel** [invited oral presentation]

10. 02/12/2018: *The Changing Landscape of Prostate Cancer Genetics Care and the GENTleMEN Study,* **Sheba Medical Center/Tel Hashomer Hospital, Tel Aviv, Israel** [invited oral presentation]

11. 03/29/2018: *Expanding Clinical and Research Horizons in Prostate Cancer Genetics.* Koch Center Seminar Series, **MD Anderson Cancer Center**, Houston, TX. [invited faculty speaker]

12. 05/20/2018: *Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized disease, and CRPC.* **Annual Meeting of the American Urological Association**, San Francisco. [educational course faculty]

13. 06/01/2018: *Genomics Versus Genetics, and Implications for Prostate Cancer Care.* **American Society of Clinical Oncology Annual Meeting**, Chicago, IL [invited session chair and oral presentation]

14. 09/15/2018: *Genetics and Genomics in Prostate Cancer: Realizing the Promise of Precision Medicine and Other Very Important Benefits.* Prostate Cancer Symposium, **Barbara Ann Karmanos Cancer Institute**, Wayne State University School of Medicine, Detroit, MI [invited Keynote Lecture]

15. 05/03/2019: *Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized disease, and CRPC.* **Annual Meeting of the American Urological Association**, San Francisco. [educational course faculty]

16. 05/31/2019*: The Genetic Landscape and Prognostic/Predictive Implications*. 2019 ASCO Genetics and Genomics Pre-Annual Meeting Seminar, **American Society of Clinical Oncology Annual Meeting**, Chicago, IL [invited faculty speaker]

17. 09/11/2019: *Expanding Clinical and Research Horizons in Prostate Cancer Genetics*. Oncology Grand Rounds, **University of Wisconsin/Carbone Cancer Center**, Madison, WI [invited Grand Rounds speaker**]**

18. 10/04/2019: *Germline Contribution to Metastatic Prostate Cancer.* Implementation of Genetic Testing for Inherited Prostate Cancer, **Philadelphia Prostate Cancer Consensus Conference 2019**. [invited speaker]

19. 10/26/2019: *Prostate Cancer Genetics.* Prostate Cancer Foundation and UsTOO International Prostate Cancer Support Network, **26th Prostate Cancer Foundation Annual Scientific Retreat**. Carlsbad, CA. [invited speaker]

20. 11/06/2019: *Molecular-Driven Therapy in GU Cancers.* **37th Annual CFS®: Innovative Cancer Therapy for Tomorrow**, New York, NY [invited faculty speaker]

21. 04/18/2020: *Prostate Cancer, DNA Repair Pathways and Predictive Testing for Inherited Cancers*. **9th Annual International Clinical Cancer Genetics and Genomics Conference, University of Chicago**; Chicago, IL [invited faculty speaker]

22. (*cancelled due to COVID19*) 05/20/2020: *Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized disease, and CRPC.* **Annual Meeting of the American Urological Association, Washington, D.C**. [educational course faculty]

23. 10/14/2020: *Prostate Cancer Genetics: Testing, Targeted Therapy and Early Detection.* **Dana-Farber Genitourinary Oncology Seminar Series**, Boston, MA [invited faculty speaker]

24. 10/15/2020: *Genetics, Genomics, and Prostate Cancer.* USToo International, Chicago, IL [invited webinar speaker]. https://www.youtube.com/watch?v=WjkAF1xixOA&feature=youtu.be

25. 11/20/2020: *Genetic Testing in Prostate Cancer.* **Facing Our Risk of Cancer Empowered Annual Conference, Philadelphia, PA.** [invited faculty]. https://www.youtube.com/watch?v=m515URd9uYk&feature=youtu.be

26. 04/29/2021: *Integrating Genetic Testing into Clinical Practice for Advanced Prostate Cancer*. Genitourinary (GU) Medical Oncology Series: The Impact of Genomic Profiling on Patients with Prostate Cancer. LUGPA Webinar [invited faculty speaker]

27. 07/29/2021: *What is Right for Me in My Prostate Cancer Treatment – Genetics & Genomics.* **USToo International, Chicago, IL** [invited national webinar speaker]

28. 09/20/2021: *Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized Disease, and CRPC.* **Annual Meeting of the American Urological Association, Washington, D.C**. [educational course faculty]

29. 09/20/2021: *Germline Genetics for Prostate Cancer Prognosis: Predicting Drug Treatment Response for Men with Advanced Prostate Cancer (Urologic Oncology Research Symposium)* **Annual Meeting of the American Urological Association, Washington, D.C**. [invited faculty speaker]

30. 09/29/2021: *What's New in Prostate Cancer Treatment*. **12th Annual FORCE Hereditary Cancer Conference, Philadelphia, PA** [invited national webinar faculty]

31. 04/29/2022: *How to take care of muscle strength for prostate cancer patients.* **Advanced Prostate Cancer Consensus Conference 2022, Lugano, Switzerland** [invited faculty speaker and session chair]

32. 05/15/2022: *Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection, Localized Disease, and CRPC.* **Annual Meeting of the American Urological Association, New Orleans, LA**. [educational course faculty]

33. 06/06/2022: *AR and PARP: Partners in Crime.* **American Society of Clinical Oncology 2022 Annual Meeting, Chicago, IL** [invited oral poster discussant]

34. *(anticipated)* 10/13/2022: *What's New in Prostate Cancer Treatment*. **13th Annual FORCE Hereditary Cancer Conference, Philadelphia, PA** [invited national webinar faculty]

35. *(anticipated)* 05/05/2023: *Bringing Prostate Cancer Risk Assessment to the Community: A GENTleMEN's PROMISE.* City of Hope/University of Chicago 11th Annual Clinical Cancer Genomics Conference, Los Angeles, CA [invited speaker]

b. Regional Invited Lectures

1. 07/15/2012: *Circulating microRNA Biomarkers in Prostate Cancer*. Oral presentation for Department of Defense/Prostate Cancer Clinical Trials Consortium. Teleconferenced nationally from Memorial Sloan Kettering Cancer Center, New York, NY

2. 11/20/2013: *A Phase I/II Trial of Concurrent Chemohormonal therapy using Enzalutamide and Cabazitaxel in Patients with Metastatic Castration Resistant Prostate Cancer.* Oral presentation, teleconferenced nationally from Memorial Sloan Kettering Cancer Center, New York, NY

3. 04/12/2014: *Circulating Biomarkers in Advanced Disease***.** Institute for Prostate Cancer Research 2014 Symposium, Fred Hutchinson Cancer Research Center, Seattle, WA.

4. 05/01/2014**:** *Comparison of plasma microRNAs with CTCs and PSA in patients treated on SWOG S0925.* Oral presentation at 2014 SWOG Genitourinary Working Group Meeting, San Francisco, CA

5. 06/20/2014: *Recent Developments and Clinical Trials in Prostate Cancer.* Oral presentation for the Seattle Cancer Care Alliance/National Comprehensive Cancer Network "Breakthroughs in Solid Tumor Oncology" Symposium; June 20, 2014, Seattle, WA

6. 10/31/2014: *Comparison of plasma microRNAs with CTCs and PSA in patients treated on SWOG S0925.* Prostate Cancer SPORE Seminar, Fred Hutchinson Cancer Research Center, teleconferenced to Oregon Health Sciences and University of British Columbia

7. 06/29/2016: *Emerging Therapies in Cancer: Cancer Genetics.* Seattle Cancer Care Alliance CME lecture for Skagit Valley Hospital, Mount Vernon, WA

8. 10/27/2016: *Prostate Cancer Foundation Women's Networking Forum*. Junior Investigator Panelist at the 2016 Prostate Cancer Foundation Retreat, Carlsbad, CA

9. 04/13/2017: *Metastatic Prostate Cancer*. Cases From Kampala, hosted by Uganda Cancer Institute/Hutchinson Cancer Center Alliance; WebEx between Seattle, WA, and Kampala, Uganda

10. 09/23/2017**:** *The Genetics of Inherited Prostate Cancer Risk: Why what has always mattered matters even more in 2017*. 17th Annual Pacific NW Prostate Cancer Conference, Seattle, WA

11. 02/01/2018: *Genetic Testing for Men with Metastatic Prostate Cancer: Changing Landscape and the GENTleMEN Study.* PPCR SPORE Seminar Series, Fred Hutch Cancer Research Center, Seattle, WA

12. 03/08/2018: *Precision Medicine for Older Adults: Delivering on a Promise*. Plein Research Symposium in Geriatric Pharmacy, Center for Urban Horticulture, Univ of Washington, Seattle, WA

13. 06/23/2018: *Prostate Cancer Pathways for Patients and Caregivers: Updates in Prostate Cancer Genetics.* UsTOO International Prostate Cancer Support Network Patient Symposium and Webcast, Evergreen Hospital, Kirkland, WA

14. 07/17/2018*: Molecular Predictors of Prostate Cancer Progression and Mortality.* PNW SPORE Symposium, Fred Hutch Cancer Research Center, Seattle, WA, , teleconferenced to Oregon Health Sciences and University of British Columbia

15. 10/12/2018: *Prostate Cancer.* Transitions in Oncology Care: Pearls for the Primary Care Provider Conference, Talaris Conference Center, Seattle, WA.

16. 10/15/2018: *Expanding Clinical and Research Horizons in Prostate Cancer Genetics.* Fred Hutch Clinical Research/University of Washington Medical Oncology/Seattle Cancer Care Alliance, Clinical Research Division Seminar Series, Seattle, WA

17. 05/11/2019: *Genetics: The GENTleMEN study and extending potential benefit to families.* Prostate Cancer Symposium, hosted by the Institute for Prostate Cancer Research; Fred Hutch Cancer Research Center, Seattle, WA

18. 07/22/2020: *Prostate Cancer Genetics.* Medscape CME Webinar; Seattle Cancer Care Alliance, Seattle WA

19. 09/24/2020: *Prostate Cancer Genetics in 2020: Testing, Targeted Therapy and Early Detection.* PPCR SPORE Seminar Series, Fred Hutch Cancer Research Center, Seattle, WA, teleconferenced to Oregon Health Sciences and University of British Columbia

20. 03/06/2021: *Updates in Genetics for Bladder and Urinary Tract Cancer.* Updates in Bladder and Urinary Tract Cancers; Seattle Cancer Care Alliance, Seattle WA

21. 7/30/2022: Risk Based Screening and Hereditary Prostate Cancer. *Breakthroughs in Prostate Cancer Research* Institute for Prostate Cancer Research Symposium; Seattle, WA

22. *(anticipated)* 10/15/2022: *What You Should Know About the Growing Importance of Genetic Testing in Prostate Cancer*. 22nd Annual Pacific NW Prostate Cancer Conference; Seattle, WA [invited national webinar faculty]

c. Local Invited Lectures

1. 09/25/2014: *Prostate Cancer: New Treatments and Ongoing Research.* Fred Hutchinson Cancer Research Center Diversity/Outreach Program to local African American Community, NW African American Museum, Seattle, WA.

2. 11/12/2014: *The Surprising Ways in Which Patients Shape our Lives.* Schwarz Center Rounds, hosted by The Schwarz Center for Compassionate Healthcare; Seattle Cancer Care Alliance, Seattle, WA

3. 04/11/2015: *Lessons from Breast Cancer: How Genes May Affect Risk, Treatment and Outcomes in Prostate Cancer.* Prostate Cancer Symposium, hosted by the Institute for Prostate Cancer Research; Fred Hutchinson Cancer Research Center, Seattle, WA

4. 05/07/2015*: Prostate Cancer: Progress Made and Research in Progress.* Research Matters Series, Seattle Cancer Care Alliance, Seattle, WA

5. 03/24/2016: *Leveraging DNA Repair Defects for Treatment of Prostate Cancer.* PPCR SPORE Seminar Series, Fred Hutchinson Cancer Research Center, Seattle, WA

6. 10/11/2016: *New Discoveries in Prostate Cancer Genetics (or: Why Breast Cancer Genes Are Not Just for Women)*". Fred Hutch Clinical Research/University of Washington Medical Oncology/Seattle Cancer Care Alliance Grand Round, Seattle, WA

7. 11/17/2016: *Prostate Cancer Genetics: Leveraging Family Traits for Early Detection***.** Fred Hutchinson Cancer Research Center Innovators Network. Seattle, WA

8. 12/23/2016: *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.

9. 03/18/2017: *Inherited Risk and Prostate Cancer Behavior.* Prostate Cancer Symposium, Institute for Prostate Cancer Research; Fred Hutchinson Cancer Research Center, Seattle, WA

10. 05/24/2017: *Prostate Cancer Genetics.* UsTOO Greater Seattle Area Prostate Cancer Patient Support Group; Greenwood Community Center, Seattle, WA.

11. 10/26/2017: *Clinical Implementation of Quality of Life Measurement in Prostate Cancer Care.* PPCR SPORE Seminar Series, Fred Hutchinson Cancer Research Center, Seattle, WA

12. 11/06/2017: *Genetics and Genomics.* CCSG Prostate Program Cancer Retreat, Fred Hutchinson Cancer Research Center, Seattle, WA

13. 01/19/2018: *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.

14. 01/26/2018: *Expanding Clinical and Research Horizons in Prostate Cancer Genetics.* **UW Medical Genetics Division Grand Rounds**, Seattle, WA

23. 04/28/2018: *Inherited Risk and GENTleMEN.* Prostate Cancer Symposium, hosted by the Institute for Prostate Cancer Research; Fred Hutch Cancer Research Center, Seattle, WA

24. 05/04/2018: *Genetic Testing for Men with Metastatic Prostate Cancer: GENTleMEN.* Seattle Cancer Care Alliance Network Summit, Fred Hutch Cancer Research Center, Seattle, WA

25. 05/07/2018: *Prostate Cancer: Screening, Treatment and Genetics.* UW Internal Medicine Residents Report, University of Washington Medical Center, Seattle, WA

26. 05/23/2018: *Prostate Cancer Genetics and the GENTleMEN Study*. CCSG Breast and Ovary Cancer Research Program Retreat, Fred Hutch Cancer Research Center, Seattle, WA

27. 08/09/2018: *Prostate Cancer Genetics and the GENTleMEN Study*. Overbaugh Lab 30th Year Symposium Retreat, Islandwood, Bainbridge Island, WA

28. 10/05/2018: *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.

29. 09/06/2019: *Germline and Somatic DNA repair mutations in Prostate Cancer.* Genitourinary Medical Oncology Research Team Staff Education Series; Fred Hutch Cancer Research Center, Seattle, WA

30. 09/06/2019: *Updates in Prostate Cancer Genetics.* Seattle Cancer Care Alliance Community Site Dinner Clinical Research Partnership Series; Seattle, WA

31. 01/09/2020: *From Cat Viruses to Men's Prostates: An Ongoing Research Journey.* UW Medical Scientist Training Program Monthly Research Meeting; Seattle, WA.

32. 01/24/2020: *Mutational Testing for Solid Tumors.* UW/Fred Hutch Hematology and Oncology Fellowship Solid Tumor Conference; Seattle, WA.

33. 01/29/2020: *Prostate Cancer: Screening, Side Effects and Survivorship.* Genitourinary Medical Oncology Research Team Staff Education Series; Fred Hutch Cancer Research Center, Seattle, WA

34. 05/27/2020: *Prostate Cancer Genetics through a Medical Oncologist's Lens.* **University of Washington, Radiation Oncology Grand Rounds**, Seattle, WA. [invited Grand Rounds]

35. 07/15/2020: *Olaparib for Metastatic Castration Resistant Prostate Cancer.* Clinical Research Division Journal Watch; Fred Hutch Cancer Research Center, Seattle, WA

36. 02/22/2021: *Prostate Cancer Genetics and Risk.* Seattle Cancer Care Alliance Board Enrichment Series; Seattle Cancer Care Alliance, Seattle WA

37. 06/06/2021: *Molecular Subtypes and Prostate Cancer Treatments.* Prostate Cancer Symposium, hosted by Institute for Prostate Cancer Research; Fred Hutch Cancer Research Center, Seattle, WA

38. 08/25/2021: *Role of Genes in Prostate Cancer and the PROMISE Study.* USToo Support Group Meeting, Seattle, WA

39. 7/21/2022: *Genetics and Genomics of Prostate Cancer*. Genitourinary Medical Oncology Research Staff Education Series; Seattle, WA

CURRICULUM VITAE

EVAN YA-WEN YU, MD
825 Eastlake Ave E, G4-830
Seattle, WA 98109
Phone: 206-606-7595
Fax: 206-606-2042
Email: evanyu@uw.edu

PERSONAL DATA

Place of birth:	Bellevue, Washington
Citizenship:	U.S.A.
Date of Birth:	[redacted]
Languages:	English, Mandarin Chinese

EDUCATION

B.S. (Zoology) University of Washington, Seattle, WA	1989-1994
M.D. University of Washington, School of Medicine, Seattle, WA	1994-1998

POSTGRADUATE TRAINING

Clinical Fellow in Medicine, Harvard Medical School, Boston, MA	1998-2004
Intern in Medicine, Brigham and Women's Hospital, Boston, MA	1998-1999
Junior Assistant Resident, Brigham and Women's Hospital, Boston, MA	1999-2000
Senior Assistant Resident, Brigham and Women's Hospital, Boston, MA	2000-2001
Fellow in Hematology-Oncology, Dana-Farber Cancer Institute, Boston, MA	2001-2004
Clinical Fellow in Medicine, Brigham and Women's Hospital, Boston, MA	2001-2004
Post-doctoral Basic Science Research Fellow, Dana-Farber Cancer Institute William C. Hahn, M.D., Ph.D., Boston, MA	2002-2004
AACR/ASCO Methods in Clinical Cancer Research Workshop	2006

FACULTY POSITIONS HELD

Assistant Professor, Department of Medicine, School of Medicine University of Washington, Seattle, WA	2004-2010
Assistant Member, Clinical Research Division Fred Hutchinson Cancer Research Center, Seattle, WA	2004-2010
Assistant Fellowship Director Medical Oncology and Hematology Fellowship Program University of Washington / Fred Hutchinson Cancer Research Center, Seattle, WA	2006-2017
Associate Professor, Department of Medicine, School of Medicine University of Washington, Seattle, WA	2010-2016
Associate Member, Clinical Research Division Fred Hutchinson Cancer Research Center, Seattle, WA	2010-2016
Clinical Trials Core Director Genitourinary Medical Oncology Research Group University of Washington / Fred Hutchinson Cancer Research Center, Seattle, WA	2012-2022

Full Professor, Department of Medicine, School of Medicine
University of Washington, Seattle, WA 2016-present

Full Member, Clinical Research Division
Fred Hutchinson Cancer Research Center, Seattle, WA 2016-present

Clinical Research Director
Genitourinary Oncology Research Group
University of Washington / Fred Hutchinson Cancer Research Center, Seattle, WA 2017-2022

Medical Director
Clinical Research Support
Fred Hutchinson Cancer Consortium, Seattle, WA 2018-present

Section Head
Medical Oncology and Cancer Medicine, Clinical Research Division
Fred Hutchinson Cancer Center, Seattle, WA 2022-present

HOSPITAL POSITIONS HELD

Member, Medical Staff, Pembroke Psychiatric Hospital, Pembroke, MA 2000-2001
Member, New England Sinai Rehabilitation Hospital, Stoughton, MA 2000-2001
Member, Medical Staff, Anna Jacques Hospital, Newburyport, MA 2000-2002
Member, Medical Staff, South Shore Hospital, Weymouth, MA 2001-2002
Member, Medical Staff, Emerson Hospital, Concord, MA 2001-2004
Member, Medical Staff, Jordan Hospital, Plymouth, MA 2000, 2004
Member, Medical Staff, Faulkner Hospital, Boston, MA 2004
Member, Medical Staff, Brigham and Women's Hospital, Boston, MA 2004
Member, Medical Staff, University of Washington Medical Center, Seattle, WA 2004-present

HONORS

Alpha Omega Alpha, School of Medicine, University of Washington 1997
Graduation with Honors, School of Medicine, University of Washington 1998
Chief Resident, Faulkner Hospital (Subsidiary of Brigham and Women's Hospital) 2001
Seattle Magazine's "Top Doctor" 2010, 2018, 2022
Who's Who in Medicine and Healthcare 2011-2012
Seattle Met Magazine's "Top Doctor" 2011
U.S. News and World Report "Top Doctor" 2011-present
Castle Connolly America's Top Doctors 2011-present
Invited Faculty for "Fellows, Residents and Junior Faculty Networking Luncheon"
Genitourinary Cancers Symposium 2012, 2013
Asian Journal of Andrology "Excellent Editorial Board Member Award" 2016
Albert Nelson Marquis Lifetime Achievement Award 2017
Who's Who in Academia 2017-present
"Triple Threat Award," Fred Hutchinson Cancer Research Center Assistant Fellowship Director 2018
"Best of the Best," Top 1% America's Most Honored Professionals 2018-present
William J. Bremner Endowed Department of Medicine Mentorship Award Nominee 2018
Outstanding Research Mentor Award, E17 University of Washington School of Medicine 2019
Philip Saccoccia Montana WWAMI Translational Medicine Speaker 2021
America's Most Honored Doctors – Top 5% 2022 2022

BOARD CERTIFICATION

American Board of Internal Medicine	2001-2011
Medical Oncology	2003-present (recertified in 2013)

MEDICAL LICENSE

State of Massachusetts	2000-2005
State of Washington (MD00044089)	2004-present
State of Montana (MED-PHYS-LIC-102493)	2021-present

NPI #1043390016

Diversity, Equity and Inclusion Activities:

Diverse Enrollment Institutional Review Board Subcommittee Fred Hutchinson Cancer Research Consortium	2021-present
Cancer Center Director's Task Force for DEI in Clinical Investigations Fred Hutchinson Cancer Research Consortium	2021-present
Asian American Cancer Disparities Webinar American Cancer Society	2022

PROFESSIONAL ORGANIZATIONS

American Association of Cancer Research
American Medical Association
American Radium Society
American Society of Clinical Oncology
American Society of Internal Medicine
American Urological Association
Association of American Cancer Institutes
European Society of Medical Oncology
Hoosier Cancer Research Network
Massachusetts Medical Society
Society for Immunotherapy of Cancer
Society of Urologic Oncology
Southwest Oncology Group (SWOG)
Washington State Medical Oncology Society

TEACHING RESPONSIBILITIES

Tutor, Basic Sciences, Microbiology and Biochemistry, School of Medicine, University of Washington	1997-1998
Adjunct Instructor, Health Sciences, Massachusetts College of Pharmacy	1999-2000
Adjunct Instructor, Health Sciences, Massachusetts School of Health Sciences	1999-2000
Preceptor, Patient-Doctor II Course, Harvard Medical School	2004
Teaching of Fellows, Residents, and Medical Students, University of Washington	2004-present
Research Mentor, American Cancer Society Medical Student Research Program, University of Washington (Student - Brian Rezvani)	2007
Preceptor, University of Washington School of Medicine (Students Andrew Stergachis, Michael Zhang, Gabriel Loeb, Erica Nees, and Qian Zhang)	2008-2011
Research Mentor (Students), University of Washington Brian B. Rezvani – Now thoracic surgeon	2007
Kevin F. Kuo – Now internal medicine faculty at Stanford University	2009-2013

Jason Flamiatos – Now Urologist 2011-2013
Daniel Lim – Current internal medicine resident at University of Washington 2017-present
Alex Carlson – Now internal medicine resident at University of Wisconsin 2018-2020
Olivia Do – Current pediatrics resident at University of Washington 2019-2021
Lorin Ferris – Current pediatrics resident at Inova L.J. Murphy Children's Hospital 2019-2021

Research Mentor (Fellows), Fred Hutchinson Cancer Research Center Oncology Fellowship

Junfeng Wang – Assistant Professor at University of Utah and Huntsman Cancer Institute (Division of Oncology, Department of Medicine) 2012
Swaminathan Murugappan – Now Executive Medical Director at Kite 2012
Heather H. Cheng – Now Associate Professor at University of Washington 2012-present
Jorge D. Ramos –Assistant Professor at University of Washington, now Medical Director at Seattle Genetics 2013-2017
Risa Wong – Now Assistant Professor at University of Pittsburgh 2019-2021
Rafee Talukder – Now Assistant Professor at Baylor 2021-present

EDITORIAL RESPONSIBILITIES

Senior/Associate Editor

Clinical Genitourinary Cancer 2016-2018
UroToday (Clinical Trials Portal) 2016-present
Clinical Cancer Research 2017-present

Editorial Board

Clinical Genitourinary Cancer 2010-2018
Journal of Cancer Therapeutics and Research 2011-2017
Asian Journal of Andrology 2015-2018
Everyday Oncology 2016-2017

"Ad hoc" Reviewer

Annals of Oncology, Asian Journal of Urology, Bladder Cancer Journal, British Journal of Cancer, BMC Cancer, British Journal of Urology International, Cancer, Cancer Control Journal, Cancer Discovery, Clinical Cancer Research, Clinical Interventions in Aging, Clinical Medicine Insights: Oncology, Drugs, European Journal of Cancer, European Urology, Expert Opinions on Investigational Drugs, Expert Review of Anticancer Therapy, Investigational New Drugs, Journal of American Medical Association, Journal of Clinical Endocrinology and Metabolism, Journal of Clinical Investigation, Journal of Clinical Oncology, JCO Clinical Cancer Informatics, Journal of ImmunoTherapy of Cancer, Journal of the National Cancer Institute, Journal of the National Comprehensive Cancer Network, Journal of Nuclear Medicine, Journal of Oncotargets and Therapy, Journal of Urology, Lancet Oncology, New England Journal of Medicine, The Oncologist, Oncotarget, PLOS ONE, Proceedings of the National Academy of Sciences, The Prostate, Prostate Cancer and Prostatic Diseases, Up-to-Date: Genitourinary Oncology, Urologic Oncology, Urology

Grant and Funding Organization Reviews

Cancer Research United Kingdom, Department of Defense, National Cancer Institute, National Institute of Health Molecular Imaging Branch Intramural Program, Prostate Cancer Charity, Prostate Cancer Foundation Challenge and Young Investigator Awards, PNW SPORE Pilot Projects, Solid Tumor Translational Research (STTR) Grant Program, V Foundation

NATIONAL RESPONSIBILITIES

Reviewer, Department of Defense 2005
Prostate Cancer Translational Grant Study Section

Steering Committee Member, Dasatinib Phase 3 Registration Study 2009-2013
Imaging Committee, Prostate Cancer Working Group 2009-2012
Co-Chair and Faculty, 2010 American Society of Clinical Oncology 2010
Genitourinary Cancer (Prostate) Oral Abstract Session
Co-Chair, Quantitative Imaging Network (QIN) Outreach Working Group 2010
Genitourinary Committee Member, SWOG 2010-present
Co-Chair and Faculty, 2011 American Society of Clinical Oncology 2011
Genitourinary Cancer (Non-Prostate) Oral Abstract Session
Advanced Prostate Cancer Chair (covering), SWOG Fall 2011 Group Meeting 2011
Genitourinary Committee
SPORE Representative, National Cancer Institute 2012-2014
Genitourinary Cancers Steering Committee
Steering Committee Member, PREDICT Biomarker Committee 2013-2016
Special Clinical Expert, National Cancer Institute (Served 1 year of 2nd 3-year term) 2014-2018
Genitourinary Cancers Steering Committee
Advisory Member, Society of Urology Oncology (Clinical Trials Consortium, Inc.) 2015-present
Board of Directors and the Prostate Organ Site Committee
Test Question Writer, American Society of Clinical Oncology and National Board of 2017-2019
Medical Examiners
ASCO University Courses, ASCO-SEP Mock Exam, In-Training Exam
Member, American Society of Oncology Annual Meeting Education Committee 2017-2020
Genitourinary (Nonprostate) Cancer
Member, Bone Metastasis Expert Panel 2017-2019
American Radium Society
GU Prostate Cancer Committee Member, SWOG 2017-present
Co-Chair (Medical Oncology), National Cancer Institute (3-year term renewed) 2018-present
Prostate Cancer Task Force
Imaging Committee Member, SWOG 2018-present
Member, Education Committee 2019-present
Association of American Cancer Institutes
Member, Board of Governors, SWOG 2020-present
Member, AACR Annual Meeting Clinical Trials Committee 2020-2022
American Association for Cancer Research
Test Question Writer, American Society of Clinical Oncology Question Writing 2021-present
Group for ASCO Self-Assessment Programs
Reviewer, National Cancer Institute 2021
Cancer Clinical Investigator Team Leadership Award (CCITLA) Grant Reviewer
Co-Chair, American Society of Clinical Oncology 2021-present
Germline and Somatic Genomic Testing for Advanced and Metastatic Prostate Cancer
Reviewer, National Cancer Institute Intramural Research Program 2021
Molecular Imaging Branch
Member, Hoosier Cancer Research Network 2021-present
Genitourinary Clincal Trial Working Group
Member, AACR Continuing Medical Education Committee 2022-present
American Association for Cancer Research
Member, Imaging Committee 2022- present
Prostate Cancer Working Group 4

LOCAL RESPONSIBILITIES

4th Floor Solutions Committee, 2004–2006

Seattle Cancer Care Alliance
Genitourinary Practice Committee 2004–2005
University of Washington Department of Medicine
Recruitment and Community Outreach Core 2004–2005
University of Washington Translational Grant Committee
Multicultural Affairs Advisory Board 2006–2007
University of Washington Department of Medicine
Translational Research Task Force 2006–2008
University of Washington Translational Grant Committee
Accreditation Council for Graduate Medical Education 2006–2017
University of Washington Medicine Residency Program
Oncology and Hematology Fellowship Program Admissions Committee 2006–present
University of Washington / Fred Hutchinson Cancer Research Center
Prostate Cancer Task Force 2007–2008
Washington Comprehensive Cancer Control Partnership
Imaging Working Group 2007–2008
Prostate Specialized Programs of Research Excellence (SPORE)
Quality Improvement/Safety Steering Committee 2007–2010
Seattle Cancer Care Alliance
Medical Student Research Training Program Committee 2008-2016
University of Washington School of Medicine
Medical Student Admissions Committee 1995-1998
University of Washington School of Medicine 2009-2016
Institute for Prostate Cancer Research Committee 2009-present
University of Washington
Grant Reviewer 2010
INBRE-WSU Spokane Institute for Translational Health Sciences
Internal Medicine Residency Education Coordinator (Oncology) 2010-2017
University of Washington
Core Faculty Designation, Internal Medicine Residency 2010-present
University of Washington
Clinical Core Director 2012-present
Pacific Northwest Prostate Cancer SPORE
Reviewer for the University of Washington 2013
American Cancer Society Summer Fellowship in Clinical Cancer Research
New Faculty Search Committee Member 2013-2015
University of Washington Pediatric Oncology and Seattle Children's Hospital
Prostate Cancer Clinical Pathways 2013-2017
Seattle Cancer Care Alliance
Scientific Review Committee, Sub-Committee B Member 2014
University of Washington / Fred Hutchinson Cancer Research Center Consortium
Scientific Review Committee, Sub-Committee B Co-Chair 2015-2017
University of Washington / Fred Hutchinson Cancer Research Center Consortium
New Radiochemistry Faculty Search Committee Member 2015-2018
University of Washington Department of Radiology
New Faculty Search Committee Member 2016-2017
University of Washington Genitourinary Oncology
Genitourinary Oncology Leadership Committee 2017-present
University of Washington / Fred Hutchinson Cancer Research Center Consortium
Clinical Trials Process Improvement Oversight Committee 2017-present

Seattle Cancer Care Alliance

External Performance Site Assessment Committee 2018
Fred Hutchinson Cancer Consortium

Site Initiation Visit Escalation Policy Committee 2017-2018
Seattle Cancer Care Alliance

New Faculty Search Committee, Director of Nuclear Medicine 2018-2019
Seattle Cancer Care Alliance

Research Ethics Committee 2018-present
Fred Hutchinson Board of Trustees

Institutional Review Board Chair Liason Committee 2018-present
Fred Hutchinson Cancer Research Consortium

Compliance Sub-Committee, Clinical Research Services 2018-present
Fred Hutchinson Cancer Research Consortium

Clinical Trial Oversight Committee, Clinical Research Services 2018-present
Fred Hutchinson Cancer Research Consortium

Institutional Sponsored IND Oversight Committee, Clinical Research Services 2018-present
Fred Hutchinson Cancer Research Consortium

NCI National Cancer Trials Network Leadership Committee 2020-present
Fred Hutchinson Cancer Research Consortium

Adult Oncology Strategic Plan: Research Advisory Group 2021-present
Seattle Cancer Care Alliance/University of Washington Medicine/Fred Hutchinson Cancer Research Center

New Faculty Search Committee, Director of Nuclear Medicine Theranostics 2021-present
Seattle Cancer Care Alliance

Co-Chair, Faculty Advisory Committee, Clinical Trials Joint Steering Committee 2022-present
University of Washington and Fred Hutchinson Cancer Center

PEER REVIEW FUNDING

1. Prostate Cancer Research Program Clinical Consortium Award.
   W81XWH-16-PCRP-CCRSA (Cheng)
   Grant amount: $1,000,000
   Source: Department of Defense
   Role: Co-site principal investigator (5% effort)
   Dates: 01/01/07 - 09/29/27 (4 successful competitive renewals)

2. Cancer Consortium Support Grant
   P30 CA015704 (Gilliland) / Clinical Research Support (Yu)
   Grant amount: $30,047,070
   Source: NIH/NCI
   Role: Medical Director, Clinical Research Support Office
   Dates: 01/01/97 – 12/31/24

3. Lead Academic Participating Site (LAPS) Grant
UG1 CA233328 (Yu)
Grant Amount: $2,992,480
Source: NIH/NCI
Role: Site co-Principal Investigator
Dates: 03/06/19 - 02/28/25

4. Guiding participation toward understanding, inclusion, diversity and equity for cancer clinical trials (GUIDE). (Mendoza)
Grant Amount: $999,993
Source: Andy Hill CARE Fund
Role: Co-Investigator
Dates: 07/01/23 - 06/30/25

5. Optimizing clinical trials access to ensure inclusion and diversity.
(Unger)
Grant Amount: $999,559
Source: Andy Hill CARE Fund
Role: Co-Investigator
Dates: 07/01/23 - 06/30/25

PEER REVIEW FUNDING: COMPLETED

1. Pilot Project - Positron Emission Tomography Imaging of Bone in Patients with Metastatic Prostate Cancer - A Pilot Study Evaluating Treatment Response.
5 P30 CA015704 (Hartwell) / Pilot (Yu)
Grant amount: $40,000
Source: NIH/NCI Cancer Center Support Grant
Role: Concept development and overall principal investigator
Dates: 10/01/05 – 12/31/07

2. Pilot Project - Positron Emission Tomography Imaging of Bone in Patients with Metastatic Prostate Cancer.
P50 CA97186 (Lange) / Pilot (Yu)
Grant amount: $50,000
Source: Pacific Northwest Prostate Cancer SPORE
Role: Concept development and overall principal investigator
Dates: 01/01/07 – 12/31/07

3. A randomized phase II study of OGX-011 in combination with docetaxel and prednisone or docetaxel and prednisone alone in patients with metastatic hormone-refractory prostate cancer.
Grant amount: $32,000
Source: National Cancer Institute of Canada (Cooperative Group Trial)
Role: Site Principal Investigator
Dates: 11/01/05 – 09/30/09

4. Phase 2 randomized trial of gemcitabine and cisplatin with or without Cetuximab in patients with urothelial carcinoma.
Grant amount: $12,260
Source: National Comprehensive Cancer Network (Cooperative Group Trial)

Role: Site principal investigator
Dates: 01/15/09 - 03/04/11

5. Phase 2, multicenter evaluation of ^{18}F-fluoride PET as a pharmacodynamic biomarker for Dasatinib, a SRC kinase inhibitor, in men with castration-resistant prostate cancer and bone metastases (ACRIN 6687).
Grant amount: $190,790
Source: American College of Radiology Imaging Network (ACRIN) (Cooperative Group Trial)
Role: Concept development, multicenter study chair, and overall principal investigator (20% effort)
Dates: 07/01/09 – 06/30/12

6. Genitourinary Oncology Clinical Trials Core.
Infrastructure Support Proposal (PI: Yu)
Grant amount: $68,181
Source: Institute of Prostate Cancer Research
Role: Core Director
Dates: 11/19/12 – 11/18/13

7. A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation with Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer (SWOG 0925).
Grant amount: $177,000
Source: Southwest Oncology Group (SWOG) (Cooperative Group Trial) and Imclone Pharmaceuticals
Role: Concept development, multicenter study chair, and overall principal investigator
Dates: 06/01/11 – 05/31/14

8. Advanced PET/CT imaging for improving clinical trials.
1U01 CA148131 (Kinahan)
Grant amount: $2,628,443
Source: National Institute of Health
Role: Leader of prostate cancer imaging trials (5% effort)
Dates: 04/16/10 – 04/15/15

9. Biomarkers of response to treatment with XL184.
Creativity Award (Co-PIs: Knudsen, Yu)
Grant amount: $300,000
Source: Prostate Cancer Foundation
Role: Concept development and leader of PET imaging effort
Dates: 05/23/12 – 08/22/16 (no cost extension)

10. A Phase II Study of MAOA Inhibitor Plus Docetaxel in Patients Currently Receiving and Progressing on Docetaxel Therapy.
Grant amount: $16,928
Source: Wayne D. Kuni and Joan E. Kuni Foundation (subcontract award from Oregon Health Sciences University)
Role: Site principal investigator

Dates: 12/01/12 – 05/31/17

11. A phase 2 study of recombinant glycosylated human interleukin-7 (CYT107) after completion of standard FDA approved therapy with sipuleucel-T for patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.
    Grant amount: $133,000
    Source: Cancer Immunotherapy Trials Network
    Role: Site principal investigator for lead site
    Dates: 02/04/15 – 02/03/18

12. A pilot study of TIL therapy generation for urothelial bladder cancer.
    Bezos family Immunotherapy Pilot Award (Yu)
    Grant amount: $150,000
    Source: Bezos family Immunotherapy Initiative
    Role: Concept development and principal investigator
    Dates: 07/01/15 – 06/30/18 (no cost extension)

13. INTense Exercise foR surVivAL among men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL – MCRPC): A multicenter, randomized, controlled, phase III study
    Grant amount: $34,588
    Source: Movember GAP4
    Role: Site principal investigator
    Dates: 10/05/16 – 10/04/21

14. Pacific Northwest Prostate Cancer SPORE – Core D (Clinical)
    P50 CA097186 (Nelson/Core D Yu and Gore)
    Grant amount: $425,000 (this funding cycle)
    Source: Pacific Northwest Prostate Cancer SPORE
    Role: Clinical Core Leader for clinical trials and biospecimen acquisition
    Dates: 9/17/13 – 08/31/23 (2 successful competitive renewals)

PHARMACEUTICAL FUNDING: INVESTIGATOR INITIATED

1. Biologic tissue effect of sipuleucel-T on metastatic castration-resistant prostate cancer.
    Grant amount: $234,898
    Source: Dendreon
    Role: Concept development and overall principal investigator
    Dates: 01/27/15 – 04/14/24

2. The impact of DNA repair pathway alterations identified by circulating tumor DNA on sensitivity to Radium-223 in bone metastatic castration-resistant prostate cancer.
    Grant amount: $929,167
    Source: Bayer HealthCare Pharmaceuticals, Inc.
    Role: Concept development and overall national principal investigator
    Dates: 01/09/20 – 09/08/24

3. Fluciclovine (FACBC) PET/CT site-directed therapy of oligometastatic prostate cancer (FLU-BLAST-PC trial)
    Grant amount: $100,000
    Source: Blue Earth
    Role: Concept development and overall principal investigator

Dates: 02/07/20 – 02/06/24

PHARMACEUTICAL FUNDING: INVESTIGATOR INITIATED: COMPLETED

1. A phase II study of BAY 43-9006 (Sorafenib) prior to prostatectomy in patients with high-risk localized prostate cancer.
   Grant amount: $102,837
   Source: Bayer Pharmaceuticals, Corp.
   Role: Concept development and overall principal investigator
   Dates: 07/01/06 – 06/31/11

2. A randomized phase II study of docetaxel + / - ZD6474 (Zactima) in metastatic transitional cell carcinoma.
   Grant amount: $65,000
   Source: Astrazeneca Pharmaceuticals, LP (subcontract award from Dana-Farber Cancer Institute)
   Role: Site principal investigator
   Dates: 05/31/07 – 03/14/12

3. A phase II trial of genomic guided therapy with dasatinib or nilutamide in metastatic castration-resistant prostate cancer.
   Grant amount: $115,000
   Source: Bristol-Myers Squibb (subcontract award from Duke University)
   Role: Site principal investigator with input into concept development
   Dates: 05/12/09 – 12/31/12

4. Phase 2, multicenter evaluation of 18F-fluoride PET as a pharmacodynamic biomarker for Dasatinib, a SRC kinase inhibitor, in men with castration-resistant prostate cancer and bone metastases.
   Grant amount: $147,143
   Source: Bristol Myers Squibb Co.
   Role: Concept development, multicenter study chair, and overall principal investigator
   Dates: 06/01/10 – 06/30/13

5. A randomized phase II study of OGX-427 (a second-generation antisense oligonucleotide to Heat Shock Protein-27) in patients with castration resistant prostate cancer who have not previously received chemotherapy for metastatic disease.
   Grant amount: $198,419
   Source: OncoGeneX Techologies, Inc.
   Role: Site principal investigator
   Dates: 11/08/11 – 08/25/15

6. A Phase II Study of BKM120 in Men with Metastatic Castration-Resistant Prostate Cancer.
   Grant amount: $97,000
   Source: Novartis (subcontract award from Duke University)
   Role: Site principal investigator
   Dates: 07/12/13 – 09/29/15

7. Retrospective analysis of clinical benefit from radium-223 in castrate resistant prostate cancer
   Grant amount: $3,600

Source: Bayer via University of Michigan
Role: Senior and site principal investigator
Dates: 05/08/15 – 05/17/17

8. PET/CT for assessment of systemic treatment response and direction of metastatic biopsy for molecular characterization of metastatic castration resistant prostate cancer
Grant amount: $315,457
Source: Bayer
Role: Concept development and overall principal investigator
Dates: 11/03/15 – 04/30/18

9. A phase 2 study of recombinant glycosylated human interleukin-7 (CYT107) after completion of standard FDA approved therapy with sipuleucel-T for patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.
Grant amount: $19,000
Sources: Dendreon
Role: Site principal investigator for lead site
Dates: 09/01/14 – 08/31/18

10. A randomized phase II study of atezolizumab plus recombinant human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma.
Grant amount: $91,100
Source: Genentech, Inc. and NCI Cancer Immunotherapy Trials Network
Role: Concept development and overall national principal investigator
Dates: 06/28/19 – 09/30/23

PHARMACEUTICAL INITIATED FUNDING

1. Phase 1b/II trial of pembrolizumab (MK-3475) combination therapies in metastatic castration-resistant prostate cancer (KEYNOTE-365).
Grant amount: $12,335,436
Source: Merck Sharp &Dohme Corp.
Role: Concept and protocol co-developed with Merck and Overall Principal Investigator for international trial
Dates: 01/13/17 – 12/31/23

2. A phase 1, open-label, non-randomized, safety, tolerability, and pharmacokinetic study of TAS3681 in patients with metastatic castration-resistant prostate cancer.
Grant amount: $107,175
Source: Taiho
Role: Site principal investigator
Dates: 09/12/19 – 05/31/24

3.. An open-label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab with or without chemotherapy, versus chemotherapy alone in previously untreated locally advanced or metastatic urothelial cancer.
Grant amount: $617,477
Source: Seattle Genetics, Inc.
Role: Site principal investigator
Dates: 12/10/19 – 04/30/25

4. A phase 1b/2 study of ibrutinib combination therapy in selected advanced gastrointestinal and genitourinary tumors.
   Grant amount: $327,713
   Source: Pharmacyclics, Inc.
   Role: Site principal investigator
   Dates: 01/06/20 – 09/25/24

5. A phase 3, randomized open-label study of pembrolizumab (MK-3475) plus olaparib versus abiraterone acetate or enzalutamide in participants with metastatic castration-resistant prostate cancer (mCRPC) who are unselected for homologous recombination repair.
   Grant amount: $2,253,803
   Source: Merck Sharp & Dohme Corp.
   Role: Site and overall international principal investigator
   Dates: 01/17/20 – 05/31/24

6. DAROL: Darolutamide observational study in nonmetastatic castration-resistant prostate cancer patients.
   Grant amount: $218,740
   Source: Bayer AG
   Role: Site and overall international principal investigator
   Dates: 05/27/20 – 10/14/24

7. A multicenter, randomized, controlled phase 2 study: Efficacy and safety of ^{131}I-1095 radiotherapy in combination with enzalutamide in metastatic castration-resistant prostate cancer patients who are ^{18}F-DCFPyL prostate-specific membrane antigen-avid, chemotherapy-naïve, and progressed on abiraterone (ARROW).
   Grant amount: $786,869
   Source: Progenics Pharmaceuticals, Inc.
   Role: Site and overall international principal investigator
   Dates: 06/03/20 – 05/31/24

8. A phase 2 basket study of Tucatinib in combination with trastuzumab in subjects with previously treated, locally-advanced unresectable or metastatic solid tumors driven by HER2 alterations.
   Grant amount: $972,764
   Source: Seagen, Inc.
   Role: Site and overall international principal investigator
   Dates: 02/24/21 – 01/31/26

9. A phase 2 trial of SRF617 in combination with AB928 (Etrumadenant) and AB122 (Zimberelimab) in patients with metastatic castration resistant prostate cancer.
   Grant amount: $548,262
   Source: Surface Oncology, Inc.
   Role: Site and overall principal investigator
   Dates: 05/17/22 – 01/31/27

10. A multicenter, open-label Phase 1/2 study of TYRA-300 in advanced urothelial carcinoma and other solid tumors with activating FGFR3 gene alterations (SURF-301).
    Grant amount: $978,157
    Source: Tyra Biosciences Inc.

Role: Steering committee member and site investigator
Dates: 02/09/23 – 09/30/27

11. A phase 2 multi-cohort, open-label, multi-center clinical study evaluating the efficacy and safety of Disitamab Vedotin (RC48-ADC) alone and in combination with pembrolizumab in subjects with locally-advanced unresectable or metastatic urothelial carcinoma.
Grant amount: $226,010
Source: Seagen, Inc.
Role: Site investigator
Dates: 02/22/23 – 11/30/27

PHARMACEUTICAL INITIATED FUNDING: COMPLETED

1. A Phase II multicenter evaluation of the safety and efficacy of Tocosol paclitaxel (s-8184 paclitaxel injectable emulsion) in patients with metastatic or locally advanced unresectable transitional cell carcinoma of the urothelium.
Grant amount: $132,981
Source: Sonus Pharmaceuticals, Inc.
Role: Site principal investigator
Dates: 12/15/04 – 12/15/08

2. A phase II multi-center open-label study of YM155 in subjects with hormone-refractory prostate cancer previously treated with at least one prior chemotherapy regimen.
Grant amount: $11,000
Source: Astellas Pharma US, Inc.
Role: Site principal investigator
Dates: 09/01/07 – 04/30/09

3. Phase II Study of Dasatinib for Androgen-Deprived Progressive Prostate Cancer.
Grant amount: $213,883
Source: Bristol Myers Squibb Co.
Role: Overall principal investigator
Dates: 05/01/07 – 04/01/10

4. A phase 1 study evaluating a second-generation antisense oligonucleotide (OGX-427) that inhibits heat shock protein 27 (HSP27).
Grant amount: $278,721
Source: OncoGeneX Technologies, Inc.
Role: Site principal investigator
Dates: 05/17/07 – 04/30/11

5. A phase III randomized placebo-controlled double-blind study to assess the efficacy and safety of once-daily orally administered ZD4054 10 mg in non-metastatic hormone-resistant prostate cancer patients.
Grant amount: $188,388
Source: AstraZeneca Pharmaceuticals, LP
Role: Site principal investigator
Dates: 04/01/08 – 03/31/11

6. A phase III randomized double-blind placebo-controlled study of abiraterone acetate (CB7630) plus prednisone in patients with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy.
   Grant amount: $263,350
   Source: Cougar Biotechnology
   Role: Site principal investigator
   Dates: 10/1/08 – 09/30/11

7. A randomized double-blind phase III trial comparing docetaxel combined with dasatinib to docetaxel combined with placebo in castration-resistant prostate cancer.
   Grant amount: $459,437
   Source: Bristol-Myers Squibb Co.
   Role: Steering committee member and site principal investigator
   Dates: 06/15/09 - 06/14/14

8. A phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate (CB7630) plus prednisone in asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer.
   Grant amount: $294,389
   Source: Cougar Biotechnology (changed to Janssen)
   Role: Site principal investigator
   Dates: 06/15/09 – 03/16/15

9. A phase II, open-label, single-arm trial evaluating KX2-391 in patients with bone-metastatic, castration-resistant prostate cancer who have not received prior chemotherapy.
   Grant amount: $151,070
   Source: Kinex Pharmaceuticals
   Role: Site principal investigator and assistance with protocol development
   Dates: 05/05/10 – 12/19/12

10. A randomized, open-label, phase 2 trial examining the sequencing of sipuleucel-T and androgen deprivation therapy in men with non-metastatic prostate cancer and a rising prostate specific antigen after primary therapy.
    Grant amount: $265,201
    Source: Dendreon
    Role: Site principal investigator
    Dates: 11/04/11 – 11/03/15

11. A randomized, double-blind phase 2 study comparing gemcitabine and cisplatin in combination with OGX-427 or placebo in patients with advanced transitional cell carcinoma.
    Grant amount: $425,884
    Source: OncoGeneX Technologies, Inc.
    Role: Site principal investigator
    Dates: 02/14/12 – 11/03/15

12. Open label study of the effect of GTx-758 on serum PSA and free testosterone levels in men with castration resistant prostate cancer and maintained on androgen deprivation therapy.
    Grant amount: $12,347
    Source: GTx, Inc.
    Role: Overall principal investigator and assistance with protocol development

Dates: 02/16/12 – 02/27/12

13. An open-label, multicenter, randomized phase 2 study evaluating the safety and efficacy of docetaxel in combination with IMC-1121B or IMC-18F1 or without investigational therapy as second line therapy in patients with metastatic transitional cell carcinoma.
    Grant amount: $206,595
    Source: Imclone Systems, Inc.
    Role: Site principal investigator
    Dates: 05/08/12 – 01/14/15

14. Phase II, open label study of the effect of GTx-758 as secondary hormonal therapy on serum PSA and serum free testosterone levels in men with metastatic castration resistant prostate cancer maintained on androgen deprivation therapy.
    Grant amount: $478,364
    Source: GTx, Inc.
    Role: Overall principal investigator
    Dates: 12/20/12 – 09/30/15

15. A phase II, multicenter, single-arm study of MPDL3280A in patients with locally advanced or metastatic urothelial bladder cancer.
    Grant amount: $306,248
    Source: Genentech/Roche
    Role: Site principal investigator
    Dates: 08/21/14 – 08/20/16

16. A phase 3, randomized, double-blind, placebo-controlled study of ramucirumab plus docetaxel vs. placebo plus docetaxel in patients with locally advanced or unresectable or metastatic urothelial carcinoma who progressed on or after platinum-based therapy.
    Grant amount: $414,203
    Source: Eli Lilly and Company
    Role: Site principal investigator
    Dates: 06/21/16 – 07/31/17

17. A multicenter, single-arm, open-label, post-marketing safety study to evaluate the risk of seizure among subjects with metastatic castration-resistant prostate cancer treated with enzalutamide who are at potential increased risk of seizure.
    Grant amount: $47,776
    Source: Astellas, Inc.
    Role: Site principal investigator
    Dates: 09/12/14 – 09/11/17

18. A phase I study of the safety and pharmacokinetics of escalating doses of AGS15E given as monotherapy in subjects with metastatic urothelial cancer.
    Grant amount: $274,502
    Source: Agensys Inc.
    Role: Site principal investigator
    Dates: 03/12/14 – 12/31/17

19. A phase II clinical trial of pembrolizumab (MK-3475) in subjects with advanced/unresectable or metastatic urothelial cancer.

Grant amount: $266,286
Source: Merck Sharp & Dohme Corp.
Role: Site principal investigator
Dates: 03/22/16 – 03/21/18

20. A phase 2 study of TGF-inhibition (Vactosertib) with Anti-PD-L1 (Durvalumab) in patients with advanced or recurrent urothelial carcinoma failing to achieve response with checkpoint inhibition.
Grant amount: $13,799
Source: MedPacto
Role: Site principal investigator
Dates: 09/01/20 – 01/04/21

21. A single-arm, open-label, multicenter study of enfortumab vedotin (ASG-22CE) for treatment of patients with locally advanced or metastatic urothelial cancer who previously received immune checkpoint inhibitor therapy.
Grant amount: $322,013
Source: Seattle Genetics, Inc.
Role: Steering committee member and Site principal investigator
Dates: 10/13/17 – 08/31/22

22. A phase 3 randomized, controlled clinical trial of pembrolizumab with or without platinum-based combination chemotherapy vs. chemotherapy in subjects with advanced or metastatic urothelial carcinoma.
Grant amount: $297,128
Source: Merck Sharp &Dohme Corp.
Role: Site principal investigator
Dates: 11/16/16 – 11/15/22

23. A phase 1b, multicenter, two-part, open label study of DS-8201A, an anti-human epidermal growth factor receptor-2 (HER2)-antibody drug conjugate in combination with nivolumab, an anti PD-1 antibody for subjects with HER2-expressing advanced breast and urothelial cancer.
Grant amount: $683,791
Source: Daiichi Sankyo
Role: Site principal investigator
Dates: 01/07/19 – 03/31/23

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ABSTRACTS (LAST 5 YEARS)

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119. Sokolova A, Gulati R, Cheng HH, Beer TM, Graff JN, Amador M, Toulouse A, Taylor K, Bailey S, Smith S, Tabatabaei S, Sinit R, Slottke R, Vuky J, Yezefski T, Grivas P, Yu EY, Schweizer MT. Durvalumab and Olaparib for the treatment of prostate cancer in men predicted to have a

high neoantigen load. *J Clin Oncol* 40, 2022 (suppl 16; abstr TPS5099). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2022.

120. Wong RL, Cheng HH, Fann JR, Hnida J, Chakoian M, Schenker Y, Yu EY, Gore JL. Longitudinal screening for depression and anxiety in prostate cancer and association with disease and treatment factors. *J Clin Oncol* 40, 2022 (suppl 16; abstr 5023). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2022.

121. Gulhane A, Talukder R, Wu ZJ, Lin DW, Dash A, Ellis WJ, Nyame YA, Schade G, Wright JL, Apisarnthanarax S, Chen J, Liao JL, Wallner K, Weg ES, Cheng HH, Grivas P, Hawley J, Hsieh AC, Lee JK, Montgomery B, Nelson PS, Schweizer MT, Yezefski T, Yu EY, Cheng DL. [^{68}Ga]-PSMA-11 can clarify equivocal lesions on conventional imaging and change management decisions among men with previously treated prostate cancer. Poster presentation at Society of Nuclear Medicine and Molecular Imaging Annual Meeting, Vancouver, BC, Jun. 2022.

122. Yu EY, Park SH, Goh JC, Shin SJ, Mehra N, McDermott R, Sala Gonzalez N, Fong P, Greil R, Retz M, Sade JP, Huang YH, Begbie SD, Rey F, Kramer G, Suzuki H, Zhang J, Kim J, Poehlein C, Antonarakis ES. Pembrolizumab plus Olaparib vs. abiraterone or enzalutamide for patients with previously treated metastatic castration-resistant prostate cancer: Randomized open-label phase 3 KEYLYNK-010 study. **Oral presentation at ESMO Congress 2022**, Paris, France, Sept 2022**.**

123. Kramer G, de Bono J, Joshua AM, Shore ND, Zhu P, Poehlein CH, Schloss C, Yu EY. Phase 1b/2 study of pembrolizumab plus Lenvatinib, vibostolimab, or platinum-based chemotherapy for adenocarcinoma metastatic castration-resistant prostate cancer or neuroendocrine metastatic prostate cancer: KEYNOTE-365 cohorts E-I. Poster presentation at ESMO Congress 2022, Paris, France, Sept 2022**.**

124. Linch MD, Ferrario C, Stoeckle M, Laguerre B, Arranz J, Todenhofer T, Fong P, Piulats JM, Berry W, Emmenegger U, Mourey L, Mar N, Appleman L, Joshua AM, Conter H, Li XT, Schloss C, Poehlein C, de Bono JS, Yu EY. Two year follow-up of KEYNOTE-365 Cohort D: Pembrolizumab plus abiraterone acetate and prednisone in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer. Poster presentation at ESMO Congress 2022, Paris, France, Sept 2022**.**

125. Galsky MD, O'Donnell PH, Burgess E, Van der Heijden M, Krieger L, Necchi A, Yu EY, Matsubara N, Campbell MT, Gadde S, Aragon-Ching JB, Koshkin VS, Zhang W, Sokolowski K, Powles T. Phase 2 clinical study evaluating the efficacy and safety of distamab vedotin with or without pembrolizumab in patients with HER2-expressing urothelial carcinoma (RC48G001, TIP). Poster presentation at 2022 Society for Immunotherapy of Cancer at Boston, MA, Nov. 2022.

126. Mehra N, Antonarakis ES, Park SH, Goh JC, McDermott R, Gonzalez NS, Fong P, Greil R, de Santis M, Weber PEY, Huang YH, Begbie SD, Rey F, Kramer G, Suzuki H, Saretsky TL, Ghate SR, Zhang J, Kim J, Yu EY. Patient reported outcomes in KEYLYNK-010: Pembrolizumab plus Olaparib vs. abiraterone acetate or enzalutamide for patients with previously treated metastatic castration-resistant prostate cancer. *J Clin Oncol* 41, no. 6_suppl (February 20, 2023) 131-131. Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2023.

127. Yu EY, Jin F, Ramos J, Tan S, Galsky MD. A phase 2 basket study of tucatinib and trastuzumab in previously treated solid tumors with HER2 alterations: urothelial cancer cohort (Trial in Progress). *J Clin Oncol* 41, no. 6_suppl (February 20, 2023) TPS587-TPS587. Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2023.

128. Buxton C, Schmeusser BN, Holt SK, Patil D, Phuong A, Marquardt JP, O'Malley R, Laidlaw G, Schade GR, Lin DW, Schweizer MT, Yezefski T, Yu EY, Montgomery B, Fintelmann FJ, Chahine S, Master VA, Psutka SP. MP50-14 - A multicenter evaluation of the prognostic utility of changes in treatment-associated body composition in men with germ cell tumors of the testis: Implications for adverse events and complications. *J Urol* Vol. 209, No. 4S:e690. Poster presentation at American Urological Association 2022 Annual Meeting, Chicago, IL, April 2023.

129. Yu EY, Pieczonka CM, Suzuki H, Bailen JL, Gotto GT, Hamilton JP, Uemura H, Murphy DG, Lebret T, Lu MD, Ortiz JA, Adorjan P, Khan J, Briganti A, Armstron AJ. Darolutamide observational study in patients with nonmetastatic castration-resistant prostate cancer: Second interim analysis. *J Clin Oncol* 41, 2023 (suppl 16; abstr e17095).

130. Raychaudhuri R, DeJong M, Yu EY, Gulati R, Rettig M, Nelson P, Pritchard CC, Montgomery RB, Cheng HH. Final results of a pilot study of docetaxel and carboplatin for treatment of patients with metastatic castration-resistant prostate cancer containing biallelic inactivation of genes in the homologous recombination DNA repair pathway. *J Clin Oncol* 41, 2023 (suppl 16; abstr 5054). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2023.

131. Wong RL, Cheng HH, Fann JR, Hnida J, Chakoian M, Jannat S, Schenker Y, Yu EY, Gore JL. Longitudinal variability in symptom burden for patients with prostate cancer. *J Clin Oncol* 41, 2023 (suppl 16; abstr e17019).

132. Vapiwala N, Chen YH, Cho SY, Duan F, Kyriakopoulos C, Morgans AK, Shevrin DH, Koontz BF, McKay RR, Yu EY, McConathy J, Liu G, Wong TZ, Carducci MA, Mankoff DA. Phase III study of local or systemic therapy intensification directed by PET in prostate cancer patients with post-prostatectomy biochemical recurrence (INDICATE): ECOG-ACRIN EA8191. *J Clin Oncol* 41, 2023 (suppl 16; abstr TPS5118). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2023.

133. Sokolova A, Graff JN, Smith CE, Beer TM, Latour E, Grivas P, Schweizer MT, Higano CS, Alumkal JJ, Vuky J, Yu EY, Cheng HH. Concurrent chemo-hormonal therapy of enzalutamide and cabazitaxel in patients with metastatic castration-resistant prostate cancer: Final analysis of objective response rate, radiographic progression-free survival, and overall survival. *J Clin Oncol* 41, 2023 (suppl 16; abstr 5047). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2023.

134. Raychaudhuri R, Mo G, Haffner MC, Morrissey C, Ha G, Yu EY, Cheng HH, Yezefski T, Hawley JE, Montgomery RB, Nelson P, Chen DL, Iravani A, Schweizer MT. PSMA expression and response to ^{177}Lu-PSMA-617 in men with vs. without DNA damage repair mutations. *J Clin Oncol* 41, 2023 (suppl 16; abstr 5055). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2023.

135. Nakamura Y, Mizuno N, Sunakawa Y, Hamilton EP, Hayashi H, Kim ST, Lee KW, Monk BJ, Nguyen D, Okines AFC, O'Malley DM, Pohlmann PR, Reck M, Yu EY, Groisberg R, Ramos J, Tan Q, Stinchcombe T, Bekaii-Saab TS. Tucatinib and trastuzumab for previous treated HER2-

positive metastatic biliary tract cancer (SGNTUC-019): A phase 2 basket study. *J Clin Oncol* 41, 2023 (suppl 16; abstr 4007). **Oral presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2023.**

136. Pachynski R, Chatta GS, Jain RK, Moon H, Sweis RF, Delacroix SE, Fang A, Fling S, Lacroix A, Kaiser JC, Sharon E, Yu EY. A randomized phase II study of atezolizumab plus recombinant human IL-7 (CYT107) vs. atezolizumab alone in patients with locally advanced or metastatic urothelial carcinoma. Poster presentation at ESMO Congress 2023, Madrid, Spain, Oct. 2023**.**

INVITED TALKS AND LECTURES

UNIVERSITY/LOCAL CONFERENCES

- Program in Prostate Cancer Research/SPORE: "Retroviral RNA interference: systems development, biologic discoveries with telomerase, and future applications." Fred Hutchinson Cancer Research Center, Seattle, WA. March 4, 2004.
- Jobson Education: "Hormone refractory prostate cancer: Early vs. late vs. asymptomatic" Seattle, WA. June 24, 2005.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: Clinical implications." Fred Hutchinson Cancer Research Center, Seattle, WA. October 21, 2005.
- Resident Teaching Conference: "A case-based approach to managing metastatic bone disease." University of Washington, Seattle, WA. October 25, 2005.
- Seattle Cancer Care Alliance Physician Educational Outreach Program: "Hormone-refractory prostate cancer; the medical oncologist's perspective." Mount Vernon, WA. October 25, 2005.
- Breast and Prostate Program Bone Metastases Retreat: "Response to treatment in patients with metastatic prostate cancer: using PET scans as a surrogate marker for bone-dominant disease." Fred Hutchinson Cancer Research Center, Seattle, WA. November 14, 2005.
- Puget Sound Oncology Consortium's Annual Highlights of ASCO meeting: "Genitourinary Oncology ASCO 2006: review of prostate, bladder and testicular cancer." Seattle, WA. June 29, 2006.
- 6th Annual Pacific Northwest Prostate Cancer Conference: "A rising PSA after local therapy…implications and utility of PSA kinetics." Seattle, WA. September 16, 2006.
- Nuclear Medicine Internal Advisory Board: "Metabolic Imaging in prostate cancer – the future with PET." University of Washington, Seattle, WA. September 25, 2006.
- Program in Prostate Cancer Research/SPORE: "PET measures response to therapy in prostate cancer." University of Washington, Seattle, WA. November 2, 2006.
- North Star Lodge: "New concepts in genitourinary oncology." Yakima, WA. November 9, 2006.
- Nuclear Medicine External Advisory Board: "Metabolic imaging of prostate cancer as a biomarker of treatment response." University of Washington, Seattle, WA. November 30, 2006.
- Asian Senior Concerns Foundation: "Bladder cancer – the basics." Bellevue, WA. January 20, 2007.
- Asian Senior Concerns Foundation: "Prostate cancer PSA screening, treatments, and public concerns." Bellevue, WA. January 20, 2007.
- Virginia Mason Medical Center: "Mediastinal germ cell tumors." Seattle, WA. February 1, 2007.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: the need for new knowledge." Fred Hutchinson Cancer Research Center, Seattle, WA. March 2, 2007.
- A&P Lecture: "Imaging biomarkers in prostate cancer: the potential impact of tumor metabolism on clinical trials and drug development." University of Washington, Seattle, WA. March 6, 2007.

- Pacific Northwest SPORE: "Positron emission tomography imaging of bone in patients with metastatic prostate cancer." Fred Hutchinson/University of Washington Cancer Center Support Grant, Seattle, WA. May 21, 2007.
- Patient Power Radio Show: "Prostate, bladder, and testicular cancer update: ASCO 2007." Seattle, WA. June 10, 2007.
- Puget Sound Oncology Consortium Annual Highlights of ASCO meeting: "ASCO 2007 prostate cancer review." Seattle, WA. June 28, 2007.
- Emerging Trends in Oncology: "Update in prostate cancer, ASCO review." Seattle, WA. June 30, 2007.
- Patient Power Radio Show: "Prostate cancer: who to treat and when." Seattle, WA. July 11, 2007.
- American College of Physicians, Seattle Internal Medicine Board Review Course: "Solid tumor oncology cases." Seattle, WA. July 13, 2007.
- University of Washington Internal Medicine Residents' Educational Lecture Series: "Prostate cancer – A chronic disease." University of Washington, Seattle, WA. October 31, 2007.
- Oncology Grand Rounds: "A case of urothelial carcinoma of the bladder with leukemoid reaction: was GCSF playing a negative role?" Fred Hutchinson Research Center, Seattle, WA. November 6, 2007.
- Hematology/Oncology Fellows' Lecture Series: "Germ cell tumors/testicular cancer – what you really need to know." Fred Hutchinson Cancer Research Center, Seattle, WA. November 16, 2007.
- Program in Prostate Cancer Research/SPORE: "Positron emission tomography imaging of bone in patients with metastatic prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. March 6, 2008.
- Gilda's Club: "Advanced prostate cancer: an update on hormones, chemotherapy, and clinical trials." Seattle, WA. March 29, 2008.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: An unmet need." Fred Hutchinson Cancer Research Center, Seattle, WA. May 2, 2008.
- Patient Power Radio Show: "Prostate cancer biomarkers." Seattle, WA. May 7, 2008.
- 8th Annual Pacific Northwest Prostate Cancer Conference: "When is PSA useful? Why it may not always be reliable?" Fred Hutchinson Cancer Research Center. September 27, 2008.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program - Multicare Tacoma: "Bladder cancer – an unmet need." Tacoma, WA. September 30, 2008.
- Program in Prostate Cancer Research/SPORE: "Bone health for men with prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. November 6, 2008.
- Hematology/Oncology Educational Lecture Series: "Germ cell tumors/testicular cancer - a boards exam favorite." Fred Hutchinson Cancer Research Center, Seattle, WA. April 3, 2009.
- University of Washington CME Current Concepts in Drug Therapy: "Primary care issues for patients with prostate cancer undergoing androgen deprivation therapy." Seattle, WA. May 8, 2009.
- Seattle Cancer Care Alliance Scientific Lunch: "Drug development for prostate cancer – rebounding well from tough times." Seattle Cancer Care Alliance, Seattle, WA. June 11, 2009.
- Radiation Oncology Residents' Educational Lecture Series: "PSA kinetics to drive decision making for men with prostate cancer." University of Washington, Seattle, WA. June 18, 2009.
- Pacific Northwest SPORE Retreat: "PET imaging as a prostate cancer bone biomarker." University of British Columbia, Vancouver, BC. July 10, 2009.
- American College of Physicians, Seattle Internal Medicine Board Review Course: "Solid tumor oncology cases." Seattle, WA. July 17, 2009.

- Scripps 6th Annual Oncology Update: "ASCO review of prostate cancer." Seattle, WA. July 25, 2009.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: is it our turn yet?" Fred Hutchinson Cancer Research Center, Seattle, WA. August 21, 2009.
- Virginia Mason Community Journal Review: "Androgen deprivation therapy induced estrogen deficiency side effects." Seattle, WA. October 13, 2009.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Skagit Valley and Olympic Medical Centers: "Upcoming new drugs for prostate cancer therapy." Mt. Vernon, WA. October 15, 2009.
- Center for Biomedical Continuing Education: "Bone health across the cancer continuum: Updates and insight to an evolving story." Seattle, WA. January 28, 2010.
- Oncology Grand Rounds: "Prostate cancer and broken bones? Only from sticks and stones…" Fred Hutchinson Cancer Research Center, Seattle, WA. March 9, 2010.
- Hematology/Oncology Fellow's Lecture Series: "Germ cell tumors/testicular cancer – hitting the ball out of the park." Fred Hutchinson Cancer Research Center, Seattle, WA. March 26, 2010.
- 13th Annual Advanced Prostate Brachytherapy Conference: "Managing androgen deprivation therapy associated side effects." Seattle Prostate Institute, Seattle, WA. May 14, 2010.
- American College of Physicians, Seattle Internal Medicine Board Review Course: "Solid tumor oncology cases." Seattle, WA. July 23, 2010.
- Scripps 7th Annual Oncology Update: "Prostate cancer update: New therapies for castration-resistant disease." Seattle, WA. August 14, 2010.
- Patient Power Radio Show: "New treatments for prostate cancer." Seattle, WA. August 27, 2010.
- University of Washington Comprehensive Oncology Review: "Bladder cancer – keeping in the loop." Seattle, WA. October 2, 2010.
- University of Washington Comprehensive Oncology Review: "Germ cell tumors/testicular cancer – keeping an eye on the ball." Seattle, WA. October 3, 2010.
- Sanofi-Aventis Roundtable Program: "Cabazitaxel: A new option for metastatic hormone-refractory prostate cancer following a docetaxel containing regimen." Seattle, WA. October 7, 2010.
- 10th Annual Pacific Northwest Prostate Cancer Conference: "Protecting bone for prostate cancer patients." Fred Hutchinson Cancer Research Center, Seattle, WA. October 9, 2010.
- Multicare Tacoma: "Cabazitaxel: A new option for metastatic hormone-refractory prostate cancer following a docetaxel containing regimen." Tacoma, WA. November 16, 2010.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: getting in the loop." Fred Hutchinson Cancer Research Center, Seattle, WA. November 19, 2010.
- Science over Lunch: "Rapidly changing paradigms in prostate cancer – new FDA approvals and local contributions." Fred Hutchinson Cancer Research Center, Seattle, WA. March 10, 2011.
- Hematology/Oncology Educational Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. March 11, 2011.
- Pacific Northwest Prostate Cancer SPORE: "Metabolic imaging and biomarkers to monitor treatment response of castration-resistant prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. March 28, 2011.
- Nuclear Medicine U01 Meeting: "Discerning Cabozantinib (XL184) biology with ^{11}C-acetate and ^{18}F-fluoride PET/CT imaging." Seattle Cancer Care Alliance, Seattle, WA. April 12, 2011.
- Scripps 8th Annual Oncology Update: "Genitourinary cancer update." Seattle, WA. August 13, 2011.
- University of Washington Comprehensive Oncology Review (2nd Annual): "Germ cell tumors/testicular cancer." Seattle, WA. September 18, 2011.

- University of Washington Comprehensive Oncology Review (2nd Annual): "Genitourinary Cancer Cases - Question and Answer Session." Seattle, WA. September 18, 2011.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: updates and local research endeavors." Fred Hutchinson Cancer Research Center, Seattle, WA. October 28, 2011.
- Hematology/Oncology Fellows' Solid Tumor Conference: "Prostate cancer: local research efforts." Seattle Cancer Care Alliance, Seattle, WA. October 28, 2011.
- Program in Prostate Cancer Research/SPORE: "Hormone-sensitive prostate cancer – updates on recent and ongoing clinical trials." Fred Hutchinson Cancer Research Center, Seattle, WA. November 3, 2011.
- Uganda Cancer Institute: "Cases from Kampala – prostate cancer case conference." Fred Hutchinson Cancer Research Center, Seattle, WA. June 14, 2012.
- University of Washington Comprehensive Oncology Review (3rd Annual): "Germ cell tumors/testicular cancer." Seattle, WA. September 23, 2012.
- Hematology/Oncology Fellows' Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. October 12, 2012.
- Updates in Oncology and Blood/Marrow Transplantation – A Spotlight on Seattle Cancer Care Alliance: "Research advancements for castration-resistant prostate cancer." Seattle, WA. October 15, 2012.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: the next big thing in genitourinary oncology." Fred Hutchinson Cancer Research Center, Seattle, WA. November 2, 2012.
- Program in Prostate Cancer Research/SPORE: "Prostate cancer bone biomarkers: clinical trial tool or ready for prime time in the clinic?" Fred Hutchinson Cancer Research Center, Seattle, WA. March 7, 2013.
- Institute for Prostate Cancer Research 2013 Symposium – Breakthroughs in prostate cancer research: "Imaging advanced prostate cancer – beyond finding the tumor." Fred Hutchinson Cancer Research Center, Seattle, WA. March 17, 2013.
- Uganda Cancer Institute: "Cases from Kampala – prostate cancer case conference." Fred Hutchinson Cancer Research Center, Seattle, WA. July 11, 2013.
- Pacific Northwest Cancer SPORE Retreat 2013: "Identification of molecular characteristics of prostate cancer with ^{11}C-acetate and ^{18}F-FDG PET/CT-directed rapid autopsy." Fred Hutchinson Cancer Research Center, Seattle, WA. July 12, 2013.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program - Multicare Tacoma: "Recent and future therapeutic advancements for metastatic castration-resistant prostate cancer." Tacoma, WA. July 19, 2013.
- Medical Oncology Faculty Sections Meeting: "Fellowship Updates 2013." Seattle Cancer Care Alliance, Seattle, WA. August 1, 2013.
- Hematology/Oncology Educational Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. September 13, 2013.
- University of Washington Comprehensive Oncology Review (4th Annual): "Germ cell tumors/testicular cancer." Seattle, WA. October 1, 2013.
- The Everett Clinic: "Cancer immunotherapy – fundamental concepts and emerging role." Everett, WA. October 1, 2013.
- Pacific Northwest SPORE Advocacy Meeting: "Sequencing of novel secondary hormonal therapies in metastatic castration-resistant prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. December 12, 2013.
- Program in Prostate Cancer Research/SPORE: "A review of PET imaging for prostate cancer: past, present and future." Fred Hutchinson Cancer Research Center, Seattle, WA. March 27, 2014.

- Institute for Prostate Cancer Research 2014 Symposium – Breakthroughs in prostate cancer research: "Imaging prostate cancer – present and future." Fred Hutchinson Cancer Research Center, Seattle, WA. April 12, 2014.
- Multicare Tacoma: "Overcoming cancer immunoevasion: the role of immunotherapy." Tacoma, WA. April 17, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program: "Role of immunotherapy for bladder cancer – a focus on the PDL1/PD1 axis." Bellevue, WA. June 25, 2014.
- Pacific NorthWest Prostate Cancer SPORE Retreat: "Clinical Core D." Fred Hutchinson Cancer Research Center, Seattle, WA. July 21, 2014.
- Hematology/Oncology Fellows' Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. September 5, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Skagit Valley Medical Center: "The promise of immunotherapy for bladder cancer." Mt. Vernon, WA. September 17, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Bend Memorial Clinic: "The promise of immunotherapy for bladder cancer." Bend, OR. September 25, 2014.
- University of Washington Comprehensive Oncology Review (5th Annual): "Germ cell tumors/testicular cancer." Seattle, WA. September 27, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Bozeman Deaconess Cancer Center: "Hot topics for prostate and bladder cancer." Bozeman, MT. October 14, 2014.
- Program in Prostate Cancer Research/SPORE: "Clinical experience with insulin-like growth factor receptor I (IGF-IR) inhibition in prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. October 30, 2014.
- Body Imaging Radiology Section Lecture Series: "Challenges in imaging of genitourinary malignancies." University of Washington Medical Center, Seattle, WA. November 12, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Spokane Valley Cancer Center: "The promise of immunotherapy for bladder cancer." Spokane, WA. November 13, 2014.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: a rapidly growing research arena." Fred Hutchinson Cancer Research Center, Seattle, WA. December 19, 2014.
- Oncology Grand Rounds: "Prostate cancer from the medical oncologist perspective…it's not all about castration-resistant disease." Fred Hutchinson Cancer Research Center, Seattle, WA. December 23, 2014.
- Us Too: "Timing and sequencing of therapeutic agents in metastatic prostate cancer." Greenwood Senior Center, Seattle, WA. March 25, 2015.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Tri Cities Cancer Center: "Metastatic prostate cancer therapeutic sequencing, combination and trials." Kennewick, WA. April 23, 2015.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – The Vancouver Clinic: "Key therapeutic questions in metastatic prostate cancer." Vancouver, WA. May 5, 2015.
- Scripps 12th Annual Oncology Update: "Genitourinary cancer update." Seattle, WA. August 15, 2015.
- Flash Rounds: "Seven tips to developing a clinical research career." Fred Hutchinson Cancer Research Center. Seattle, WA. September 4, 2015.
- Genentech Educational Presentation: "Current challenges in managing bladder cancer." Seattle, WA. October 22, 2015.

- Hematology/Oncology Fellows' Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center. Seattle, WA. October 23, 2015.
- Fred Hutch Clinical Oncology Grand Rounds: "PET imaging in prostate cancer: Will it ever be more than a research tool?" Fred Hutchinson Cancer Research Center. Seattle, WA. January 12, 2016.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Bozeman Deaconess Cancer Center: "Urothelial carcinoma – Life after platinum." Bozeman, MT. May 20, 2016.
- Pacific NorthWest Prostate Cancer SPORE Retreat: "Clinical Core D." Fred Hutchinson Cancer Research Center, Seattle, WA. July 25, 2016.
- Genitourinary Oncology Staff Education Sessions: "ASCO 2016 prostate and bladder cancer updates." Seattle Cancer Care Alliance, Seattle, WA. August 11, 2016.
- Society for Immunotherapy of Cancer's (SITC) Advances in Cancer Immunotherapy – Washington Program: "Immunotherapy for genitourinary cancers." Seattle, WA. August 19, 2016.
- Remedica Medical Education and Publishing CME – Lecture to Seattle Cancer Care Alliance Advanced Practice Providers: "P3 – Patient selection and Practice in Prostate cancer." Seattle, WA. November 21, 2016.
- Providence Regional Medical Center: "P3 – Patient selection and Practice in Prostate cancer." Everett, WA. December 8, 2016.
- Remedica Medical Education and Publishing CME – Lecture to Fred Hutchinson Cancer Research Center Hematology/Oncology Fellows: "P3 – Patient selection and Practice in Prostate cancer." Seattle, WA. December 14, 2016.
- Seattle Cancer Care Alliance Educational Lecture: "Emerging immunotherapies and systemic therapies for metastatic urothelial carcinoma." Seatac, WA. March 1, 2017.
- 2016 6th Annual Institute of Prostate Cancer Research Symposium: "PET imaging in prostate cancer: Finding local recurrences and management of oligometastatic disease." Fred Hutchinson Cancer Research Center, Seattle, WA. March 18, 2017.
- Pacific NorthWest Prostate Cancer SPORE Retreat: "Clinical Core D." Fred Hutchinson Cancer Research Center, Seattle, WA. July 24, 2017.
- Seattle Genetics Lecture Series: "The evolving urothelial carcinoma landscape." Bothell, WA. August 4, 2017.
- University of Washington Comprehensive Hematology and Oncology Review (8th Annual): "Prostate cancer board review." Seattle, WA. September 25, 2017.
- Clinical Research Division: "Informed consent elements documentation." Fred Hutchinson Cancer Research Center, Seattle, WA. November 13, 2017.
- Medical Oncology Sections Meeting: "Informed consent elements documentation." Seattle Cancer Care Alliance, Seattle, WA. December 7, 2017.
- **University of Washington Medicine Grand Rounds: "Clinical research in prostate cancer." University of Washington School of Medicine, Seattle, WA. January 11, 2018.**
- Clinical Research Services, Fred Hutchinson Cancer Research Consortium: "Prostate cancer overview and impactful clinical research." Fred Hutchinson Cancer Research Center, Seattle, WA. January 11, 2018.
- Solid Tumor Conference, Fred Hutchinson Hematology-Oncology Fellowship Program: "GU boards review for fellows – Key points to remember." Fred Hutchinson Cancer Research Center, Seattle, WA. April 27, 2018.
- Institute for Prostate Cancer Research 2018 Symposium – Breakthroughs in prostate cancer research: "Prostate Cancer Tumor Board." Fred Hutchinson Cancer Research Center, Seattle, WA. April 28, 2018.

- External Advisory Board Meeting, Fred Hutchinson/University of Washington Cancer Consortium: "Clinical Protocol and Data Management." Fred Hutchinson Cancer Research Center, Seattle, WA. June 15, 2018.
- Oncology Grand Rounds: "Treatment intensification for castration-sensitive prostate cancer and management of oligometastatic disease." Fred Hutchinson Cancer Research Center, Seattle, WA. June 19, 2018.
- University of Washington Comprehensive Hematology and Oncology Review (9th Annual): "Prostate cancer board review." Seattle, WA. September 15, 2018.
- Genitourinary Oncology Staff Education Sessions: "Prostate cancer overview – clinical and research impact." Seattle Cancer Care Alliance, Seattle, WA. February 7, 2019.
- External Advisory Board Meeting, Fred Hutchinson/University of Washington Cancer Consortium: "Clinical Protocol and Data Management." Fred Hutchinson Cancer Research Center, Seattle, WA. March 8, 2019.
- Institute for Prostate Cancer Research 2019 Symposium – Breakthroughs in prostate cancer research: "Imaging in prostate cancer – state of the field." Fred Hutchinson Cancer Research Center, Seattle, WA. May 11, 2019.
- Program in Prostate Cancer Research/SPORE: "Implications of next generation PET imaging in prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. May 16, 2019.
- NCI Cancer Center Support Grant Site Visit: "Clinical drotocol and data management." Fred Hutchinson Cancer Research Center, Seattle, WA. May 29, 2019.
- 7th Annual International Conferences on Advances in Hematology and Oncology: "Bladder cancer updates from ASCO 2019." Seattle, WA. June 30, 2019.
- Seattle (Bellevue) UsToo: "Prostate cancer disease states and treatments." Bellevue, WA. July 15, 2019.
- Seattle (Bellevue) UsToo: "Next generation PET imaging in prostate cancer." Bellevue, WA. July 15, 2019.
- Medical Oncology Sections Meeting: "Genitourinary Medical Oncology (GUMO) research interests and updates." Seattle Cancer Care Alliance, Seattle, WA. August 1, 2019.
- Genitourinary Oncology Staff Education Sessions: "Immunotherapy for genitourinary cancers." Seattle Cancer Care Alliance, Seattle, WA. October 10, 2019.
- Institute of Prostate Cancer Research Development Lecture: "Proving the impact of next generation PET imaging in prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. October 17, 2019.
- Seattle Cancer Care Alliance NeuroEndocrine Tumor Board: "Iobenguane ^{131}I for the treatment of advanced neuroendocrine tumors that are norepinephrine transporter avid on imaging, in a multicenter, open-label phase 2 basket trial (FORESIGHT)." Seattle Cancer Care Alliance, Seattle, WA. December 20, 2019.
- Seattle UsToo: "The future impact of next generation PET imaging in prostate cancer." Seattle, WA. January 22, 2020.
- GU Medical Oncology Research Staff: "Recent updates in the last year for advanced prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. January 23, 2020.
- Curio Science – Community Opinions in Prostate Cancer: "Current and emerging therapies for practice with metastatic castration-sensitive prostate cancer." Seattle, WA. March 5, 2020.
- Medical Oncology Sections Meeting: "Clinical research updates – Learning from feedback on our competitive renewals and upcoming process improvments." Seattle Cancer Care Alliance, Seattle, WA. April 2, 2020.
- Lead Academic Performance Site National Clinical Trials Network Leadership Meeting: "NCTN Leadership Team introduction." Seattle Cancer Care Alliance, Seattle, WA. September 2, 2020.

- Medical Oncology Sections Meeting: "Clinical trials startup process improvements." Seattle Cancer Care Alliance, Seattle, WA. September 3, 2020.
- Genitourinary Leadership Committee Meeting: "Clinical trials startup process improvements – specific to Genitourinary Oncology." Seattle Cancer Care Alliance, Seattle, WA. October 20, 2020.
- Clinical Research Division Faculty Meeting: "Clinical trials startup process improvements – specific to CRD." Fred Hutchinson Cancer Research Center, Seattle, WA. November 2, 2020.
- Curio Science – Opinions in Bladder Cancer: "Treatment of metastatic urothelial cancer in the post-platinum, post-immunotherapy setting." Seattle, WA by Virtual Meeting. November 11, 2020.
- Institutional Perspectives in Cancer presented by OncLive: "Increasing awareness of nonmetastatic (M0) castration-resistant prostate cancer." Seattle, WA by Virtual Meeting. November 24, 2020.
- University of Washington Clinical Research Director Meeting: "Clinical trial start-up process improvements and challenges." Seattle, WA by Virtual Meeting. February 1, 2021.
- Seattle Cancer Care Alliance Board of Directors' Enrichment Series: "Paving the path forward with next generation PET imaging in prostate cancer." Seattle, WA by Virtual Meeting. February 22, 2021.
- Program in Prostate Cancer Research/SPORE: "Antibody drug conjugates in bladder cancer – reaching new targets." Fred Hutchinson Cancer Research Center, Seattle, WA. February 25, 2021.
- National Cancer Trials Network Leadership Committee Meeting: "Bi-annual Spring Meeting." Fred Hutchinson Cancer Research Center, Seattle, WA. March 26, 2021.
- University of Washington Clinical Research Director Meeting: "Race and ethnicity clinical trial accrual data." Seattle Cancer Care Alliance, Seattle, WA. May 3, 2021.
- Fred Hutchinson Cancer Research Consortium Institutional Review Board Diverse Enrollment Subcommittee: "Race and ethnicity clinical trial accrual data." Fred Hutchinson Cancer Research Center, Seattle, WA. May 14, 2021.
- Genitourinary Oncology Leadership Meeting: "Race and ethnicity clinical trial accrual data." Seattle Cancer Care Alliance, Seattle, WA. May 18, 2021.
- Fred Hutchinson Cancer Consortium Executive Committee: "Race and ethnicity clinical trial accrual data." Seattle Cancer Care Alliance, Seattle, WA. June 1, 2021.
- Institute for Prostate Cancer Research (IPCR) 2021 Symposium – Advanced prostate cancer: "PSMA-targeted therapy – The next big thing?" Fred Hutchinson Cancer Research Center, Seattle, WA. June 5, 2021.
- Targeted Oncology and HRA: "Case-based round table meeting on castration resistant prostate cancer." Virtual Meeting, Washington. June 15, 2021.
- 2021 Seattle Cancer Care Alliance Genitourinary Oncology Retreat: "Next generation imaging." Seattle, WA. June 17, 2021.
- 2021 Seattle Cancer Care Alliance Genitourinary Oncology Retreat: "Expanding research in the community – NCTN pilot." Seattle, WA. June 17, 2021.
- Seattle UsToo: "PSMA-targeted theranostics for prostate cancer." Virtual Meeting, Seattle, WA. July 28, 2021.
- Medical Oncology Sections Meeting: "Race and ethnicity clinical trial accrual data." Seattle Cancer Care Alliance, Seattle, WA. September 2, 2021.
- External Advisory Board Meeting, Fred Hutchinson/University of Washington Cancer Consortium: "Clinical Protocol and Data Management." Fred Hutchinson Cancer Research Center, Seattle, WA. September 27, 2021.

- National Cancer Trials Network Leadership Committee Meeting: "Bi-annual Virtual Fall Meeting." Fred Hutchinson Cancer Research Center, Seattle, WA. October 1, 2021.
- University of Washington and Fred Hutchinson Cancer Research Center Assistant Professors' Meeting: "Consortium trial startup and clinical trial process improvement." Fred Hutchinson Cancer Research Center, Seattle, WA. February 8, 2022.
- University of Washington and Fred Hutchinson Cancer Research Center Associate Professors' Meeting: "Consortium trial startup and clinical trial process improvement." Fred Hutchinson Cancer Research Center, Seattle, WA. March 1, 2022.
- University of Washington Internal Medicine Residency Program: "How to think about the PSA test and prostate cancer screening." March 18, 2022.
- External Advisory Board Meeting, Fred Hutchinson/University of Washington Cancer Consortium: "Clinical Research Overview and Clinical Protocol and Data Management." Fred Hutchinson Cancer Research Center, Seattle, WA. May 26, 2022.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post-platinum or post immunotherapy, and subsequent therapy for locally advanced/metastatic urothelial carcinoma." Seattle, WA. August 31, 2022.
- Medical Oncology Sections Meeting: "Ongoing Genitourinary Medical Oncology (GUMO) clinical/translational research highlights." Fred Hutchinson Cancer Center, Seattle, WA. November 3, 2022.
- Fred Hutchinson Cancer Center Strategic Planning Meeting: "Clinical research updates from the lab to the bedside" Fred Hutchinson Cancer Center, Seattle, WA. November 4, 2022.
- Aptitude Health Live CASES: "Management of metastatic hormone sensitive prostate cancer." Seattle, WA. November 19, 2022.
- Aptitude Health Live CASES: "Management of metastatic castration resist prostate cancer." Seattle, WA. November 19, 2022.
- Aptitude Health Live CASES: "First-line therapy for advanced urothelial carcinoma." Seattle, WA. November 19, 2022.
- Aptitude Health Live CASES: "Second-line and subsequent management of advanced urothelial carcinoma." Seattle, WA. November 19, 2022.
- Fred Hutchinson Cancer Center Board of Advisors Science and Technology Advisory Committee Meeting: "Clinical trials overview." Fred Hutchinson Cancer Center. Seattle, WA. January 11, 2023.
- Medical Oncology Sections Meeting: "Clinical trial accrual update." Fred Hutchinson Cancer Center. Seattle, WA. February 2, 2023.
- University of Washington Clinical Research Director Meeting: "Clinical trial accruals and investment priorities." Fred Hutchinson Cancer Center. Seattle, WA. February 6, 2023.
- Program in Prostate Cancer Research/SPORE: "Inflammatory commentary on checkpoint inhibitors for prostate cancer and methods for reversal of the immune-exclusive microenvironment." Fred Hutchinson Cancer Center, Seattle, WA. March 9, 2023.
- Curio Science Local Workshop – Opinions in Advanced Bladder Cancer, An Interactive Local Workshop: "Post-platinum or post immunotherapy, and subsequent therapy for locally advanced/metastatic urothelial carcinoma." Seattle, WA. May 9, 2023.

INVITED SPEAKER NATIONAL/INTERNATIONAL

- Genentech, Inc.: "Retroviral RNA interference: systems development and biologic discoveries with telomerase." San Francisco, CA. April 6, 2004.
- **Stanford University Medical Center: "Retroviral RNA interference: systems development and biologic discoveries with telomerase." Stanford, CA. April 27, 2004.**

- **University of California Davis School of Medicine: "Retroviral RNA interference: systems development and biologic discoveries with telomerase." Sacramento, CA. April 30, 2004.**
- 8th Annual Western Hawaii Cancer Symposium: "Clinical implications of angiogenesis in solid tumor oncology." Kona, HI. September 10, 2005.
- Novartis Oncology: "Current issues in the treatment of bone metastases." Reno, NV. February 20, 2007.
- Novartis Oncology: "Treatment of solid tumor bone metastases with bisphosphonates." Anchorage, AK. June 13, 2007.
- Southwest Oncology Group Fall GU Committee Meeting: "Tissue inhibitor of metalloproteinase-1 (TIMP-1) as a prognostic and predictive biomarker for men receiving chemotherapy for hormone-refractory prostate cancer." Huntington Beach, CA. October 4, 2007.
- American Urologic Association Northeastern Section: "Emerging role of selective estrogen receptor modulators in prostate cancer." Santa Ana Pueblo, NM. September 20, 2008.
- American Urologic Association New England Section: "Emerging role of selective estrogen receptor modulators in prostate cancer." Rio Grande, Puerto Rico. September 26, 2008.
- **Prostate Cancer Foundation Scientific Symposium: "Prostate cancer bone metastasis biomarkers." Lake Tahoe, NV. October 16, 2008.**
- Southwest Oncology Group Spring GU Committee Meeting: "A phase 2 study of combined androgen deprivation and IMC-A12 for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. April 23, 2009.
- 12th Annual Western Hawaii Cancer Symposium: "Translational oncology in clinical practice." Kona, HI. September 4, 2009.
- **Prostate Cancer Research Institute (PCRI) 2009 Prostate Cancer Conference: "Reducing side effects of testosterone deprivation." Los Angeles, CA. September 12, 2009.**
- Southwest Oncology Group Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and IMC-A12 for patients with new hormone-sensitive metastatic prostate cancer." Chicago, IL. October 24, 2009.
- Second Annual Roche Diagnostics Bone Metastatic Cancer Advisory Board: "Prognostic markers for metastatic bone disease in prostate cancer." Arlington, VA. October 29, 2009.
- Prostate Cancer Clinical Trials Consortium Annual Review: "Using metabolic imaging to assess response to therapy in prostate cancer bone metastases." Vienna, VA. November 18, 2009.
- Prostate Cancer Educational Council: "Beyond screening and diagnosis – utility of prostate specific antigen by disease state." Content Development Working Group Moderator. Philadelphia, PA. November 20, 2009.
- 10th Annual Meeting of the Society of Urologic Oncology: "Androgen deprivation therapy induced estrogen deficiency side effects." Bethesda, MD. December 4, 2009.
- Center for Biomedical Continuing Education: "Bone health across the cancer continuum: Updates and insight to an evolving story." Chicago, IL. February 9, 2010.
- Billings Clinic Tumor Board: "Bone health across the cancer continuum: Updates and insight to an evolving story." Billings, MT. March 30, 2010.
- Center for Biomedical Continuing Education: "Bone health across the cancer continuum: Updates and insight to an evolving story." New York, NY. April 8, 2010.
- Southwest Oncology Group Spring GU Committtee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and IMC-A12 for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. April 18, 2010.
- Mercy Regional Medical Center Grand Rounds: "Bone health across the cancer continuum: Updates and insight to an evolving story." Durango, CO. April 20, 2010.

- Sparrow Professional Building Grand Rounds: "Bone health across the cancer continuum: Updates and insight to an evolving story." Lansing, MI. April 30, 2010.
- **Education Session, Evolving Standards of Care in Metastatic Castration-resistant Prostate Cancer: "Bone directed therapy for prostate cancer: present standards and potential new options." 2010 American Society of Clinical Oncology, Chicago, IL. June 7, 2010.**
- **University of Texas Southwestern Combined Modality Conference: "Boning up with prostate cancer." Dallas, TX. July 2, 2010.**
- **Wayne State University / Karmanos Cancer Institute Prostate Cancer Working Group Conference: "Bone health in prostate cancer: The basics and some propaganda." Detroit, MI. August 20, 2010.**
- 13th Annual Western Hawaii Cancer Symposium: "Emerging new therapies for metastatic castration resistant prostate cancer." Kona, HI. September 4, 2010.
- South Texas Institute of Cancer: "Clinical debates in castration-refractory prostate cancer." Corpus Christi, TX. September 7, 2010.
- Texas Hematology/Oncology: "Clinical debates in castration-refractory prostate cancer." McKinney, TX. September 9, 2010.
- **Prostate Cancer Foundation Scientific Symposium: "Imaging prostate cancer bone metastases with sodium fluoride (NaF) PET." Washington, DC. September 16, 2010.**
- **City of Hope Oncology Grand Rounds: "Clinical decision making in castration-resistant prostate cancer." Duarte, CA. October 5, 2010.**
- Mount Clemens Regional Medical Center Oncology Grand Rounds: "Clinical debates in castration-refractory prostate cancer." Mount Clemens, MI. October 13, 2010.
- Great Falls Clinic Cancer Center: "Clinical debates in castration-refractory prostate cancer." Great Falls, MT. October 14, 2010.
- Southwest Oncology Group Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." Chicago, IL. October 23, 2010.
- Mercy Hospital: "Clinical debates in castration-refractory prostate cancer." Bakersfield, CA. November 3, 2010.
- **University of California San Diego Hematology/Oncology Grand Rounds: "Prostate Cancer: Honing in on the bones." San Diego, CA. January 14, 2011.**
- Southwest Oncology Group Spring GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. April 16, 2011.
- Providence Alaska Medical Center: "Advances in castration-resistant prostate cancer." Anchorage, AK. April 27, 2011.
- Bristol-Myers Squibb ASCO Dasatinib Investigator Initiated Trial Meeting: "Determining pharmacodynamic effects of Dasatinib on bone with ^{18}F-fluoride PET imaging in men with castration resistant prostate cancer." Chicago, IL. June 4, 2011.
- Millennium Pharmaceuticals, Inc. Prostate Cancer Update Educational Program: "Hormone-sensitive prostate cancer – recent updates and ongoing trials." Cambridge, MA. October 4, 2011.
- SWOG Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Antonio, TX. October 15, 2011.

- OncoGeneX OGX-427-02 Bladder Cancer Phase 2 Investigator Meeting: "A phase 1 trial of OGX-427, a 2-methoxyethyl antisense oligonucleotide against Heat Shock Protein 27." Scottsdale, AZ. November 5, 2011.
- **Yale Cancer Center NP Conference: "Prostate cancer: It's all about the bones." New Haven, CT. November 18, 2011.**
- **2012 Genitourinary Cancers Symposium, General Session II: Castrate Resistant Prostate Cancer – Treatment Sequencing and Implementation: "Novel targets, agents, and trials." San Francisco, CA. February 2, 2012.**
- **2012 Genitourinary Cancers Symposium, General Session II: Castrate Resistant Prostate Cancer – Treatment Sequencing and Implementation: "Case study and panel discussion." San Francisco, CA. February 2, 2012.**
- Prostate Cancer Skeletal Metastasis Workshop, Combined P01 Meeting: "Imaging response to therapy in prostate cancer bone metastases – PET as a biomarker." Ann Arbor, MI. April 12, 2012.
- SWOG Spring GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. April 14, 2012.
- Astellas Pharma Medical Science Liaison Education Lecture: "The dynamic treatment landscape for castration-resistant prostate cancer." Internet lecture. May 4, 2012.
- **Vanderbilt University: "Dem bones, dem bones, dem prostate cancer bones." Nashville, TN. May 17, 2012.**
- **Genitourinary (Prostate) Cancer Poster Discussion Session: "Sex, Drugs, and Bones." 2012 American Society of Clinical Oncology, Chicago, IL. June 4, 2012.**
- Dendreon Advisory Meeting: "The oncologist's perspective of Provenge for patients with asymptomatic/minimally symptomatic metastatic castrate-resistant prostate cancer." San Diego, CA. June 15, 2012.
- Dendreon Oncology Summit Advisory Board: "Provenge and the evolving treatment landscape for advanced prostate cancer." San Francisco, CA. June 23, 2012.
- Dendreon Oncology Summit Advisory Board: "Sequencing metastatic castration-resistant prostate cancer treatments of the future." San Francisco, CA. June 23, 2012.
- **University of California Davis 13th Annual Advances in Oncology 2012: "New therapeutic options in advanced castration-resistant prostate cancer." Sacramento, CA. September 22, 2012.**
- SWOG Fall Prostate Cancer Organ Site Meeting: "A randomized phase 2-3 trial of intermittent androgen deprivation therapy using Enzalutamide with a GnRH agonist versus Bicalutamide with a GnRH agonist in patients with non-metastatic castration-sensitive prostate cancer." Chicago, IL. October 19 and 20, 2012.
- SWOG Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." Chicago, IL. October 20, 2012.
- South Texas Comprehensive Cancer Center: "Optimizing care for patients with advanced prostate cancer: evolving targets and emerging treatment paradigms." Corpus Christi, TX. December 4, 2012.
- Hoag Memorial Hospital Oncology Grand Rounds: "Optimizing care for patients with advanced prostate cancer: evolving targets and emerging treatment paradigms." Newport Beach, CA. February 28, 2013.
- Dendreon Oncology Advisory Board Meeting: "Sipuleucel-T and its use in community-based oncology practices." Washington, DC. April 18, 2013.

- SWOG Spring GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. May 2, 2013.
- Medivation Preclinical ASCO Advisory Board Meeting: "The role of SRC in prostate cancer – are there still potential clinical implications?" Chicago, IL. May 30, 2013.
- Dendreon Medical Oncologist Advisory Board: "Early detection of metastatic castration-resistant prostate cancer." Chicago, IL. May 31, 2013.
- Dendreon Medical Oncologist Advisory Board: "Metastatic castration-resistant prostate cancer, a changing landscape." Chicago, IL. May 31, 2013.
- **Genitourinary (Prostate) Cancer Poster Discussion Session: "Prognosis and predication of outcomes in castration-resistant prostate cancer." 2013 American Society of Clinical Oncology, Chicago, IL. June 1, 2013.**
- Janssen Post-ASCO Educational Update Meeting: "Updates on metastatic castration-resistant prostate cancer studies from ASCO 2013." Chicago, IL. June 4, 2013.
- Dendreon: "Cancer immunotherapy – fundamental concepts and emerging role." Las Vegas, NV. July 25, 2013.
- Challenging Cases in Oncology powered by Xcenda: "Case 6 – Advanced prostate cancer prognosis and treatment." Las Vegas, NV. July 27, 2013.
- Challenging Cases in Oncology powered by Xcenda: "Prostate cancer debrief." Las Vegas, NV. July 27, 2013.
- Compass Oncology 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Portland, OR. September 19, 2013.
- Abilene Regional Medical Center 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Abilene, TX. September 24, 2013.
- Mercy Medical Center 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Canton, OH. October 4, 2013.
- SWOG Fall Prostate Cancer Organ Site Meeting: "A randomized phase 2-3 trial of intermittent androgen deprivation therapy using Enzalutamide with a GnRH agonist versus a GnRH agonist alone in patients with non-metastatic castration-sensitive prostate cancer." Chicago, IL. October 11, 2013.
- SWOG Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." Chicago, IL. October 11, 2013.
- Myriad Genetics and Laboratories: "Prostate cancer/Prolaris medical oncology advisory board meeting." Salt Lake City, UT. October 19, 2013.
- **18th Brazilian Oncology Conference: "Post-ADT phase 3 clinical evidence: Efficacy of abiraterone acetate." Brasilia, Brazil. October 23, 2013.**
- Janssen Dinner Launch: "Metastatic castration-resistant prostate cancer cases." Brasilia, Brazil. October 24, 2013.
- **Chemotherapy Foundation Symposium: "Novel PET imaging in prostate cancer." New York City, NY. November 8, 2013.**
- St. Lukes Mountain States Tumor Institute 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Boise, ID. November 13, 2013.
- Bergan Mercy Medical Center 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Omaha, NE. November 20, 2013.

- Medivation Incorporated: "A randomized phase 2-3 trial of intermittent androgen deprivation therapy using enzalutamide with a GnRH agonist versus a GnRH agonist alone in patients with non-metastatic castration-sensitive prostate cancer." San Francisco, CA. November 22, 2013.
- Elsevier Urology Round Table: "Measuring immune response in men with metastatic castration-resistant prostate cancer." Washington, DC. December 7, 2013.
- Dendreon: "Cancer immunotherapy – fundamental concepts and emerging role." Santa Barbara, CA. December 19, 2013.
- Hoag Memorial Hospital Oncology Grand Rounds: "Integration of novel management strategies for castrate-resistant prostate cancer." Newport Beach, CA. January 23, 2014.
- Dendreon Medical Oncologist Advisory Board: "Cancer immunotherapy – fundamental concepts and emerging role." Santa Barbara, CA. February 6, 2014.
- Dendreon: "Cancer immunotherapy – fundamental concepts and emerging role." Honolulu, HI. February 19, 2014.
- **7th Annual IntraSPORE Prostate Cancer Program Retreat: "Prostate cancer and the clinical sciences – where are we and what we need to do?" Fort Lauderdale, FL. March 17, 2014.**
- St. Lukes Mountain States Tumor Institute: "Overcoming cancer immunoevasion: the role of immunotherapy." Boise, ID. April 3, 2014.
- Dendreon: "Overcoming cancer immunoevasion: the role of immunotherapy." Billings, MT. April 22, 2014.
- SWOG Spring GU Organ Site Working Group Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. May 1, 2014.
- Dendreon Junior Faculty ASCO Advisory Meeting: "A new era of immunotherapy in treating prostate cancer." Chicago, IL. May 29, 2014.
- Janssen Post-ASCO 2014 Educational Update Meeting: "Developments in initial treatment approaches for advanced prostate cancer." Chicago, IL. June 3, 2014.
- Dendreon Sales Training Workshop: "Health care provider training for clinical proficiency." Atlanta, GA. June 18, 2014.
- Enzalutamide Medical Advisory Board: "Current clinical practice landscape incorporating ASCO 2014 data and upcoming key clinical trials in prostate cancer." New York, NY. July 26, 2014.
- **Best of ASCO 2014: "Prostate cancer 2014 – Progress! Not progression." Seattle, WA. August 23, 2014.**
- Meet the Expert for Zytiga – a community forum: "The metastatic castration-resistant prostate cancer treatment paradigm: more choices, more questions." Yokohama, Japan. August 27, 2014.
- **52nd Annual Meeting of Japanese Society of Clinical Oncology: "The metastatic castration-resistant prostate cancer treatment paradigm: more choices, more questions." Yokohama, Japan. August 28, 2014.**
- Meet the Expert for Castration-Resistant Prostate Cancer – an academician forum: "The metastatic castration-resistant prostate cancer treatment paradigm: more choices, more questions." Yokohama, Japan. August 29, 2014.
- Challenging Cases in Prostate Cancer powered by Xcenda: "The metastatic castration-resistant prostate cancer smorgasbord." Las Vegas, NV. September 19, 2014.
- Regional Summit on Practical and Emerging Agents in Prostate Cancer: "Immunotherapy approaches to prostate cancer." New York, NY. October 4, 2014.
- **15th Annual Meeting of the Society of Urologic Oncology: "Prostate cancer sequencing prior to chemotherapy." Bethesda, MA. December 5, 2014.**

- **University of Chicago: "Immunotherapy for genitourinary malignancies." Chicago, IL. December 18, 2014.**
- Elmhurst Memorial Clinic: "Overcoming cancer immunoevasion: the role of immunotherapy." Elmhurst, IL. December 18, 2014.
- Tolmar Advisory Council Meeting: "Maximal castration for advanced prostate cancer? Correlations between testosterone levels and outcomes." San Diego, CA. January 9, 2015.
- Regional Summit on Practical and Emerging Agents in Prostate Cancer: "Sipuleucel-T: Current status and optimal patient selection." Dallas, TX. January 17, 2015.
- Rocky Mountain Cancer Center Boulder: "Overcoming cancer immunoevasion: the role of immunotherapy." Boulder, CO. February 5, 2015.
- Dendreon: "Overcoming cancer immunoevasion: the role of immunotherapy." Denver, CO. February 5, 2015.
- The Urology Center of Colorado: "Immunotherapy for bladder cancer." Denver, CO. February 6, 2015.
- **2015 Genitourinary Cancers Symposium, General Session II: Evolving role of multimodality treatment in low volume hormone-sensitive metastatic disease: "Selection of systemic therapy: Chemotherapy and androgen axis agents." Orlando, FL. February 26, 2015.**
- PeerView Live CME: Clinical challenges in castration-resistant prostate cancer - How to choose the right treatment for the right patient at the right time: "Current and future directions with hormone therapy in prostate cancer." Orlando, FL. February 27, 2015.
- **University of Texas Houston: "Overcoming cancer immunoevasion: the role of immunotherapy." Houston, TX. March 16, 2015.**
- **University of Arizona Oncology Grand Rounds: "Clinical research in prostate cancer – exploring the castration-sensitive disease state." Tucson, AZ. March 27, 2015.**
- Genentech Bladder Cancer Steering Committee: "Urothelial bladder cancer disease states education." Dallas, TX. April 17, 2015.
- Dendreon Advisory Meeting – Integrating Leading-Edge Data Into Prostate Cancer Treatment and Research: "Impact of recent data on treatment considerations in prostate cancer: Resistance to androgen-targeted agents." Chicago, IL. May 28, 2015.
- Dendreon Advisory Meeting – Integrating Leading-Edge Data Into Prostate Cancer Treatment and Research: "Antigen spread following sipuleucel-T treatment." Chicago, IL. May 28, 2015.
- Peerview Live CME – Applying the Latest Evidence to Treatment Decisions in CRPC: Real Cases, Difficult Choices – You Make the Call: "Management options for previously treated metastatic CRPC: Latest data and considerations." Chicago, IL. May 29, 2015.
- Urologic Oncology Summit: "Castration-resistant prostate cancer: Biology and definitions." Panama City, Panama. June 27, 2015.
- Urologic Oncology Summit: "An overview of non-metastatic (M0) castration-resistant prostate cancer." Panama City, Panama. June 27, 2015.
- Urologic Oncology Summit: "Placing the evidence together in metastatic castration-resistant prostate cancer: Sequencing, combination?" Panama City, Panama. June 27, 2015.
- Urologic Oncology Summit: "Panel discussion: Special clinical scenarios for advanced prostate cancer." Panama City, Panama. June 27, 2015.
- Urologic Oncology Summit: "Role of docetaxel in the management of castration-sensitive prostate cancer." Panama City, Panama. June 27, 2015.
- 6th International Pacrim Breast and Prostate Cancer Meeting: PET imaging in prostate cancer: Research tool of standard clinical practice?" Stevenson, WA. July 21, 2015.
- Enzalutamide Medical Advisory Board: "ASCO 2015 data review." New York, NY. July 31, 2015.

- 3rd Annual International Conferences on Advances in Hematology and Oncology: "Metastatic prostate cancer – Management in the era of novel agents." Coeur d'Alene, ID. August 29, 2015.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Portland, OR. November 10, 2015.
- Janssen West Community Oncology Advisory Board Meeting: "Data review of abiraterone and enzalutamide, clinical sequencing and future directions in prostate cancer." Los Angeles, CA. November 11, 2015.
- **16th Annual Meeting of the Society of Urologic Oncology: "Clinical implications of genomics in treating prostate cancer." Washington, DC. December 3, 2015.**
- Merck Genitourinary Oncology Global Advisory Board Meeting: "Current treatment options for metastatic castration-resistant prostate cancer and potential role for checkpoint inhibitors in the future." Barcelona, Spain. January 29, 2016.
- Merck Genitourinary Oncology Global Advisory Board Meeting: "Update on checkpoint inhibitor data in bladder cancer." Barcelona, Spain. January 29, 2016.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Irvine, CA. March 10, 2016.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Anchorage, AK. March 16, 2016.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Phoenix, AZ. March 24, 2016.
- Florida Society of Clinical Oncology (FLASCO) Spring Session: "Sequencing agents in metastatic prostate cancer." Kissimmee, FL. April 9, 2016.
- Seattle Cancer Care Alliance 1st Comprehensive Cancer Update: "Treatment decision making for patients with metastatic prostate cancer." Honolulu, HI. April 16, 2016.
- Seattle Cancer Care Alliance 1st Comprehensive Cancer Update: "Bladder cancer – Major advancements coming soon." Honolulu, HI. April 16, 2016.
- Seattle Cancer Care Alliance 1st Comprehensive Cancer Update: "Testicular cancer – Winning the ball game." Honolulu, HI. April 16, 2016.
- Bayer West Area Meeting: "Metastatic castration-resistant prostate cancer overview." Phoenix, AZ. April 28, 2016.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Oxnard, CA. May 24, 2016.
- Bayer Corporation: "Post-ASCO 2016 Point of View." Global Webex. June 23, 2016.
- 4th Annual Canadian Urological Association and Canadian Urologic Oncology Group Multidisciplinary Meeting: "The promise of checkpoint inhibitors in urothelial cancer." Vancouver, BC, Canada. June 25, 2016.
- Janssen Medical Oncology Advisory Board: "Janssen oncology clinical development program in genitourinary malignancies." Chicago, IL. July 14, 2016.
- Genentech Lung and Urothelial Cancer Advisory Board: "Atezolizumab in urothelial cancer." Seattle, WA. July 16, 2016.
- **Best of ASCO 2016: "Genitourinary (Non-prostate) Cancer." San Diego, CA. August 13, 2016.**
- 4th Annual International Conferences on Advances in Hematology and Oncology: "Choices and decisions in metastatic prostate cancer." Coeur d'Alene, ID. August 14, 2016.
- **American Urological Association Advanced Prostate Cancer: Managing the Spectrum of Disease Symposium: "Comorbidities and side effect profiles: Considerations for various castration-resistant prostate cancer therapeutic strategies." Chicago, IL. September 24, 2016.**

- Merck KEYNOTE-365 Investigator Meeting: "Metastatic castration-resistant prostate cancer overview, current treatment and future directions." Baltimore, MD. October 20, 2016.
- 3rd Annual Summit on Genitourinary Malignancies: "Identifying prostate cancer patients for immunotherapy approaches." New York, NY. October 23, 2016.
- prIME Oncology, 2nd Annual West Cancer Center Oncology Conference, Collaboration for the Future Cure – Precision Medicine and Immuno-Oncology: "Immunotherapy in genitourinary cancers: The new frontier." Memphis, TN. November 18, 2016.
- **17th Annual Meeting of the Society of Urologic Oncology: "Immunotherapy for prostate cancer: What is the way forward?" San Antonio, TX. December 2, 2016.**
- **American Urological Association Advanced Prostate Cancer: Managing the Spectrum of Disease Symposium: "Comorbidities and side effect profiles: Considerations for various castration-resistant prostate cancer therapeutic strategies." Washington, DC. December 10, 2016.**
- **Society of Government Service Urologists – 2017 Kimbrough Urological Seminar: "Considerations for the symptomatic metastatic castration resistant prostate cancer patient: Beyond Abiraterone and Enzalutamide." San Diego, CA. January 14, 2017.**
- Annenberg Center for Health Sciences CME: Experts in Residence – "Bridging the gap from knowledge to practice in castration-resistant prostate cancer." Cancer Treatment Centers of America, Zion, IL. January 27, 2017.
- St. Lukes Mountain States Tumor Institute - Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Boise, ID. February 7, 2017.
- Targeted Oncology Case-Based Peer Perspectives: "Immunotherapy in advanced bladder cancer." Orlando, FL. February 24, 2017.
- Annenberg Center for Health Sciences CME: Experts in Residence – "Bridging the gap from knowledge to practice in castration-resistant prostate cancer." Beaumont Hospital, Royal Oak, MI. March 7, 2017.
- Annenberg Center for Health Sciences CME: Experts in Residence – "Bridging the gap from knowledge to practice in castration-resistant prostate cancer." Summerlin Hospital, Las Vegas, NV. March 14, 2017.
- Bayer Pharmaceuticals - Meet the Professor: "Overview of data related to sequential use of novel hormonal therapies in metastatic castration-resistant prostate cancer." Hanover, NJ. March 24, 2017.
- Hawaii Pacific Health - Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Honolulu, HI. April 10, 2017.
- SWOG Spring GU Organ Site Working Group Meeting: "Combination immune-oncology therapeutics in metastatic castration-resistant prostate cancer." San Francisco, CA. April 28, 2017.
- **American Urological Association 2017 Castration-Resistant Prostate Cancer Live Forum for Residents & Fellows: "Role of chemotherapy for metastatic castration-resistant prostate cancer." Boston, MA. May 11, 2017.**
- **PROSPECT 2017 Symposium Keynote Presentation: "What's hot in advanced prostate cancer today?" Melbourne, Australia. May 19, 2017.**
- **PROSPECT 2017 Symposium Diagnosis, Staging and Management of Locally Advanced Prostate Cancer: "Advances in imaging and implications for treatment of oligometastatic disease." Melbourne, Australia. May 20, 2017.**
- **PROSPECT 2017 Symposium Sequencing in Advanced Prostate Cancer – Current Therapies: "Therapeutic sequencing in metastatic castration-resistant prostate cancer." Melbourne, Australia. May 20, 2017.**

- **PROSPECT 2017 Symposium Rapid Fire Multidisciplinary Cases: "Case – sequencing in metastatic castration-resistant prostate cancer." Melbourne, Australia. May 20, 2017.**
- **PROSPECT 2017 Symposium A Look to the Future – Personalised and Supportive Care in Advanced Prostate Cancer: "High-risk non-metastatic (M0) castration-resistant prostate cancer – an evolving landscape." Melbourne, Australia. May 20, 2017.**
- Denali Oncology Group's 34th Educational Program Oncology in the Last Frontier: "Comorbidities and side effects and their effect on how we use therapeutic agents for advanced prostate cancer." Barrow, AK. June 24, 2017.
- Denali Oncology Group's 34th Educational Program Oncology in the Last Frontier: "Considerations with next generation sequencing results and precision medicine in prostate cancer." Barrow, AK. June 24, 2017.
- Bozeman Health - Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Bozeman, MT. July 6, 2017.
- 5th Annual International Conferences on Advances in Hematology and Oncology: "Metastatic prostate cancer: How to sequence newer agents." Coeur d'Alene, ID. August 12, 2017.
- 18th Future Directions in Urology Symposium: "Updates on use of radiopharmaceuticals in prostate cancer clinical trials." Colorado Springs, CO. August 22, 2017.
- **American Urological Association 2017 Castration-Resistant Prostate Cancer Live Forum for Residents & Fellows: "Role of chemotherapy for metastatic prostate cancer." Dallas, TX. September 9, 2017.**
- **American Urological Association Practical Management of Metastatic Prostate Cancer: Guidelines and Beyond: "Comorbidities and side effect profiles: Considerations for various castration-resistant prostate cancer therapeutic strategies." Dallas, TX. September 10, 2017.**
- **American Urological Association Practical Management of Metastatic Prostate Cancer: Guidelines and Beyond: "Future directions in systemic therapy for prostate cancer." Dallas, TX. September 10, 2017.**
- **University of Utah/Huntsman Cancer Institute - Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Salt Lake City, UT. September 28, 2017.**
- Urological Oncology Committee of Taiwan Urological Association Preceptorship: "Novel therapies for the management of advanced prostate cancer." Taipei, Taiwan. October 14, 2017.
- Bayer Taiwan and Southeast Asia Advisory Meeting: "Real life experience with Radium-223 and new clinical evidence." Taipei, Taiwan. October 15, 2017.
- Bayer Taiwan and Southeast Asia Advisory Meeting: "Insights from evaluation criteria to treatment outcomes of Radium-223." Taipei, Taiwan. October 15, 2017.
- **American Urological Association 2017 Castration-Resistant Prostate Cancer Live Forum for Residents & Fellows: "Role of chemotherapy for metastatic prostate cancer." Los Angeles, CA. October 28, 2017.**
- **American Urological Association Practical Management of Metastatic Prostate Cancer: Guidelines and Beyond: "Comorbidities and side effect profiles: Considerations for various castration-resistant prostate cancer therapeutic strategies." Los Angeles, CA. October 29, 2017.**
- **American Urological Association Practical Management of Metastatic Prostate Cancer: Guidelines and Beyond: "Future directions in systemic therapy for prostate cancer." Los Angelese, CA. October 29, 2017.**

- Cancer Immunotherapy Trials Network Annual Meeting: "A randomized phase 2 study of atezolizumab plus recombinant human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma." National Harbor, MD. November 9, 2017.
- Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Summerlin Hospital, Las Vegas, NV. November 27, 2017.
- Purdue University PeerView CME: "Candid conversations in prostate cancer: State of the science and implications for improving patient care and outcomes." VA Southern Nevada Health Care System, Las Vegas, NV. December 19, 2017.
- Annenberg Center for Health Sciences CME: "Optimizing patient outcomes in castration-resistant prostate cancer: Moving urologists from knowledge to action." Holy Cross Hospital (Sinai Health System), Chicago, IL. February 28, 2018.
- Merck/MSD Prostate Cancer Global Advisory Board: "PARP inhibition and DNA repair deficiency in metastatic castration-resistant prostate cancer." San Francisco, CA. May 17, 2018.
- **Society for Basic Urology Research (SBUR)/Suociety of Urologic Oncology (SUO) Joint Meeting at the American Urological Association Annual Meeting: "Treatment of cisplatin-ineligible muscle-invasive bladder cancer patients." San Francisco, CA. May 19, 2018.**
- Onclive 2018 State of the Science: Genitourinary Cancers: "Treatment intensification for castration-sensitive prostate cancer." Salt Lake City, UT. May 24, 2018.
- **Huntsman Cancer Institute Genitourinary Oncology Symposium:** "Future of immuno-oncology in prostate cancer." Huntsman Cancer Institute/University of Utah, Salt Lake City, UT. May 25, 2018.
- Peerview Live CME – Newest Advances and Strategies in Prostate Cancer – Science and Stories on the Evolving Treatment Landscape and Implications for Patient Cancer: "DNA repair deficiency and implications for men with prostate cancer." Chicago, IL. June 1, 2018.
- **Education Session, Role of Precision Therapy in the Treatment of Advanced Urothelial Cancer: "Targeted therapies in advanced urothelial cancer." 2018 American Society of Clinical Oncology, Chicago, IL. June 4, 2018.**
- Annenberg Center for Health Sciences CME: "Optimizing patient outcomes in castration-resistant prostate cancer: Moving urologists from knowledge to action." North Side Hospital, Atlanta, GA. June 14, 2018.
- 6th Annual International Conferences on Advances in Hematology and Oncology: "Prostate cancer: Optimizing the use of newer agents." Coeur d'Alene, ID. August 5, 2018.
- 19th Future Directions in Urology Symposium: "Next generation anti-androgen therapies." Colorado Springs, CO. August 13, 2018.
- 19th Future Directions in Urology Symposium: "Next generation advanced and endocrine refractory prostate cancer." Colorado Springs, CO. August 14, 2018.
- Prostate Cancer Research Institute (PCRI) 2018 Prostate Cancer Patient Conference: "Pills, immune boosters & radiopharmaceuticals for prostate cancer treatment: Who, Where, When, How and Now?!" Los Angeles, CA. September 8, 2018.
- Singapore Urological Association: "Targeted alpha therapy in metastatic castration-resistant prostate cancer: Dawn or Dusk" Singapore. September 25, 2018.
- Asia-Pacific Metastatic Castration-Resistant Prostate Cancer Expert Exchange Summit: "Optimizing survival in metastatic castration-resistant prostate cancer: Radium-223 and its place in treatment plans: Clinician's perspective." National Cancer Center, Singapore. September 26, 2018.
- National University Hospital: "Targeted alpha therapy in metastatic castration-resistant prostate cancer: Dawn or Dusk" Singapore. September 27, 2018.
- Prostate Cancer Academy: "Role of androgen receptor blockers in advanced prostate cancer." Los Angeles, CA. October 13, 2018.

- Prostate Cancer Academy: "Role of chemotherapy and radiopharmaceuticals in the management and treatment of advanced prostate cancer." Los Angeles, CA. October 13, 2018.
- ESMO Satellite Symposium – Checkpoint inhibition in the treatment of cancer: Building the new standard of care across multiple solid tumors: "Checkpoint inhibition for the treatment of genitourinary cancers." Munich, Germany. October 19, 2018.
- Cancer Immunotherapy Trials Network Annual Meeting: "A randomized phase 2 study of atezolizumab plus recombinant human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma." Washington, DC. November 7, 2018.
- Windsor Regional Cancer Centre: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Windsor, ON, Canada. November 13, 2018.
- Ottowa Dinner Round: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Ottowa, ON, Canada. November 13, 2018.
- **Juravinski Cancer Centre Grand Rounds: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Hamilton, ON, Canada. November 14, 2018.**
- Sherbrooke Dinner Rounds: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Montreal, QC, Canada. November 14, 2018.
- **Princess Margaret Cancer Centre Grand Rounds: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Toronto, ON, Canada. November 15, 2018.**
- Greater Toronto Area Dinner Rounds: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Etobicoke, ON, Canada. November 15, 2018.
- Radium-223 dichloride Oncology Hospital Advisory Board: Management and unmet needs in metastatic castration-resistant prostate cancer: Radium-223 new clinical trials data. Dallas, TX. December 8, 2018.
- Peerview Live CME – Unraveling the Complexities of Prostate Cancer Management – Focus on Therapeutic Decisions for Early-Stage Disease and the Implications for Later-Stage Disease: "Androgen-targeting therapy in nonmetastatic (M0) castration-resistant prostate cancer." San Francisco, CA. February 15, 2019.
- **44th Annual UCLA State of the Art Urology Conference: "Late breaking news – treatment of oligometastatic prostate cancer." Marina Del Rey, CA. March 9, 2019.**
- **44th Annual UCLA State of the Art Urology Conference: "Pragmatic sequencing therapy for castrate resistant prostate cancer." Marina Del Rey, CA. March 9, 2019.**
- **44th Annual UCLA State of the Art Urology Conference: "Making the immune system work for the urologist." Marina Del Rey, CA. March 9, 2019.**
- Enfortumab Vedotin Community Advisory Board: "Metastatic urothelial cancer community patient profile." Dallas, TX. March 15, 2019.
- Enfortumab Vedotin Community Advisory Board: "Potential future treatment options for metastatic urothelial carcinoma." Dallas, TX. March 15, 2019.
- **Food & Drug Administration Mini-Symposium on Pathologic Complete Response in Bladder Cancer: "Clinical restaging in muscle-invasive bladder cancer – How do we do it and what does it mean?"** Silver Spring, MD. March 27, 2019.
- Annenberg Center for Health Sciences CME: "Optimizing patient outcomes in castration-resistant prostate cancer: Moving urologists from knowledge to action." Eisenhower Medical Center, Rancho Mirage, CA. March 28, 2019.
- Bayer Pharmaceuticals - Meet the Professor: "Earlier use of novel hormones for advanced prostate cancer and impact on the metastatic castration-resistant prostate cancer population." Hanover, NJ. April 4, 2019.

- Merck Pharmaceuticals – Prostate Program Phase III Studies Investigator Meeting Series: "KEYNOTE-365 Cohort A: Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castrate-resistant prostate cancer." Jersey City, NJ. April 12, 2019.
- **American Urological Association 2019 Evolving Role of the Urologist in Metastatic and Castration Resistant Prostate Cancer: A Guidelines and Case-Based Discussion: "Role of chemotherapy, treatment sequencing and future approaches." Chicago, IL. May 2, 2019.**
- Peerview Live CME – New Concepts in Prostate Cancer – What Oncologists Need to Know to Optimize Patient Outcomes: "Non-metastatic castration resistant prostate cancer." Chicago, IL. June 1, 2019.
- **Education Session Genitourinary (Non-prostate) Cancer – Formidable Scenarios in Urothelial and Variant Cancers of the Urinary Tract: "Cisplatin-ineligible patients with urothelial carcinoma – medical oncology perspective." 2019 American Society of Clinical Oncology Annual Meeting. Chicago, IL. June 2, 2019.**
- Washington State Urology Association Annual Conference: "Unraveling the complex treatment landscape of prostate cancer – Guidance for delivering evidence-based, patient-centered care." Leavenworth, WA. June 22, 2019.
- ASCO Direct Highlights – 2019 Official Annual Meeting Review: "Genitourinary cancers – The advances continue." New York, NY. July 19, 2019.
- FDA – Bladder Cancer Advocacy Network Workshop: "Clinical restaging in muscle-invasive bladder cancer – How do we do it and what does it mean?" Washington, DC. August 8, 2019.
- Clovis Prostate Cancer Clinical Immersion: "Biochemically-recurrent prostate cancer and implifcations of next generation PET imaging." Boulder, CO. August 27, 2019.
- Clovis Prostate Cancer Clinical Immersion: "Advanced prostate cancer and treatment sequencing." Boulder, CO. August 27, 2019.
- Clovis Prostate Cancer Clinical Immersion: "Prostate cancer biology, mechanisms of castration-resistance and drug-resistance." Boulder, CO. August 27, 2019.
- Prostate Cancer Academy: "Role of androgen receptor blockers in advanced prostate cancer." Los Angeles, CA. September 21, 2019.
- Prostate Cancer Academy: "Role of chemotherapy and radiopharmaceuticals in the management and treatment of advanced prostate cancer." Los Angeles, CA. September 21, 2019.
- GU Connect Face to Face Meeting at ESMO 2019: "GU Connect educational focus and priorities 2020." Barcelona, Spain. September 28, 2019.
- Janssen Advisory Board 2019 Meeting: "Current approach and treatment patterns in metastatic castration sensitive prostate cancer." San Francisco, CA. October 12, 2019.
- Targeted Oncology and HRA: "Case-based perspectives in prostate cancer." Orlando, FL. November 14, 2019.
- Sanofi Genzyme Key Opinion Leader Expert Seminar: "Future treatment options for advanced prostate cancer." Webex. November 21, 2019.
- Bayer Oncology Advisory Board: "Cognitive impairment: Impact in prostate cancer." San Diego, CA. November 23, 2019.
- Bayer Oncology Advisory Board: "Non-metastatic castration-resistant prostate cancer: Definitions and deciding to treat." San Diego, CA. November 23, 2019.
- **American Urological Association / Society of Urologic Oncology 2019 Evolving Role of the Urologist in Metastatic and Castration Resistant Prostate Cancer: A Guidelines and Case-Based Discussion: "Role of chemotherapy, treatment sequencing and future approaches." Washington, DC. December 3, 2019.**
- Merck Pharmaceuticals – Prostate Scientific Input Engagement: "KEYNOTE-365 Cohort A, B, C ASCO GU 2019 – 1st data release." San Francisco, CA. February 12, 2020.

- Peerview Live CME – Mapping the Pathways to Better Patient Outcomes in Prostate Cancer: Personal Insights and Guidance from the Patient Casebook: "Emerging novel strategies in metastatic prostate cancer." San Francisco, CA. February 14, 2020.
- Institute of Molecular Medicine and Biomedical Research – Optimal Treatment of Prostate Cancer (converted to Virtual Meeting): "Treatment of metastatic castration-resistant prostate cancer." Athens, Greece. March 13, 2020.
- Institute of Molecular Medicine and Biomedical Research – Optimal Treatment of Urothelial Cancer (converted to Virtual Meeting): "Treatment of locally advanced unresectable and metastatic disease." Athens, Greece. March 13, 2020.
- Prostate Cancer Research Institute (PCRI) 2020 Prostate Cancer Patient Conference – Mid Year Update (converted to Virtual Meeting): "Updates in advanced prostate cancer." Los Angeles, CA. March 28, 2020.
- Targeted Oncology: "Case based peer perspectives in prostate cancer." Virtual Meeting. May 7, 2020.
- Peerview Live CME: "How I think, How I treat – Learning to navigate the modern prostate cancer landscape." Virtual Meeting. June 9, 2020.
- Medscape Oncology CME: "Managing a patient with BCG-Unresponsive non-muscle-invasive bladder cancer." Virtual Meeting. June 10, 2020.
- West Coast Bayer Community Advisory Board: "Understanding the perceptions and practices shaping community oncologists' use of radium-223 dichloride." Virtual Meeting. June 18, 2020.
- Advanced Accelerator Applications Advanced Prostate Cancer Virtual Advisory Board: "Harnessing phenotypes in precision medicine and advanced prostate cancer." Virtual Meeting. June 19, 2020.
- Advanced Accelerator Applications Advanced Prostate Cancer Virtual Advisory Board: "Overview of targeted radioligand therapy and ^{177}Lu-PSMA-617 clinical trials." Virtual Meeting. June 19, 2020.
- **Section of Hematology/Oncology Special Seminar: "The future of advanced prostate cancer – curing patients with genotypic and phenotypic precision." University of Chicago by Virtual Meeting. July 17, 2020.**
- 2020 UroGPO Virtual Uro-Onc Symposium – Implications for Independent Urologists: "2020 Prostate cancer updates." Virtual Meeting. July 24, 2020.
- American Urological Association Summer Course Webinar Series - What's new in the management of hormone naïve and castrate resistant prostate cancer: "Metastatic castration-resistant prostate cancer." Virtual Meeting. August 25, 2020.
- Curio Science – Opinions in Prostate Cancer: "Metastatic castration-sensitive prostate cancer: Current treatment landscape and use of PARP inhibitors." Virtual Meeting. August 25, 2020.
- Prostate Cancer Academy: "The evolving role of novel hormonal therapy agents in advanced prostate cancer." Atlanta, GA by Virtual Meeting. October 3, 2020.
- Prostate Cancer Academy: "Optimizing the use of chemotherapy and introducing radiopharmaceuticals into our treatment paradigm for advanced prostate cancer." Atlanta, GA by Virtual Meeting. October 3, 2020.
- Curio Science – Opinions in Prostate Cancer: "Metastatic castration-sensitive prostate cancer: Current treatment landscape and use of PARP inhibitors." Dallas, TX by Virtual Meeting. October 27, 2020.
- Bayer Advisory Board: "Current approaches to managing metastatic castration-sensitive prostate cancer." Virtual Meeting. October 29, 2020.
- GU Connect Prostate Cancer Virtual MasterClass: "Non metastatic castration resistant prostate cancer." Plenary session, Virtual Meeting. November 7, 2020.

- GU Connect Prostate Cancer Virtual MasterClass: "A case-based journey through the treatment of castration-sensitive and castration-resistant prostate cancer." Virtual Meeting. November 7, 2020.
- GU Connect Prostate Cancer Virtual MasterClass: "Delivering integrated care with a multidisciplinary team – from theory to reality and the future vision." Virtual Meeting. November 7, 2020.
- Exelixis Prostate Cancer Virtual Advisory Board: "Prostate cancer current and evolving treatment landscape and practice patterns." Virtual Meeting. December 1, 2020.
- **21st Annual Meeting of the Society of Urologic Oncology: "Evaluating novel therapies and strategies – A look at the changing treatment landscape for metastatic castration-resistant prostate cancer an implications for patient care." Dallas, TX by Virtual Meeting. December 4, 2020**
- Curio Science – Opinions in Bladder Cancer: "Treatment of metastatic urothelial cancer in the post-platinum, post-immunotherapy setting." Atlanta, GA by Virtual Meeting. December 8, 2020.
- Taiwan Urological Association: "Positioning radium-223 in the metastatic castration-resistant prostate cancer treatment paradigm." Taipei, Taiwan. December 22, 2020.
- 2021 UroGPO Virtual Uro-Onc Symposium – Implications for Independent Urologists: "2021 Prostate cancer updates." Virtual Meeting. March 25, 2021.
- Targeted Oncology and HRA: "Case-based perspectives on prostate cancer." Portland, OR. March 25, 2021.
- Rocky Mountain Urological Society – Peerview Live CME: "Understanding the evolving treatment landscape in prostate cancer – How to leverage the latest advances and strategies." Denver, CO. April 9, 2021.
- IntrinsiQ – Emerging Perspectives in Prostate Cancer Focus Group: "M0 castration-resistant prostate cancer." Virtual Meeting. April 10, 2021.
- Mid Atlantic American Urological Association Mondays – Peerview Live CME: "Understanding the evolving treatment landscape in prostate cancer – How to leverage the latest advances and strategies." Virtual Meeting. April 12, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post platinum or post immunotherapy treatment for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for San Francisco, Los Angeles, and Palm Desert, CA. April 22, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Subsequent therapy for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for San Francisco, Los Angeles, and Palm Desert, CA. April 22, 2021.
- Targeted Oncology and HRA: "Case-based round table meeting on prostate cancer." Virtual Meeting, Northwest United States. April 29, 2021.
- IntrinsiQ – Emerging Perspectives in Prostate Cancer Focus Group: "M0 castration-resistant prostate cancer." Virtual Meeting. May 1, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Subsequent therapy for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for Kentucky and Tennessee. May 25, 2021.
- **Education Session Genitourinary Cancer – Kidney and Bladder: "Optimizing Urothelial Cancer Management From Organ-Confined to Metastastic Disease." 2021 American Society of Clinical Oncology Annual Virtual Meeting. Chicago, IL. June 4, 2021.**
- **Translational Medicine Speaker Series – Montana WWAMI Program: "Forward and reverse translation in oncology: Lessons learned from a career in prostate cancer." Montana State University, Bozeman, MT. June 11, 2021.**

- Merck Global Prostate Cancer Post-ASCO Expert Input Forum: "ASCO and GU ASCO 2021 key updates – PSMA theranostics." Virtual Meeting. June 24, 2021.
- Amgen Incorporated Monthly Grand Rounds: "That's hot! Inflaming prostate cancer." Virtual Grand Rounds Meeting. June 24, 2021.
- Genitourinary Cancer Virtual Symposium – Urothelial cancer: "Real world clinical outcomes of FGFR targeted treatment in metastatic urothelial carcinoma." Taiwan Urological Association, Virtual Meeting, Taiwan. July 24, 2021.
- Advanced Accelerator Applications: "Precision medicine in advanced prostate cancer: A phenotypic approach." Advanced Prostate Cancer Virtual Advisory Board. August 13, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post platinum or post immunotherapy treatment for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for Iowa and Minnesota. September 7, 2021.
- **American Urological Association 2021 - What's new in the management of hormone naïve and castrate resistant prostate cancer: "Metastatic castration-resistant prostate cancer." Virtual Meeting. September 12, 2021.**
- **American Urological Association 2021 – Live from AUA 2021: "Highlights in advanced prostate cancer." Virtual Meeting. September 12, 2021.**
- Bayer United States Medical Affairs Prostate Cancer Virtual Advisory Board: "Optimizing prostate cancer diagnostics – biomarker testing." Virtual Meeting. September 28, 2021.
- Onclive Institutional Perspectives in Cancer: Renal Cell Carcinoma and Bladder Cancer: "Second and later-line treatment of metastatic urothelial carcinoma." Virtual Meeting. September 30, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post platinum or post immunotherapy treatment and adverse events for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for Denver, CO. October 5, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post platinum or post immunotherapy treatment, subsequent therapy, and adverse events for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for, California. October 27, 2021.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post platinum or post immunotherapy treatment, subsequent therapy, and adverse events for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for, Portland, OR. November 18, 2021.
- 29th Annual Perspectives in Urology - Point Counterpoint: "PSMA Theranostics – ^{177}Lu-PSMA-617 recent data and considerations." Coronado Island, San Diego, CA. November 20, 2021.
- 25th Annual Southwest Prostate Cancer Symposium: "Immunotherapy in metastatic prostate cancer." Scottsdale, AZ. December 11, 2021.
- Oncternal Therapeutics R&D Day: "Metastatic castration-resistant prostate cancer: Present and Future." Virtual Meeting to San Diego, CA. January 25, 2022.
- **2022 Genitourinary Cancers Symposium: Primary Track – Urothelial Carcinoma: "Demystifying next-generation sequencing in urothelial carcinoma: A case-based approach." San Francisco, CA. February 18, 2022.**
- Bayer ARASENS Data Advisory Board: "Current approaches to managing metastatic hormone-sensitive prostate cancer and ARASENS data and planning." Seattle, WA. March 12, 2022.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post platinum or post immunotherapy treatment, subsequent therapy, and adverse events for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for Pacific Northwest. March 17, 2022.

- SWOG Spring GU Committee Meeting: "SWOG 2210: Targeted neoadjuvant treatment for patients with localized prostate cancer and germline DNA repair deficiency." Seattle, WA. April 9, 2022.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Adjuvant, front-line, post platinum or post immunotherapy, and subsequent therapy for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for Portland, OR. May 26, 2022.
- Prostate Cancer Academy: "ASCO-GU/AUA/ASCO: Advanced prostate cancer highlights." Chicago, IL. June 17, 2022.
- Prostate Cancer Academy: "Metastatic hormone sensitive prostate cancer: Is monotherapy still an option? – Case studies." Chicago, IL. June 17, 2022.
- Prostate Cancer Academy: "Beyond first-line novel hormonal therapy: considerations for optimizing treatment sequence." Chicago, IL. June 17, 2022.
- ASCO Direct Highlights: 2022 Official Annual Meeting Review: "Prostate cancer." Seattle, WA. June 18, 2022.
- IntrinsiQ – Virtual Emerging Perspectives in Metastatic Hormone Sensitive Prostate Cancer Focus Group: "Metastatic hormone sensitive prostate cancer." Virtual Meeting. June 25, 2022.
- ASCO Direct Highlights: 2022 Official Annual Meeting Review: "Prostate cancer." Las Vegas, NV. July 17, 2022.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post-platinum or post immunotherapy, and subsequent therapy for locally advanced/metastatic urothelial carcinoma." San Francisco, CA. July 20, 2022.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post-platinum or post immunotherapy, and subsequent therapy for locally advanced/metastatic urothelial carcinoma." Las Vegas, NV. July 28, 2022.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Adjuvant therapy for muscle-invasive urothelial cancer and front-line therapy for locally advanced/metastatic urothelial carcinoma." San Diego, CA. August 11, 2022.
- IntrinsiQ – Virtual Emerging Perspectives in Metastatic Hormone Sensitive Prostate Cancer Focus Group: "Metastatic hormone sensitive prostate cancer." Virtual Meeting. September 17, 2022.
- Targeted Oncology and HRA - Case-Based Round Table Meetings: "Later line therapy for metastastic castration-resistant prostate cancer." Virtual Meeting for Arizona. September 19, 2022.
- IntrinsiQ – Virtual Challenging Cases: "Treatment of metastatic urothelial carcinoma." Virtual Meeting. September 17, 2022.
- Florida Cancer Specialists Retreat with Dr. Neil Love: "Oprimal integration of antibody drug conjugates and targeted treatment in metastatic urothelial bladder cancer." Orlando, FL. October 22, 2022.
- Merck, Sharpe, and Dohme Advisory Meeting: "Neuroendocrine determination in prostate cancer." Virtual meeting. November 14, 2022.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post-platinum or post immunotherapy, and subsequent therapy for locally advanced/metastatic urothelial carcinoma." San Antonio, TX. November 17, 2022.
- Targeted Oncology and HRA - Case-Based Round Table Meetings: "Therapeutic sequencing for metastastic castration-resistant prostate cancer." Virtual Meeting for California, Oregon & Washington. November 22, 2022.

- IntrinsiQ – Virtual Challenging Cases: "Treatment of metastatic urothelial carcinoma." Virtual Meeting. December 13, 2022.
- Physicians' Education Resource (PER) CME: "Current treatment landscape for metastatic castration-resistant prostate cancer: Current paradigms and unmet needs." Why is PSMA so effective? To Affinity and Beyond. San Francisco, CA. February 15, 2023.
- Curio Science Community Opinions – Opinions in Bladder Cancer, An Interactive Local Workshop: "Post-platinum or post immunotherapy, and subsequent therapy for locally advanced/metastatic urothelial carcinoma." San Antonio, TX. April 11, 2023.
- **American Urological Association 2023 Plenary Session – Treatment intensification for newly diagnosed metastatic castration-sensitive prostate cancer: "Triplet therapy debate in metastatic castration-sensitive prostate cancer treatment intensification – the demographics." Chicago, IL. April 28, 2023.**
- **American Urological Association 2023 Plenary Session – Crossfire controversies in Urology: Impact of PSMA-PET on treatment decision-making: "Metastasis directed therapy in prostate cancer." Chicago, IL. April 28, 2023.**
- Curio Science Local Workshop – Opinions in Advanced Bladder Cancer, An Interactive Local Workshop: "Post-platinum or post immunotherapy, and subsequent therapy for locally advanced/metastatic urothelial carcinoma." Virtual Meeting for Southwest United States. May 16, 2023.
- Prostate Cancer Clinical Trials Consortium Scientific Oversight Committee Meeting: "ONCT-534 preclinical and early clinical development." Chicago, IL. June 2, 2023.
- Physicians' Education Resource (PER) Live Hot Seat – Maximizing PARP inhibitors in patients with castration-resistant prostate cancer: "Review of safety and adverse event management of PARP inhibitors." Chicago, IL. June 4, 2023.
- IntrinsiQ – Virtual Challenging Cases in Oncology: "Genitourinary Cancer." Virtual Meeting. June 17, 2023.
- Curio Science Local Workshop – Opinions in Advanced Bladder Cancer, An Interactive Local Workshop: "Adjuvant immunotherapy for muscle invasive urothelial carcinoma and first-line, second-line therapy and beyond for locally advanced/metastatic urothelial carcinoma." Sacramento, CA. June 20, 2023.
- IntrinsiQ – Virtual Challenging Cases in Oncology: "Metastatic Urothelial Cancer." Virtual Meeting. June 27, 2023.
- IntrinsiQ – Virtual Challenging Cases in Oncology: "Renal Cell Carcinoma." Virtual Meeting. June 29, 2023.
- IntrinsiQ – Virtual Challenging Cases in Oncology: "Renal Cell Carcinoma." Virtual Meeting. July 26, 2023.
- 23rd Future Directions in Urology Symposium: "Future directions in advanced bladder cancer." Colorado Springs, CO. August 13, 2023.
- 23rd Future Directions in Urology Symposium: "Choosing metastatic castration-resistant prostate cancer treatment pathways depending on prior treatment." Colorado Springs, CO. August 14, 2023.
- IntrinsiQ – Virtual Challenging Cases in Oncology: "Metastatic Urothelial Cancer." Virtual Meeting. September 12, 2023.
- Curio Science Local Workshop – Opinions in Advanced Bladder Cancer, An Interactive Local Workshop: "Adjuvant immunotherapy for muscle invasive urothelial carcinoma and first-line therapy for locally advanced/metastatic urothelial carcinoma." Irvine, CA. September 21, 2023.
- 18th Annual Meeting of the National Alliance of State Prostate Cancer Coalitions: "Antibody drug conjugates – The future of prostate cancer is now!" Washington, DC. October 7, 2023.

September 15, 2023

Michael Schweizer, MD

1. [redacted]

2. Education:

2004 – 2008	*Temple University School of Medicine*, Philadelphia, PA Doctor of Medicine, May 2008
1999 – 2004	*University of Delaware*, Newark, DE Bachelor of Chemical Engineering, May 2004

3. Postgraduate Training:

2011 – 2014	Medical Oncology Fellowship, *The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University*, Baltimore, MD
2008 – 2011	Internal Medicine Residency, *The University of Chicago*, Chicago, IL

4. Faculty Positions Held:

2014 – Present	Assistant Professor Internal Medicine, Division of Medical Oncology, *The University of Washington*, Seattle, WA
2014 – 2019	Assistant Professor, Clinical Research Division, *Fred Hutchinson Cancer Center*, Seattle, WA
2019 – Present	Associate Professor, Clinical Research Division, *Fred Hutchinson Cancer Center*, Seattle, WA
2020 – Present	Associate Professor Internal Medicine, Division of Medical Oncology, *The University of Washington*, Seattle, WA

5. Hospital Positions Held:

2014 – Present	Attending Physician, *University of Washington Medical Center*, Seattle, WA
2014 – Present	Attending Physician, *Fred Hutchinson Cancer Center*, Seattle, WA

6. Honors:

2015	Department of Defense Physician Research Training Award
2015	Prostate Cancer Foundation Young Investigator Award
2014 – 2020	NIH Loan Repayment Program Award Recipient
2013-2014	Chief Fellow, Medical Oncology, Johns Hopkins University
Inducted 2008	Alpha Omega Alpha Medical Honor Society
Inducted 2003	OXE Chemical Engineering Honor Society
1999 – 2004	The University of Delaware Dean's List

7. Board Certification:

2013 – 2023	Medical Oncology Board Certification
2011 – 2021	Internal Medicine Board Certification

8. Current License(s) to Practice:

2014 – present	Washington State Medical License: MD60473280

9. Professional Organizations:

2012 – present	American Society of Clinical Oncology, Member ID: 166489
2012 – 2013	American Association for Cancer Research, Member ID: 274966
2014 – Present	Southwest Oncology Group, Genitourinary Oncology Committee

10. Teaching Responsibilities:

2015 – present	Precept oncology fellows in clinic approximately one ½ day per week and attend on the inpatient oncology teaching service
2015 – present	Lecture every 6-12 months at the Prostate Cancer SPORE Lecture Series
2016 – 2021	Mentor to Laura Graham MD, Currently faculty in the Division of Oncology at the University of Colorado
2016 – 2019	Small group leader, UW School of Medicine: Blood and Cancer Course
2016 – present	MED 505: First year medical student preceptorship elective (2-4 students per year)
2016 – 2020	Precept urology residents in clinic approximately one ½ day per month
2016 – present	Lecture every 12 months at Department of Medicine Core Teaching Conference Series
2016 – present	Lecture every 12 months at Fellow's Lecture Series

11. Editorial Responsibilities:

2014 – Present	Editorial Board: *Medical Oncology*
2020 – Present	Associate Editor: *Frontiers in Oncology*
2022 – Present	Editorial Board: *The Prostate*

12. Special National Responsibilities:

2014 – 2018, 2020	Grant and Funding Organization Reviews: Department of Defense Prostate Cancer Research Program

13. Special Local Responsibilities: University and hospital committees.

2015 – 2019	SPORE Pilot Grant Review
2017 – present	Member, UW/FHCRC Cancer Consortium Scientific Review Committee

2017 – present	Leader, Fred Hutchinson Cancer Center, Prostate Cancer Clinical Pathway Team
2017 – 2022	Member, Scientific Review Committee, Fred Hutch / University of Washington Cancer Consortium
2022 – present	Chair, Scientific Review Committee, Fred Hutch / University of Washington Cancer Consortium
2022 – present	Clinical Research Director, Genitourinary Oncology, Fred Hutch / University of Washington Cancer Consortium

14. Research Support

Title: A Phase 1 Study of JNJ-78278343, a T-Cell-Redirecting Agent Targeting Human Kallikrein 2 (KLK2), for Advanced Prostate Cancer
Major Goals: Determine recommended Phase 2 dose(s) (RP2Ds) of JNJ-78278343 and determine the safety at the RP2D(s)
Status of Support: Active
Project Number: 78278343PCR1001
Role: Site PI
Source of Support: Janssen Research & Development, LLC
Project/Proposal Start and End Date: N/A
Total Award Amount: N/A

Title: A Phase 1 Study of EP31670, a Dual BET and CBP/p300 Inhibitor in Patients with Targeted Advanced Solid Tumors
Major Goals: To assess safety and determine the maximum tolerated dose of EP31670 administered orally once a day for 7 consecutive days followed by 14 days of rest in patients with targeted advanced solid tumors.
Status of Support: Active
Project Number: EP31670-01 (A1)
Role: Site PI
Source of Support: EPIGENETIX INC.
Project/Proposal Start and End Date: 10/18/2022 - 5/31/2027
Total Award Amount: [redacted]

Title: A Phase 1/2, Multicenter, Open-label, Dose-escalation, and Dose-expansion Study to Evaluate the Safety, Pharmacokinetics, and Anti-tumor Activity of ARX517, with Randomized Comparison to Investigator s Choice of Treatment, in Subjects with Metastatic Castration-resistant Prostate Cancer who are Resistant or Refractory to Prior Standard Therapies
Major Goals: To assess the safety and tolerability of ARX517, and To determine the maximum tolerated dose (MTD) and/or establish recommended phase 2 doses (RP2D[s])
Status of Support: Active
Project Number: ARX517-2011
Role: Site PI
Source of Support: AMBRX INC.
Project/Proposal Start and End Date: 8/18/2022 - 5/31/2026
Total Award Amount: [redacted]

Title: A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Plus ADT Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) (KEYNOTE-991)

Major Goals: The major goal is to evaluate Pembrolizumab (MK-3475) Plus Enzalutamide Plus ADT Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer.
Status of Support: Active
Project Number: MK-3475-991-0258
Role: Site PI
Source of Support: Merck Sharp & Dohme Corp.
Project/Proposal Start and End Date: 03/23/2020 – 02/28/2025
Total Award Amount: [redacted]

Title: Durvalumab (MEDI4736) and Olaparib (AZD2281) for treatment of biochemically recurrent prostate cancer in men predicted to have a high neoantigen load: a pilot study
Major Goals: The major goal of this study is to assess clinical activity of durvalumab and olaparib in men with biochemically recurrent prostate cancer predicted to have a high neoantigen load.
Status of Support: Active
Project Number: ESR-19-14545
Role: Overall PI
Source of Support: AstraZeneca Pharmaceuticals, LP
Project/Proposal Start and End Date: 05/15/2020 – 02/28/2025
Total Award Amount: [redacted]

Title: CYCLONE 1: A Phase 2 Study of Abemaciclib in Metastatic Castration-Resistant Prostate Cancer Patients Previously Treated with a Novel Hormonal Agent and Taxane-based Chemotherapy
Major Goals: The major goal of this study is to characterize the efficacy of abermaciclib monotherapy.
Status of Support: Active
Project Number: 13Y-MC-JPCY
Role: Site PI
Source of Support: ELI LILLY AND COMPANY
Project/Proposal Start and End Date: 09/24/2020 – 07/31/2025
Total Award Amount: [redacted]

Title: Detection of prostate cancer in archived blocks of benign biopsies using open-top light-sheet microscopy
Major Goals: The major goal of this study is to screen and match benign biopsies with no diagnosis of prostate cancer, matched on age and PSA.
Status of Support: Active
Project Number: 1R3CA250885-01A1
Role: Project PI
Source of Support: LIGHTSPEED MICROSCOPY LLC
Project/Proposal Start and End Date: 06/21/2021 – 03/31/2026
Total Award Amount: [redacted]

Title: REASSURE: Radium-223 alpha Emitter Agent in non-intervention Safety Study in mCRPC popUlation for long-teRm Evaluation
Major Goals: The major goal of this project is to observe and assess the incidence of second primary malignancies among patients with metastatic Castration Resistant Prostate Cancer (mCRPC) receiving Radium-223 in routine clinical practice.
Status of Support: Active
Project Number: 16913
Role: Site PI
Source of Support: BAYER HEALTHCARE PHARMACEUTICALS, INC.
Project/Proposal Start and End Date: 03/16/2016 – 02/29/2024
Total Award Amount: [redacted]

Title: A Phase I Dose Escalation and Expanded Cohort Study of PF-06821497 in the Treatment of Adult Patients with Relapsed/Refractory Small Cell Lung Cancer (SCLC), Castration Resistant Prostate Cancer (CRPC) and Follicular Lymphoma (FL)
Major Goals: The major goal of this project is to assess safety and tolerability at increasing dose levels of PF-06821497 in successive cohorts of patients with SCLC, CRPC, DLBCL and FL in order to establish a safe dose or maximum tolerated dose (MTD).
Status of Support: Active
Project Number: PF-06821497
Role: Site PI
Source of Support: PFIZER, INC.
Project/Proposal Start and End Date: 06/28/2018 – 02/28/2024
Total Award Amount: [redacted]

Title: A Phase 1 Study Exploring the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of INCB099280 in Participants With Select Advanced Solid Tumors
Major Goals: The major goal of this project is to determine the safety, tolerability, PAD and/or MTD of INCBO99280. To evaluate the PK of INCB099280 in participants with advanced solid tumors.
Status of Support: Active
Project Number: INCB 99280-112
Role: Site PI
Source of Support: INCYTE CORPORATION
Project/Proposal Start and End Date: 08/10/2020 – 08/31/2025
Total Award Amount: [redacted]

Title: PSMAfore: A phase III, Open-label, Multi-Center, Randomized Study Comparing 177Lu-PSMA-617 vs. a Change of androgen receptor-directed therapy in the Treatment of Taxane Naïve Men with Progressive Metastatic Castrate Resistant Prostate Cancer
Major Goals: The major goal of this study is to evaluate whether treatment with 177Lu-PSMA-617 improves the time to radiographic progression by PCWG3-modified RECIST v1.1 or death in participants with progressive PSMA-positive mCRPC compared to participants treated with ARDT.
Status of Support: Active
Project Number: AAA617B12302
Role: Site PI
Source of Support: NOVARTIS PHARMACEUTICALS CORPORATION
Project/Proposal Start and End Date: 01/25/2021 – 02/11/2026
Total Award Amount: [redacted]

Title: A Phase 2 Multiple-Dose, Multiple-Arm, Parallel Assignment Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of XmAb20717 Alone or in Combination with Chemotherapy or Targeted Therapies in Selected Subjects with Metastatic Castration-Resistant Prostate Cancer
Major Goals: The major goal of this study is to determine the safety and tolerability of XmAb20717 as monotherapy and in combination with other anticancer therapies in subjects with metastatic castration-resistant prostate cancer (mCRPC) who have progressed after treatment with at least 2 prior lines of anticancer therapy.
Status of Support: Active
Project Number: XmAb20717
Role: Site PI
Source of Support: XENCOR, INC.
Project/Proposal Start and End Date: 07/28/2021 – 08/31/2026
Total Award Amount: [redacted]

Title: Randomized Phase 2b Study of ZEN003694 in Combination with Enzalutamide versus Enzalutamide Monotherapy in Patients with Metastatic Castration-Resistant Prostate Cancer

Major Goals: To assess the effect of ZEN003694 in combination with enzalutamide versus single agent enzalutamide on radiographic progression-free survival (rPFS) in patients with metastatic castration-resistant prostate cancer (mCPRC), as assessed by blinded independent central review (BICR) in patients with poor response to prior abiraterone
Status of Support: Active
Project Number: ZEN003694
Role: Site PI
Source of Support: Zenith Epigenetics Ltd.
Project/Proposal Start and End Date: 10/13/2021 – 08/31/2026
Total Award Amount: [redacted]

Title: Olaparib in Prostate Cancer Patients With Evidence of Homologous Recombination Deficiency As Assessed Using an Integrated Genomic Signature
Major Goals: Determine the percent of patients achieving a ≥50% reduction in PSA (PSA50 response) following at least 12 weeks of treatment with olaparib 300mg twice daily in men with metastatic castration-resistant prostate cancer (mCRPC) who are iHRD+ and who have progressed on a second-generation hormonal agent (e.g. abiraterone or enzalutamide).
Status of Support: Active
Project Number: 20693 IISR
Role: Site PI
Source of Support: ASTRAZENECA PHARMACEUTICALS, LP
Project/Proposal Start and End Date: 8/17/21 – 4/30/26
Total Award Amount: [redacted]

Title: A Randomized Phase II Study Comparing Sequential High dose Testosterone and Enzalutamide to Enzalutamide alone in Asymptomatic Men with Castration Resistant Metastatic Prostate Cancer: The STEP-UP Trial (Sequential Testosterone and Enzalutamide Prevents Unfavorable Progression)
Major Goals: The primary objective of the study is to compare clinical/radiographic progression-free survival (crPFS) between standard dose Enza (Arm A) to sequential testosterone Enza (STE) (Arm B) and compare Enza (Arm A) to variable STE (Arm C) in men with mCRPC, who have progressed on abiraterone.
Status of Support: Active
Project Number: J2060sIRB
Role: Site PI
Source of Support: DOD/Johns Hopkins University
Project/Proposal Start and End Date: 8/1/22 – 3/31/24
Total Award Amount: [redacted]

Title: Pacific NW Prostate Cancer SPORE Project 4: SPECTRA: SupraPhysiological androgen to Enhance Chemotherapy TReatment Activity
Major Goals: The primary objective is to determine the PSA_{50} response (i.e. ≥50% decline in PSA from baseline) rate following treatment with combination BAT and genotoxic chemotherapy.
Status of Support: Pending
Project Number: TBD
Name of PD/PI: Michael Schweizer
Source of Support: Fred Hutch Cancer Center
Project/Proposal Start and End Date: 9/1/2023 - 8/31/2028
Total Award Amount: TBD

Title: Genomic Biomarker-Selected Umbrella Neoadjuvant Study (GUNS) for high Risk Localized Prostate Cancer
Major Goals: To determine whether complete pathological responses can be improved through genomic biomarker-directed combinatorial regimens compared to standard of care.

Status of Support: Pending
Project Number: TBD
Name of PD/PI: Michael Schweizer
Source of Support: University of British Columbia/Janssen LP
Project/Proposal Start and End Date: TBD
Total Award Amount: TBD

Title: Vorinostat to Augment Response to ^{177}Lutetium-PSMA-617 in the treatment of patients with PSMA-low metastatic castration-resistant prostate cancer
Major Goals: the primary objective is to determine the effectiveness of the histone deacetylase inhibitor (HDACi) vorinostat in increasing PSMA expression from PSMA-low (defined as PSMA SUV_{mean} <10) to PSMA-high (defined as PSMA SUV_{mean} ≥10) as determined by ^{68}Ga-PSMA-11 PET in patients with PSMA-low mCRPC.
Status of Support: Pending
Role: Overall PI
Source of Support: NOVARTIS PHARMACEUTICALS CORPORATION
Project/Proposal Start and End Date: TBD
Total Award Amount: TBD

Title: Enhancing PSMA-Directed Therapies Through Epigenetic Priming
Major Goals: AIM 1: Determine the efficacy of epigenetic priming on PSMA expression in mCRPC patients. AIM 2: Refine pharmacological approaches to increase PSMA expression in PC. AIM 3: Define molecular alterations associated with ^{177}Lu-PSMA-617 resistance.
Status of Support: Pending
Role: Overall PI
Source of Support: National Institutes of Health R01 Grant
Project/Proposal Start and End Date: TBD
Total Award Amount: TBD

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92. **Schweizer, M.T.**, Huang, P., Kattan, M.W., Kibel, A.S., de Wit, R., Sternberg, C.N., Epstein, J.I. & Eisenberger, M.A. Adjuvant leuprolide with or without docetaxel in patients with high-risk prostate cancer after radical prostatectomy (TAX-3501): important lessons for future trials. Cancer 119, 3610-3618 (2013). [original work]

93. **Schweizer, M.T.** & Carducci, M.A. From bevacizumab to tasquinimod: angiogenesis as a therapeutic target in prostate cancer. Cancer journal (Sudbury, Mass.) 19, 99-106 (2013). [review]

94. **Schweizer, M.T.** & Antonarakis, E.S. Abiraterone acetate: a hat trick of clinical benefits. The Lancet. Oncology 13, 1173-1174 (2012). [review]

95. **Schweizer, M.T.** & Antonarakis, E.S. Abiraterone and other novel androgen-directed strategies for the treatment of prostate cancer: a new era of hormonal therapies is born. Therapeutic advances in urology 4, 167-178 (2012). [review]

96. **Schweizer, M.T.**, Mehta, R., Salgia, R. & Villaflor, V.M. Takotsubo cardiomyopathy in a patient with squamous cell esophageal carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 29, e598-600 (2011). [case report]

Book chapters.

1. **Schweizer MT**, Montgomery RB. Sequencing Therapies in Metastatic Castration Resistant Prostate Cancer. In: Balaji K, ed. Castration Resistant Prostate Cancer: Springer Science; 2015.

Published books, videos, software, etc.

N/A

Other publications (e.g., in non-refereed journals and letters to the editor).

N/A

Abstracts

1. **Schweizer, M.T.**, Penkov, K.D., Tolcher, A.W., Choudhury, A.D., Doronin, V., Aljumaily, R., Calvo, E., Frank, R.C., Hamm, J.T., Moreno Garcia, V., Vorobyev, V., Billotte, S., Bowler, T., Chen, J., Lin, T., Liu, L., Maity, A., Sharma, S. & Johnson, M.L. Phase I trial of PF-06821497, a potent and selective inhibitor of enhancer of zeste homolog 2 (EZH2), in follicular lymphoma (FL), small cell lung cancer (SCLC) and castration-resistant prostate cancer (CRPC). in *ESMO Congress*, Paris, France.

2. **Schweizer MT**, Gulati R, Yezefski T, Cheng HH, Sievers C, Dumpit R, Alexander K, McDonald N, Lai M, Nega K, Hammond J, Grivas P, Hsieh A, Montgomery B, Nelson PS, Yu EY. Bipolar Androgen Therapy (BAT) plus Olaparib in Men with Metastatic Castration-resistant Prostate Cancer (mCRPC). Poster presented at: 2021 ESMO Annual Meeting. Virtual.

3. **Schweizer MT**, True L, Ellis W, Schade G, Montgomery RB, Goyal S, Nega K, Pienta K, Nelson P, Lin D, Wright J. Resetting the Active Surveillance Clock: Apalutamide in Lower Risk Prostate Cancer. Oral Presentation at: 2020 Society of Urologic Oncology Annual Meeting. Virtual

4. Graham L, Reder N, Gulati R, Grivas P, Wright J, Yu E, Hou W, Nega K, Yezefski T, Montgomery RB, Mostaghel E, Ellis W, True L, Lin DW, Nelson P, **Schweizer MT**. Targeting Backdoor Androgen Synthesis Through AKR1C3 Inhibition: A Presurgical Hormonal Ablative Neoadjuvant Trial in High Risk Localized Prostate Cancer (PC). Poster presented at: 2019 ASCO Annual Meeting, Chicago, IL.

5. **Schweizer MT**, Haugk K, Cheng H, Dumpit R, Nelson PS, Montgomery RB, Plymate SR, Yu EY. Challenges in Enrolling to Metastatic Castration-Resistant Prostate Cancer (mCRPC) Studies that Require Androgen Receptor Splice Variant (AR-V) Positivity. Poster presented at: 2017 Genitourinary Cancers Symposium, Orlando, FL

6. **Schweizer MT**, Wang H, Luber B, et al. Bipolar Androgen Therapy (BAT) in Men with Hormone Sensitive (HS) Prostate Cancer (PC). Poster presented at: 2016 Genitourinary Cancers Symposium, San Francisco, CA.

7. **Schweizer MT**, Antonarakis ES, Wang H, et al. A Pilot Study of Parenteral Testosterone and Oral Etoposide in Men with Castrate-Resistant Prostate Cancer. Poster presented at: 2014 ASCO Annual Meeting, Chicago, IL.

8. **Schweizer MT**, Antonarakis ES, Wang H, et al. A Pilot Study of Parenteral Testosterone and Oral Etoposide in Men with Castrate-Resistant Prostate Cancer. Poster presented at: 2014 ASCO Genitourinary Cancers Symposium, San Francisco, CA.

9. **Schweizer MT**, Zhou XC, Wang H, et al. The Effect of Prior Abiraterone Treatment on Subsequent Response to Docetaxel in Men with Metastatic Castrate-Resistant Prostate Cancer (CRPC). Poster presented at: 2014 ASCO Genitourinary Cancers Symposium, San Francisco, CA.

10. **Schweizer MT**, Huang P, Sternberg CN, De Wit R, Ecstein-Fraisse EB, Kattan MW, Kibel AS, Eisenberger, MA. Prospective evaluation of testosterone (T) recovery and PSA relapse following 18 months of androgen deprivation (ADT) after prostatectomy (RP): Results from the TAX-3501 trial. J Clin Oncol 31, 2013 (suppl; abstr 5023). Poster discussion presented at: 2013 ASCO Annual Meeting, Chicago, IL.

11. **Schweizer MT**, Bardia A, Blackford A, Lin J, Armstrong AJ, King A, Rudek MA, Yegnasubramanian A, Carducci MA. A Prostate Cancer Clinical Trials Consortium Trial of Disulfiram (D) in Men with Non-metastatic Recurrent Prostate Cancer (PCa). J Clin Oncol 31, 2013 (suppl 6; abstr 219). Poster presented at: 2013 ASCO Genitourinary Cancers Symposium, Orlando, FL.

12. **Schweizer MT**, Zhou XC, Wang H, Yang T, Shaukat F, Eisenberger MA, Antonarakis ES. Metastasis-Free Survival (MFS) is Associated with Overall Survival (OS) in Men with PSA-Recurrent Prostate Cancer Treated with Deferred Androgen Deprivation Therapy. J Clin Oncol 31, 2013 (suppl 6; abstr 109). Poster presented at: 2013 ASCO Genitourinary Cancers Symposium, Orlando, FL.

13. **Schweizer MT**, Zhang Y, Kunnavakkam R, Karrison R, Le Beau MM, Larson RA. Detection of combinations of cytogenetic abnormalities in chronic lymphocytic leukemia (CLL) by fluorescent in situ hybridization (FISH) probes. J Clin Oncol 28:15s, 2010 (suppl; abstr 6591). Poster presented at: 2010 ASCO Annual Meeting, Chicago, IL.

16. Other:

2022 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Prostate Cancer*, Seattle, WA. September, 2022.

2022 Speaker, 2022 ASCO Annual Meeting, *Innovative I mmune Approaches in Prostate Cancer: A Case-Based Review of CAR T, T cell Engagers, and Next-Generation Agents*, Chicago, IL. June 6, 2022

2021 Speaker, 21st Annual Pacific NW Prostate Cancer Conference, *Changing Landscape of Metastatic Prostate Cancer*, Virtual. October 2, 2021

2021 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Prostate Cancer*, Virtual. June, 2021.

2021 Speaker, Society for Immunotherapy of Cancer: Advances in Cancer Immunotherapy, *Immunotherapy for the Treatment of Genitourinary Malignancies*, Virtual. April 2, 2021.

2020 Speaker, Society of Urologic Oncology Annual Meeting, *Resetting the Active Surveillance Clock: Apalutamide in Lower Risk Prostate Cancer*, virtual meeting. December 3, 2020

2020 Speaker, Medscape CME*, Immune Checkpoint and PARP Inhibitors in Prostate Cancer*, virtual. December 2020

2020 Speaker, Opinions in Genitourinary Malignancies Global Summit, *Great Debates in GU Malignancies*, virtual. September 28, 2020

2020 Speaker, Opinions in Prostate Cancer: An Interactive Workshop, *Genomic Testing and Interpretation*, virtual. August 25, 2020

2020 Speaker, Community Opinions in Prostate Cancer, *Patient and Disease Characteristics that Influence Treatment Selection in mCSPC*, Seattle, WA. March 3, 2020

2019 Speaker, 26th Annual Prostate Cancer Foundation Scientific Retreat. *FGFR-inhibition in Double Negative Prostate Cancer: Rationale and Future Directions,* Carlsbad, CA. October 25, 2019

2019 Speaker, 5th Annual Men's Health Update. *Prostate Cancer: A Lifelong Disease*, Seattle, WA. August 23, 2019

2019 Speaker, Gordon's Research Conference: Hormone-dependent Cancers. *Targeting Prostate Cancer Drug Resistance*, Newry, ME. August 7, 2019

2019 Keynote Speaker, Brotman Baty Institute for Precision Medicine: Cell-free DNA Symposium, *Applications of cfDNA in Prostate Cancer*, Seattle, WA. April 17, 2019.

2019 Speaker, UWMC Chief of Medicine Conference, *Germ Cell Tumors/Testicular Cancer*, Seattle, WA. March 19, 2019

2019 Speaker, Selected Topics in Hematology / Oncology Fellow's Lecture Series, *Bladder Cancer*, Seattle, WA. March 15, 2019

2019 Speaker, Nuclear Medicine Topical Conference, *Prostate Cancer 101*, Seattle, WA. March 12, 2019.

2019 Speaker, Prostate Cancer SPORE Seminar, *Targeting Backdoor Androgen Synthesis vis AKR1C3 Inhibition,* Seattle, WA. February 28, 2019

2019 Speaker, Skagit Valley Hospital, *Emerging Therapies in Cancer: New Treatments for Prostate Cancer*, Mt Vernon, WA. February 27, 2019

2019 Speaker, VA Puget Sound Health Care System, *Oncologic Emergencies*, Seattle, WA. February 26, 2019.

2018 Speaker, Cancer Immunotherapy Trial Network Meeting, *CDK12 Mutation as a Biomarker for Response to Immune Checkpoint Blockade*, Washington, D.C. November 7, 2018.

2018 Speaker, Society for Immunotherapy of Cancer: Advances in Cancer Immunotherapy, *Immunotherapy for the Treatment of Genitourinary Malignancies*, Seattle, WA. November 3, 2018.

2018 Speaker, Fred Hutchinson Cancer Research Center Grand Rounds, *Targeting Prostate Cancer Drug Resistance*, Seattle, WA. October 2, 2018.

2018 Speaker, Society of Utah Medical Oncologists, *Urothelial Carcinoma: Updates and Future Directions*, Park City, UT. September 22, 2018.

2018 Speaker, Prostate Cancer SPORE Seminar, *PNW Prostate Cancer Clinical Trials Overview: UW/SCCA,* Seattle, WA. September 6, 2018

2018 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Systemic Therapy In The Treatment of Bladder Cancer*, Seattle, WA. September 15, 2018.

2018 Speaker, Fellow Research Flash Rounds, *Translational Prostate Cancer Research*, Seattle, WA. July 31, 2018.

2018 Speaker, University of Utah: Huntsman Cancer Institute Genitourinary Oncology Symposium, *MSI-high Prostate Cancer: Finding the Needle in the Haystack*, Salt Lake City UT. May 25, 2018

2018 Speaker, University of Utah: Huntsman Cancer Institute Translational Oncology Seminar, *High-dose Testosterone Therapy for Prostate Cancer: Biomarkers and Combination Strategies*, Salt Lake City UT. May 24, 2018.

2018 Speaker, Institute for Prostate Cancer Research Symposium, *Improving Survival with Combination Therapy*, Seattle, WA. April 28, 2018.

2018 Speaker, City of Hope: Special Lecture, *Prostate Cancer: Histologic Subtypes and Molecular Correlates*, Duarte, CA. January 18, 2018.

2017 Speaker, CCSG Retreat, *State of Research: Clinical Trials*, Seattle, WA. November 9, 2017.

2017 Speaker, Everett Clinic, *Evolving Options for GU Cancer*s, Everett, WA. November 6, 2017

2017 Speaker, Selected Topics in Hematology / Oncology Fellow's Lecture Series, *Systemic Therapy in the Treatment of Bladder Cancer*, Seattle, WA. October 20, 2017.

2017 Speaker, Prostate Cancer Clinical Trials Consortium, *High-dose Testosterone Plus PARP Inhibition in mCRPC*, teleconferenced nationally. August 29, 2017.

2017 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Systemic Therapy in The Treatment of Bladder Cancer*, Seattle, WA. September 25, 2017.

2017 Speaker, SWOG GU Organ Site Meeting: Prostate Organ Site, *Bipolar Androgen Therapy for Metastatic Castration-Resistant Prostate Cancer*, San Francisco, CA. April 28, 2017.

2017 Speaker, Prostate Cancer Clinical Trials Consortium, *Durvalumab in MSI-high CRPC*, teleconferenced nationally. April 20, 2017.

2017 Speaker, Institute for Prostate Cancer Research Symposium, *Liquid Tumor Biopsies to Guide Precision Medicine*. Seattle, WA. March 18, 2017.

2017 Speaker, Fred Hutchinson Cancer Research Center Grand Rounds, *High-dose Testosterone to Treat Prostate Cancer*, Seattle, WA. January 31, 2017.

2016 Speaker, Selected Topics in Hematology / Oncology Fellow's Lecture Series, *Systemic Therapy in the Treatment of Bladder Cancer*, Seattle, WA. December 30, 2016.

2016 Speaker, Department of Medicine Core Teaching Conference, *Prostate Cancer: Screening and Beyond*, Seattle, WA. October 17, 2016.

2016 Speaker, Prostate Cancer SPORE Seminar, *Immunotherapy in Hypermutated Prostate Cancers*, Seattle, WA. September 29, 2016.

2016 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Systemic Therapy in The Treatment of Bladder Cancer*, Seattle, WA. September 24, 2016.

2016 Speaker, Prostate Cancer SPORE Seminar, *A Phase I Study of Niclosamide in Combination with Enzalutamide in Men with Androgen Receptor Splice Variant Positive Castration- Resistant Prostate Cancer*, Seattle, WA. July 28, 2016.

2016 Speaker, Institute for Prostate Cancer Research Symposium, *Cancer Immunology 101,* Seattle, WA. April 30, 2016.

2015 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Systemic Therapy in The Treatment of Bladder Cancer*, Seattle, WA. September 27, 2015

2015 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Germ Cell Tumors/Testicular Cancer*, Seattle, WA. September 27, 2015

2015 Speaker, Coffey-Holden Prostate Cancer Academy Meeting, *Moving Chemotherapy Earlier in the Disease Process*, La Jolla, CA. June 26, 2015.

2015 Speaker, Institute for Prostate Cancer Research Symposium**,** *Testosterone Therapy: Science, Rationale and Caution*, Seattle, WA. April 11, 2015.

2015 Speaker, Prostate Cancer SPORE Seminar, *Old Drugs, New Tricks: Repurposing Approved Drugs to Treat Prostate Cancer*, Seattle, WA. February 5, 2015.

2014 Speaker, Annual Multi-Institutional Prostate Cancer Program Retreat, *A Pilot Study of Supraphysiologic Testosterone and Oral Etoposide in Men with Castrate-Resistant Prostate Cancer*, Fort Lauderdale, FL. March 17, 2014.