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University of Washington (UWash)

PRINCIPAL INVESTIGATOR: Heather Cheng, MD, PhD

CONTRACTING ORGANIZATION: University of Washington, Seattle, WA

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14. ABSTRACT Purpose: Participate as an active and productive member of the Prostate Cancer Clinical Trial Consortium (PCCTC) throughout the funding period. Scope: This is the annual report summarizing the site activities for the University of Washington (UWash) for the funding period 01Oct2019-30Sep2020. Major Progress: In the last year, UWash was the lead/co-lead site on 10 trials and completed accrual on 5 trials. Results: UWash accrued 28 patients to PCCTC trials. 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.					
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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 28 patients (goal 25) to PCCTC trials, 19 to therapeutic and 9 patients to non-therapeutic trials. See Appendix 1 for details.
- ii. 5 of 28 patients (actual 18%, goal >5%) accrued during this reporting period were members of disproportionately affected populations.
- iii. Site submitted the following LOIs (4) during the current report period: c19-244 (jointly with OHSU), c19-248, c20-258 & c20-259.
- iv. Site participated in 11 PCCTC trials: 2 trials initiated by other PCCTC sites, 4 initiated by UWash with another site, and 5 initiated by UWash.
- v. Site met requirements of timely submission of quality data.
- vi. Dr. Cheng is the Chairperson of the Germline Genetics Working Group, and Dr. Yu is a member of same. Drs. Cheng and Yu are members of the Recognizing/Tackling Disparities Working Group. Dr. Higano was a member of the Scientific Oversight Committee, and Chairperson of the Publications Committee until her retirement on 30Jun2020.
- vii. PCCTC meetings at GU ASCO, ASCO, and PCF were attended by Drs. Cheng, Yu, Schweizer and Higano. In addition, UWash was the presenting institution for the PCCTC PI call on 20Aug2020, with presentation by Dr. Alexandra Sokolova,

“PARPi and Immune Checkpoint Inhibitors for Biochemical Recurrent Prostate Cancer.”

- viii. Coordinator participates in site conference calls. PI and/or co-I and sub-investigators participate in all monthly PI conference calls.
- ix. Drs. Cheng, Yu and Higano attended the EAB meeting held on 31May2020 at virtual ASCO.
- x. Procedures are in place and 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, was nominated to chair the PCCTC Germline Genetics Working Group by Dr. Higano. She led the development and is the senior or co-senior author on three PCCTC-led papers on this topic, which have also fostered opportunities for other faculty to become more engaged and involved in prostate cancer genetics. Dr. Cheng's participation in the PCCTC helped accelerate her reputation as a recognized national expert in germline genetics in prostate cancer. As a result, she was invited to co-author a JNCCN paper with Drs. Mohler and Higano and was also a special invitee to the NCCN Prostate Guidelines committee for her expertise on genetics and genomics in prostate cancer. Dr. Cheng is also partnering with Dr. Channing Paller at Johns Hopkins, together with PCCTC, to lead the PROMISE prostate cancer genetics registry.

Dr. Schweizer is leading “A Phase II Trial of Durvalumab and Olaparib for treatment of biochemically-recurrent prostate cancer in men predicted to have a high neoantigen load” (LOI in process, presented by Dr. Alexandra Sokolova (UWash fellowship, joining faculty of OHSU) on 8/20/2020 at Monthly PI Call). The trial will also be conducted at DFCI (Dr. Berman). In addition, following the August PI call and discussion, Drs. Schweizer and Sokolova are in discussions with Dr. Karen Autio of MSKCC and PI of PCCTC trial c17-192 about collaborating with biospecimens on biomarker studies from respective studies.

Thus PCCTC participation has fostered both collaboration and academic growth for trainees and junior faculty at our institution.

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 have two annual meetings directed at men with prostate cancer:

The Institute for Prostate Cancer Research (IPCR) at UWash was co-founded by Dr. Celestia Higano and Dr. Paul Lange 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. Due to the COVID pandemic, the 9th annual meeting was cancelled.

The Pacific NW Prostate Cancer Symposium is a joint effort, initially between OHSU and UWash, that now includes University of British Columbia. This meeting has historically been attended by 400+ individuals in Portland, OR, Seattle, WA, and Vancouver, BC and covered topics such as advances in radiation therapy, the role of exercise and nutrition, localized therapy options, and new agents in clinical trials. Due to the COVID pandemic, the 20th annual symposium was held virtually.

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 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).

e. What do you plan to do during the next reporting period to accomplish the goals?

Continue current activities including opening and accruing patients to new PCCTC trials and proposing new LOIs. In addition, Dr. Cheng was awarded a 2020 NCI Cancer Clinical Investigator Team Leadership Award, which will support her efforts to increase clinical trials accrual in the UWash cancer consortium catchment region through more effective communication and outreach among community colleagues and patients.

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 for 2020 and published extensively with the PCCTC Germline Genetic Working Group and through efforts such as the PROMISE registry.

b. What was the impact on other disciplines?

- Provide guidance to primary care physicians and urologists on the importance of an accurate family history.
- Educate oncologists about germline genetic testing for understanding cancer risk versus tumor biomarker testing for treatment decisions.
- 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 and rucaparib 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 have also arisen from work from our group. These guidelines impact not only the quality of clinical practice but also reimbursement.

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**

The COVID pandemic caused delays in opening trials, accruing patients and inaccurate assessment and monitoring during trial conduct. Despite these challenges, we have managed to continue to meet our goals and have effectively and efficiently adapted to changes. We will continue to collaborate with other PCCTC sites with the goal of eliminating deaths from prostate cancer and enhancing the well-being of men experiencing the impact of prostate cancer.

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)**

George, D, Mucci, L, 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, Omlin, A, Davis, I, Villanti, P, Vinson, J, Kantoff, P, First 500 patients of IRONMAN: International Registry for Men with Advanced Prostate Cancer. Prostate Cancer Foundation Annual Meeting, Carlsbad, CA (2019) [Abstract]

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]

Morris, MJ, De Wit, R, Vogelzang, NJ, Tagawa, ST, Higano, CS, A phase III trial of docetaxel versus docetaxel and radium-223 (Ra-223) in patients with metastatic castration-resistant prostate cancer (mCRPC): DORA. *J Clin Oncol* 38: 2020 (suppl; abstr TPS5594)

Graff, JN, Cheng, HH, Vuky, J, Alumkal, JJ, Kreitner, D, Petreaca, D, Grivas, P, Schweizer, MT, Higano, CS, Chen, Y, Yu, EY, Beer, TM, Phase II study of cabazitaxel (CAB) plus enzalutamide (ENZ) in metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 38, 2020 (suppl 6; abstr 86)

Higano, CS, Saad, F, Sartor, AO, Miller, K, Conti, P, George, DJ, Sternberg, CN, Shore, ND, Sade, JP, Bellmunt, J, Smith, MR, Logothetis, C, Verholen, F, Kalinovsky, J, Bayh, I, Tombal, BF, Clinical outcomes and patient (pt) profiles in REASSURE: An observational study of radium-223 (Ra-223) in metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 38, 2020 (suppl 6; abstr 32)

Aggarwal, RR, Alumkal, JJ, Szmulewitz, RZ, Higano, CS, Bryce, AH, Lopez-Gitlitz, A, McCarthy, SA, Miladinovic, B, McQuarrie, K, Thomas, S, Small, EJ, A randomized phase II study of apalutamide (APA), androgen deprivation therapy (ADT), or APA + ADT in patients (pts) with biochemically relapsed (BCR) prostate cancer (PC). *J Clin Oncol* 38, 2020 (suppl 6; abstr 320)

Morris, MJ, Fong, L, Petrylak, DP, Sartor AO, Higano, CS, Pagliaro, LC, Alva, AS, Appleman, LJ, Tan, W, Vaishampayan, UN, Porcu, R, Tayama, D, Kadel, EE, Yuen, KCY, Datye, A, Armstrong, AJ, Safety and clinical activity of atezolizumab (atezo) + radium-223 dichloride (r-223) in 2L metastatic castration-resistant prostate cancer (mCRPC): Results from a phase Ib clinical trial. *J Clin Oncol* 38: 2020 (suppl; abstr 5565)

Sokolova, A, Marshall, CH, Lozano, R, Grivas, P, Higano, CS, Lotan, TL, Montgomery, RB, Nelson, P, Olmos, D, Schweizer, MT, Yezefski, TA, Yu, EY, Paller, CJ, Castro, E, Antonarakis, ES, Cheng, HH, Treatment response comparisons between ATM and BRCA2 germline carriers for mCRPC., *J Clin Oncol* 38, 2020 (suppl 6; abstr 63)

Francini, E, Montagnani, F, Nuzzo, PV, Gonzalez-Velez, M, Alimohamed, NS, Cigliola, A, Moreno, I, Rubio, J, Crivelli, J, Shaw, G, Petrioli, R, Bengala, C, Francini, G, Foncillas, JG, Sweeney, C, Higano, CS, Bryce, AH, Harshman, LC, Lee-Ying, R, Heng, DY, Clinical outcomes of abiraterone acetate + prednisone (AA) + bone resorption inhibitors (BRI) versus AA alone as first-line therapy for castration-resistant prostate cancer (CRPC) with bone metastases (BM) in an international multicenter database, *J Clin Oncol* 38, 2020 (suppl 6; abstr 30)

Ledet, EM, Jaeger, E, Hatton, W, Moses, MW, Sokolova, AO, Nakazawa, M, Zhu, J., Dellinger, B, Elrefai, S, McKay, RR, Cheng, HH, Burgess, EF, Antonarakis, ES, Sartor, AO. Comparison of germline mutations in African American and Caucasian men with metastatic prostate cancer. *J Clin Oncol* 38, 2020 (suppl; abstr 5568). Poster presentation at American Society for Clinical Oncology Annual Meeting, virtual (2020).

Sokolova, AO, Miyamoto, AN, Pouv, DL, Cheng, HH, Montgomery, RB. Implementation of Systematic Germline Genetic Testing (GT) for Metastatic Prostate Cancer (mPC) Patients at the Puget Sound VA Prostate Oncology Clinic. *J Clin Oncol* 38, 2020 (suppl;abstr 1578). Poster presentation at American Society for Clinical Oncology Annual Meeting, virtual (2020).

Cheng, HH. *Germline Contribution to Metastatic Prostate Cancer*. Implementation of Genetic Testing for Inherited Prostate Cancer, Philadelphia Prostate Cancer Consensus Conference 2019, October 4, 2019.

Cheng, HH. *Prostate Cancer Genetics*. Prostate Cancer Foundation and UsTOO International Prostate Cancer Support Network, 26th Prostate Cancer Foundation Annual Scientific Retreat. Carlsbad, CA. October 26, 2019

Cheng, HH. *Molecular-Driven Therapy in GU Cancers*. 37th Annual CFS®: Innovative Cancer Therapy for Tomorrow, New York, NY. November 6, 2019.

Cheng, HH. *Men's Health—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. April 18, 2020.

Cheng, HH. *Prostate Cancer Genetics*. Medscape CME Webinar; Seattle Cancer Care Alliance, Seattle WA. July 22, 2020.

<https://www.medscape.org/viewarticle/937493>

b. Journal publications (UWash author)

Higano CS, Armstrong AJ, Sartor AO, Vogelzang NJ, Kantoff PW, McLeod DG, Pieczonka CM, Penson DF, Shore ND, Vacirca J, Concepcion RS, Tutrone RF, Nordquist LT, Quinn DI, Kassabian V, Scholz MC, Harmon M, Tyler RC, Chang NN, Tang H, Cooperberg MR. Real-World outcomes of sipuleucel-T treatment in PROCEED, a prospective registry of men with metastatic castration-resistant prostate cancer. *Cancer*. 2019 Dec 1;125(23):4172-4180. doi: 10.1002/cncr.32445. Epub 2019 Sep 4. PMID: 31483485; PMCID: PMC6856402.

Danila DC, Szmulewitz RZ, Vaishampayan U, Higano CS, Baron AD, Gilbert HN, Brunstein F, Milojic-Blair M, Wang B, Kabbarah O, Mamounas M, Fine BM, Maslyar DJ, Ungewickell A, Scher HI. Phase I Study of DSTP3086S, an Antibody-Drug conjugate Targeting Six-Transmembrane Epithelial Antigen of Prostate 1, in Metastatic Castration-Resistant Prostate Cancer. *J Clin Oncol*. 2019 Dec 20;37(36):3518-3527. doi: 10.1200/JCO.19.00646. Epub 2019 Nov 5. PMID: 31689155.

Aggarwal RR, Schweizer MT, Nanus DM, Pantuck AJ, Heath EI, Campeau E, Attwell S, Norek K, Snyder M, Bauman L, Lakhota S, Feng FY, Small EJ, Abida W, Alumkal JJ. A Phase Ib/Ila Study of the Pan-BET Inhibitor ZEN-3694 in Combination with Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer. *Clin Cancer Res*. 2020 Jul 21. doi: 10.1158/1078-0432.CCR-20-1707. Epub ahead of print. PMID: 32694156.

Giri VN, Knudsen KE, Kelly WK, Cheng HH, Cooney KA, Cookson MS, Dahut W, Weissman S, Soule HR, Petrylak DP, Dicker AP, AlDubayan SH, Toland AE, Pritchard CC, Pettaway CA, Daly MB, Mohler JL, Parsons JK, Carroll PR, Pilarski R, Blanco A, Woodson A, Rahm A, Taplin ME, Polascik TJ, Helfand BT, Hyatt C, Morgans AK, Feng F, Mullane M, Powers J, Concepcion R, Lin DW, Wender R, Mark JR, Costello A, Burnett AL, Sartor O, Isaacs WB, Xu J, Weitzel J, Andriole GL, Beltran H, Briganti A, Byrne L, Calvaresi A, Chandrasekar T, Chen DYT, Den RB, Dobi A, Crawford ED, Eastham J, Eggener S, Freedman ML, Garnick M, Gomella PT, Handley N, Hurwitz MD, Izes J, Karnes RJ, Lallas C, Languino L, Loeb S, Lopez AM, Loughlin KR, Lu-Yao G, Malkowicz SB, Mann M, Mille P, Miner MM, Morgan T, Moreno J, Mucci L, Myers RE, Nielsen SM, O'Neil B, Pinover W, Pinto P, Poage W, Raj GV, Rebbeck TR, Ryan C, Sandler H, Schiewer M, Scott EMD, Szymaniak B, Tester W, Trabulsi EJ, Vapiwala N, Yu EY, Zeigler-Johnson C, Gomella LG. Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019. *J Clin Oncol* 2020; 38(24):2798-2811. Epub June 9, 2020. PMID: 32516092. PMCID: 7430215.

Szymaniak, BM, Facchini, LA, Giri, VN, Antonarakis, EA, Beer, TM, Carlo, MI, Danila, DC, Dhawan, M, George, D, Graff, JN, Gupta, S, Heath, EI, Higano, CS, Liu, G, Molina, AM, Paller, CJ, Patnaik, A, Petrylak, DP, Reichert, Z, Rettig, MB, Ryan, CJ, Taplin, ME, Whang, YE, Morgans, AK*, Cheng, HH*, McKay, RR*. Practical Considerations and Challenges for Germline Genetic Testing in Prostate Cancer Patients: Recommendations from the Germline Genetics Working Group of the PCCTC. *JCO Oncology Practice*. 2020, Sept 28, (*co-senior author)

Sokolova AO, Cheng HH. Genetic Testing in Prostate Cancer. *Curr Oncol Rep*. 2020 Jan 23;22(1):5. doi: 10.1007/s11912-020-0863-6. PMID: 31974718.

Sokolova AO, Yu EY, Cheng HH. Honing in on PARPi Response in Prostate Cancer: from HR Pathway to Gene-by-Gene Granularity. *Clin Cancer Res*. 2020 Jun 1;26(11):2439-2440. doi: 10.1158/1078-0432.CCR-20-0707. Epub 2020 Mar 31. PMID: 32234758; PMCID: PMC7269828.

Schweizer, MT, Cheng, HH, Nelson, PS, Montgomery, R, Two steps forward and one step back for precision in prostate cancer treatment. *JCO*. 2020, Sept 8: JCO2001755.

Carlson, AS, Rigo I, Acevedo, RI, Lim, DM, Gulati, R, Gawne, A, Sokolova, AO, Cheng, HH, Nelson, PS, Montgomery, B, Yu, EY, Schweizer, MT. Impact of DNA damage repair mutations on treatment outcomes in men receiving conventional therapy for metastatic castration resistant prostate cancer (*in press, PLOS ONE*)

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

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

e. **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>

f. **Technologies or techniques**

Nothing to report.

g. **Inventions, patent applications, and/or licenses**

Nothing to report.

h. **Other Products**

Nothing to report

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

a. **What individuals have worked on the project?**

Name:	Heather Cheng, MD, PhD
Project Role:	Principal Investigator (effective 01Jul2020)
Person months worked:	1
Contribution to project:	Responsible for site's overall performance, assures site's goals are being met as outlined in the SOW, participates as a senior PCCTC member and mentor.

Name:	Celestia Higano, MD
Project Role:	Principal Investigator (retired 30Jun2020)
Person months worked:	2
Contribution to project:	Responsible for site's overall performance, assures site's goals are being met as outlined in the SOW, participates as a senior PCCTC member and mentor.

Name:	Evan Yu, MD
Project Role:	Co-Principal Investigator
Person months worked:	1
Contribution to project:	Conducts and recruits to PCCTC clinical trials, participates in weekly research and monthly PCCTC protocol meetings, attends face-to-face PCCTC meetings.

Name:	Sarah Finkelstein
Project Role:	Clinical Research Coordinator & Budget/Contract Mgr
Person months worked:	3
Contribution to project:	Tracks trial accruals, LOI submissions, and provides updates to PCCTC. Serves as point person for PCCTC activities. Participates in PCCTC coordinator conference calls. Manages consortium budgets and contract, provides monthly reports, oversees start-up process for PCCTC clinical trials, and post award accounting of the DoD grant.

Assists PI and co-PI with preparation and submission of required semi-annual and annual reports.

Name: Michelle Haug
Project Role: Interim Clinical Research Coordinator
Person months worked: 1
Contribution to project: Tracked trial accruals, LOI submissions, and provided monthly updates to PCCTC. Served as point person for PCCTC activities and participated in PCCTC conference calls.

Name: Zoya Bauer
Project Role: Assistant Clinical Research Coordinator
Person months worked: 2
Contribution to project: Participates in PCCTC conference calls. Oversees research team in management of protocol adherence and timeliness/quality of data collection. Supports data and regulatory coordinators, ensuring data collection is accurate and timely, and that all regulatory procedures meet local IRB requirements.

Name: Sara Fernandez
Project Role: Correlative Science Coordinator
Person months worked: 1
Contribution to project: Manages acquisition, delivery, and storage of biological samples. Oversees collection, processing, and mailing of research samples as specified per protocol.

Name: Randall Davis
Project Role: Budget Startup Specialist
Person months worked: 1
Contribution to project: Develops site budgets for PCCTC studies, and negotiates amendments based on protocol modifications as needed.

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), Schweizer (sub-I), and Higano (former PI, retired 30Jun2020)

APPENDIX 1

PCCTC trials, status, and accruals at UWash clinical research site
01Oct2019-30Sep2020

PCCTC#	Trial Title	UWash accrual	Status	Lead Site(s)	Protocol Specific Biomarkers
c15-160	A Phase 1b Study of Enzalutamide plus CC-115 in Men with CRPC	1	Closed 02/2020	MSKCC	CTC, ctDNA, IMPACT, Explant Culturing, Organoids, IHC, Targeted RNA Seq
c16-169	A Phase 1 Study... of Escalating Doses of a Vaccine Based Immunotherapy Regimen (VBIR) for Prostate Cancer	1	Open	UWash Duke MSKCC	PK, PD, AChR, PBMC, PSMA & IgG Serology, MDSCa, CTCs, and NGS on tumor tissues
c16-174	Phase III Trial of Docetaxel vs Docetaxel and Radium-223 for mCRPC (DORA)	1	Closed 07/2020	MSKCC UWash	CTC, ctDNA, AR-V7, aBSI
c16-181	A Phase Ib/II Trial of Pembrolizuman (MK-3475) Combination Therapies in mCRPC	6	Closed 04/2020	UWash	PKs, NGS on tumor tissue and blood, mRNA expression, PD-1/PD-L1
c17-189	A Phase 2 Efficacy and Safety Study of Niraparib in Men with mCRPC and DNA-Repair Anomalies	1	Open	UWash OHSU	PK, PD, Biomarkers: DNA Repair Mutations (NGS on tumor tissue)
c17-198	A Multi-Center Trial Comparing the Occurrence of Major Adverse Cardiovascular Events in Patients with Prostate Cancer and Cardiovascular Disease Receiving Degarelix (GnRH Receptor Antagonist) or Leuprolide (GnRH Receptor Agonist) PRONOUNCE	0	Closed 03/2020	MSKCC UWash	NA
c18-211	A Phase 2, Open-label, Response Rate Study of Talazoparib in Men with DNA Repair Defects and mCRPC who Previously Received Taxane-Based Chemotherapy and Progressed on at least 1 Novel Hormonal Agent (Enzalutamide and/or Abiraterone Acetate/Prednisone)	0	Closed 03/2020	UWash	PK, CTC, ctDNA, Biomarkers, DNA repair mutations
c19-244	A phase 1, open-label, dose escalation clinical trial to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ARV-110 in patients with metastatic castration-resistant prostate cancer who have progressed on least two prior systemic therapies.	0	Did Not Open	OHSU UWash	

PCCTC#	Trial Title	UWash accrual	Status	Lead Site(s)	Protocol Specific Biomarkers
c19-248	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)	5	Open	UWash	PK, PD, Biomarkers
c20-259	A Phase I, First-in-Human, Dose Escalation Study of JNJ-63898081 in Subjects with Advanced Stage Solid Tumors	4	Open	UWash	PK, PD, Biomarkers
Total Therapeutic Accruals		19			
c16-170	Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men with Advanced Prostate Cancer (IRONMAN)	9	Open	Duke MSKCC DFCI	ctDNA, germline DNA, RNA, exosomes
c20-258	The impact of DNA repair pathway alterations identified by circulating tumor DNA on sensitivity to Radium-223 in bone metastatic castration-resistant prostate cancer	0	Start Up	UWash	NGS for DNA repair mutations
Total Non-Therapeutic Accruals		9			

Appendix 2

Copies of original journal articles

Real-World Outcomes of Sipuleucel-T Treatment in PROCEED, a Prospective Registry of Men With Metastatic Castration-Resistant Prostate Cancer

Celestia S. Higano, MD¹; Andrew J. Armstrong, MD, ScM ^{2,3}; A. Oliver Sartor, MD ⁴; Nicholas J. Vogelzang, MD⁵; Philip W. Kantoff, MD⁶; David G. McLeod, MD, JD⁷; Christopher M. Pieczonka, MD⁸; David F. Penson, MD, MPH^{9,10}; Neal D. Shore, MD¹¹; Jeffrey Vacirca, MD¹²; Raoul S. Conception, MD¹³; Ronald F. Tutrone, MD¹⁴; Luke T. Nordquist, MD¹⁵; David I. Quinn, MBBS, PhD¹⁶; Vahan Kassabian, MD¹⁷; Mark C. Scholz, MD¹⁸; Matt Harmon, JD¹⁹; Robert C. Tyler, PhD²⁰; Nancy N. Chang, PharmD²⁰; Hong Tang, MD²⁰; and Matthew R. Cooperberg, MD, MPH^{21,22}

BACKGROUND: The large registry, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data (PROCEED) (NCT01306890), evaluated sipuleucel-T immunotherapy for asymptomatic/minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). **METHODS:** PROCEED enrolled patients with mCRPC receiving 3 biweekly sipuleucel-T infusions. Assessments included overall survival (OS), serious adverse events (SAEs), cerebrovascular events (CVEs), and anticancer interventions (ACIs). Follow-up was for ≥ 3 years or until death or study withdrawal. **RESULTS:** In 2011–2017, 1976 patients were followed for 46.6 months (median). The median age was 72 years, and the baseline median prostate-specific antigen level was 15.0 ng/mL; 86.7% were white, and 11.6% were African American. Among the patients, 1902 had 1 or more sipuleucel-T infusions. The median OS was 30.7 months (95% confidence interval [CI], 28.6–32.2 months). Known prognostic factors were independently associated with OS in a multivariable analysis. Among the 1255 patients who died, 964 (76.8%) died of prostate cancer (PC) progression. The median time from the first infusion to PC death was 42.7 months (95% CI, 39.4–46.2 months). The incidence of sipuleucel-T-related SAEs was 3.9%. The incidence of CVEs was 2.8%, and the rate per 100 person-years was 1.2 (95% CI, 0.9–1.6). The CVE incidence among 11,972 patients with mCRPC from the Surveillance, Epidemiology, and End Results–Medicare database was 2.8%; the rate per 100 person-years was 1.5 (95% CI, 1.4–1.7). One or more ACIs (abiraterone, enzalutamide, docetaxel, cabazitaxel, or radium 223) were received by 77.1% of the patients after sipuleucel-T; 32.5% and 17.4% of the patients experienced 1- and 2-year treatment-free intervals, respectively. **CONCLUSIONS:** PROCEED provides contemporary survival data for sipuleucel-T-treated men in a real-world setting of new life-prolonging agents, which will be useful in discussing treatment options with patients and in powering future trials with sipuleucel-T. The safety and tolerability of sipuleucel-T in PROCEED were consistent with previous findings. **Cancer 2019;125:4172–4180.** © 2019 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: immunotherapy, overall survival, prostate cancer, safety.

INTRODUCTION

Sipuleucel-T is an autologous cellular immunotherapy for asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). In the pivotal phase 3 trial Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT; NCT00065442), sipuleucel-T significantly reduced the risk of death among patients with mCRPC and improved median overall survival (OS) by 4.1 months versus a placebo.¹ Sipuleucel-T is recommended

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across multiple guidelines²⁻⁷ and as a first-line mCRPC treatment option^{2,3,7} (category 1 recommendation by the National Comprehensive Cancer Network). In patients with low baseline prostate-specific antigen (PSA) levels (≤ 22.1 ng/mL) in IMPACT, retrospective analyses demonstrated a 13-month greater improvement in OS with sipuleucel-T versus a placebo.⁸

Sipuleucel-T was generally well tolerated across several prostate cancer (PC) trials.^{1,9-14} The most common adverse events ($\geq 15\%$) were chills, fatigue, fever, back pain, nausea, joint ache, and headache of mostly mild to moderate severity. Incidences of grade 3 and 4 adverse events were 23.6% and 4.0%, respectively, with sipuleucel-T and 25.1% and 3.3%, respectively, with a placebo. Serious adverse events (SAEs) included acute infusion reactions and cerebrovascular events (CVEs).¹⁴ Data from 4 randomized, double-blind, placebo-controlled clinical trials (D9901 [NCT00005947],^{12,13} D9902A [NCT01133704],¹³ IMPACT,¹ and PROTECT [NCT00779402]⁹) showed that CVEs, excluding transient ischemic attacks (TIAs), occurred in 3.5% (sipuleucel-T) and 2.6% (placebo) of patients (not statistically significant).¹⁴ The clinical significance and causal relationship are uncertain.

The PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data (PROCEED; NCT0136890), evaluated real-world safety data and provided an opportunity to analyze efficacy outcomes of mCRPC management involving sipuleucel-T during a time of rapidly evolving management protocols.

MATERIALS AND METHODS

Study Design and Patients

PROCEED was a multicenter, open-label, observational registry conducted at urology and medical oncology clinics in private practice and at academic sites (see the Supporting Methods section in the supporting information). The primary and secondary objectives were to quantify CVE risk and OS, respectively. SAEs were collected. For a protocol-specified, exploratory objective, the proportion of patients receiving subsequent anticancer interventions (ACIs) was assessed. Both the protocol and its single amendment were approved by each center's Institutional Review Board before patient enrollment. Before participation, patients provided written informed consent.

Treatment

No randomization, blinding, or treatment masking was conducted. Patients underwent a 1.5 to 2.0 $\times$ blood

volume leukapheresis for antigen-presenting cell (APC) isolation with a sipuleucel-T infusion 3 to 4 days later; this was repeated at approximately 2-week intervals for 3 infusions.

Study Procedures

Safety and survival were assessed during normal clinical practice and were reported every 3 months after the final sipuleucel-T infusion. Use of central venous catheters at the physician's discretion was recorded. PROCEED did not require the recording of all PC-related events after sipuleucel-T treatment. ACI use after the first infusion of sipuleucel-T was recorded. Decisions to use further treatment and the choice and timing of ACI use were at the physician's discretion.

All SAEs (according to MedDRA version 19.1) from the first sipuleucel-T infusion through 60 days after the final infusion were captured. Thereafter, SAEs at least possibly related to sipuleucel-T were recorded. All CVE data were collected, regardless of causality, severity, or outcome, throughout PROCEED. CVEs, adjudicated by an independent neurologist, included all strokes (ischemic and hemorrhagic), intracranial hemorrhage, and TIAs (focal neurologic deficit episodes resolving within 24 hours).¹⁵

Patients were followed for ≥ 3 years or until death or study withdrawal. The cause of death was reported on a case report form. An end-of-study closeout form was completed to ascertain death. For patients lost to follow-up, sites performed a death-sweep search for obituaries.

Statistical Analyses

The sample size was based on an evaluation of the CVE rate. With ≥ 1500 patients followed for ≥ 3 years (4500 person-years), the 95% confidence interval (CI) for estimating the CVE incidence rate per 100 patient-years would have a width of <1 unit as long as the observed rate was $<2.8/100$ patient-years.¹⁶ For 1500 patients, the probability of observing 1 or more occurrences of a rare event (1 in 1000) would be 0.78. The sample size was increased from 1500 to allow for 4500 person-years of follow-up.

The predefined analysis population was all patients receiving 1 or more full or partial (>0 mL) sipuleucel-T infusions. Endpoints were summarized descriptively unless otherwise stated. All analyses were performed with SAS (versions 9.2 and 9.4; SAS Institute, Inc, Cary, North Carolina).

OS was measured from the date of the first sipuleucel-T infusion for ≥ 3 years or until the patient had

otherwise gone off the study. If death was not reported, patients were censored from the last study visit. OS data were analyzed with Kaplan-Meier methodology; Cox proportional hazards regression was used to calculate hazard ratios and 95% CIs. These were post hoc analyses with *P* values that were not adjusted for multiplicity. Univariable, stepwise Cox modeling and multivariable analysis were performed to assess for independent baseline predictors of OS that had both clinical and statistical relevance. Variables were selected in a stepwise process for the final multivariable analysis model at a .1 significance level (see the Supporting Methods for more details). The association of OS with natural logarithm-transformed sipuleucel-T product parameters (APC activation, APC cell count, and total nucleated cell count) was estimated with a Cox proportional hazards regression model; statistical significance was a 2-tailed *P* value <.05. A post hoc analysis evaluated OS by baseline PSA quartiles; hazard ratios and 95% CIs were calculated by the Cox regression model.

Primary summarization of CVEs excluded TIAs for consistency with how CVE rates had been previously defined.¹⁴ CVEs including TIAs were summarized separately. The PROCEED CVE incidence was compared with a retrospective analysis of the incidence of first-time CVEs in men 65 years old or older with PC, including those with metastatic PC and a castrated state, within the Surveillance, Epidemiology, and End Results (SEER)–Medicare database in 1999-2013 (see the supporting information).

An exploratory analysis described the proportion of patients receiving ACIs after the first sipuleucel-T infusion. The Kaplan-Meier method estimated the proportion of ACI use at 1 and 2 years.

RESULTS

Patients and Treatment

PROCEED was conducted from January 27, 2011 (the first patient registered), to January 17, 2017 (the last patient visit); 1976 consenting patients were enrolled across 192 sites. Overall, 1902 patients received 1 or more sipuleucel-T infusions: 1248 (65.6%) were treated in oncology practices, and 654 (34.4%) were treated in urology practices. Most patients (79.1%) received sipuleucel-T at 140 community clinics; the remainder received it at 52 academic centers (see the Supporting Results in the supporting information for study discontinuation reasons).

Central venous catheters were used in 891 patients (46.8%). Overall, 1813 patients (95.3%) received

3 sipuleucel-T infusions, 57 (3.0%) received 2, and 32 (1.7%) received 1. Reasons for 3 or fewer infusions included an SAE (34 [1.8%]), other (32 [1.7%]), disease progression after the first infusion (22 [1.2%]), patient refusal (16 [0.8%]; including a refusal to transfer location or answer study questions), and venous access problems (4 [0.2%]). Multiple reasons for noninfusion were possible.

Table 1 lists patient characteristics for PROCEED and for IMPACT sipuleucel-T–treated patients for comparison.¹ The median patient age was 72 years; 86.7% were white, and 11.6% were African American. Most patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. The median baseline PSA level was 15.0 ng/mL (interquartile range, 5.2-46.1 ng/mL). Some patients received prior docetaxel, abiraterone, or enzalutamide (commercially or as an investigational agent). Most had bone-dominant metastases with or without lymph node involvement. The metastatic site or status was not reported for 19 patients (1.0%). Supporting Table 1 lists PROCEED baseline CVE risk factors.

Overall Survival

The median OS was 30.7 months (95% CI, 28.6-32.2 months; Fig. 1); the median follow-up was 46.6 months. During follow-up, 1255 patients (66.0%) died. Death or survival could not be ascertained for 45 patients. The main cause of death was PC progression (964 of 1255 [76.8%]); the median time to PC-specific death was 42.7 months (95% CI, 39.4-46.2 months). Other causes of death were unknown (154 [12.3%]), other (136 [10.8%]), a cardiac event (42 [3.3%]), a CVE (17 [1.4%]), and a new primary cancer (8 [0.6%]). More than 1 cause of death could be recorded for a patient.

A post hoc analysis indicated that the median OS was longer for patients in the lowest baseline PSA quartile (≤ 5.27 ng/mL) than patients in the second (> 5.27 to ≤ 15.08 ng/mL), third (> 15.08 to ≤ 46 ng/mL), and fourth quartiles (> 46 ng/mL): 47.7 months (95% CI, 43.5-50.7 months), 33.2 months (95% CI, 30.9-35.5 months), 27.2 months (95% CI, 24.1-29.8 months), and 18.4 months (95% CI, 15.9-21.2 months), respectively. The hazard ratios for each quartile versus the lowest quartile were 1.6 (95% CI, 1.3-1.9), 2.0 (95% CI, 1.7-2.4), and 3.0 (95% CI, 2.6-3.6), respectively.

Univariable analyses showed that 15 evaluated baseline characteristics were significant predictors of OS (Supporting Table 2). Eleven characteristics were included in the final primary multivariable analysis. Of these, 10 were associated with OS at a significance level

TABLE 1. Demographics, Baseline Disease Characteristics, and Prior Prostate Cancer Treatments in PROCEED and IMPACT¹

Parameter	PROCEED Safety Population (n = 1902)	IMPACT Sipuleucel-T-Treated Arm (n = 341)
Age, median (range, min-max), y	72 (42-97)	72 (49-91)
Race, No. (%)		
White	1649 (86.7)	305 (89.4)
Black or African American	221 (11.6)	23 (6.7)
Asian	22 (1.2)	2 (0.6)
Other	10 (0.5)	11 (3.2)
ECOG performance status, No. (%)		
0	1265 (66.5)	280 (82.1)
1	571 (30.0)	61 (17.9)
≥2	42 (2.2)	0
Unknown	24 (1.3)	0
Gleason sum reported, No. (%)		
≤7	790 (41.5)	257 (75.4)
≥8	963 (50.6)	84 (24.6)
Unknown	149 (7.8)	0
Charlson Comorbidity Index, No. (%)		NA
Low (0-1)	1682 (88.4)	
High (≥2)	220 (11.6)	
Bone metastases, No. (%)	n = 1595	
1-10	1117 (70.0)	195 (57.2)
>10	274 (17.2)	146 (42.8)
Unknown	204 (12.8)	0
Disease locations, No. (%)	n = 1883	n = 340
Bone only	1223 (64.3)	173 (50.7)
Bone and lymph nodes	313 (16.5)	143 (41.9)
Lymph nodes only	257 (13.5)	24 (7.0)
Visceral ± bone or lymph nodes	90 (4.7)	0
Liver	21 (1.1)	0
Lung	61 (3.2)	0
Brain	2 (0.1)	0
Visceral site(s) not reported	13 (0.7)	0
Laboratory parameters, median (IQR, Q1-Q3)		
ALP, U/L	82 (63-115) n = 1499	99 (75-146)
Hemoglobin, g/dL	12.8 (11.8-13.7) n = 1794	12.9 (11.7-13.7)
Lactate dehydrogenase, U/L	186 (159-218) n = 644	194 (172-224) n = 340
PSA, ng/mL	15.0 (5.2-46.1) n = 1884	51.7 (22.5-140.3)
Interval from diagnosis to first sipuleucel-T infusion, median (IQR, Q1-Q3), y	5.0 (2.3-9.4) n = 1599	7.1 (4.4-10.7)
Prior local cancer therapy, No. (%)		
No local therapy (systemic therapy only)	429 (22.6)	85 (24.9)
Radical prostatectomy alone	310 (16.3)	46 (13.5)
Radical prostatectomy + radiation	379 (19.9)	73 (21.4)
Radiation therapy alone (external beam/brachytherapy)	564 (29.7)	112 (32.8)
Prior systemic cancer therapy, No. (%)		
Androgen-targeting therapy ^a	1881 (98.1)	279 (81.8) ^b
LHRH antagonist	382 (20.1)	—
LHRH agonist	1566 (82.3)	341 (100) ^c
Abiraterone	157 (8.3)	0
Enzalutamide	54 (2.8)	0
Chemotherapy		
Docetaxel	215 (11.3)	53 (15.5)
Cabazitaxel	32 (1.7)	0
Radium 223	1 (0.1)	0

Abbreviations: ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group; IMPACT, Immunotherapy for Prostate Adenocarcinoma Treatment; IQR, interquartile range; LHRH, luteinizing hormone releasing hormone; max, maximum; min, minimum; NA, not applicable; PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data; PSA, prostate-specific antigen; Q1, first quartile; Q3, third quartile.

PROCEED was observational, so calculations were based on values from the number of patients for whom data were available.

^aExcluded enzalutamide.

^bPatients received complete androgen blockade treatment.

^cPatients received an LHRH analogue.

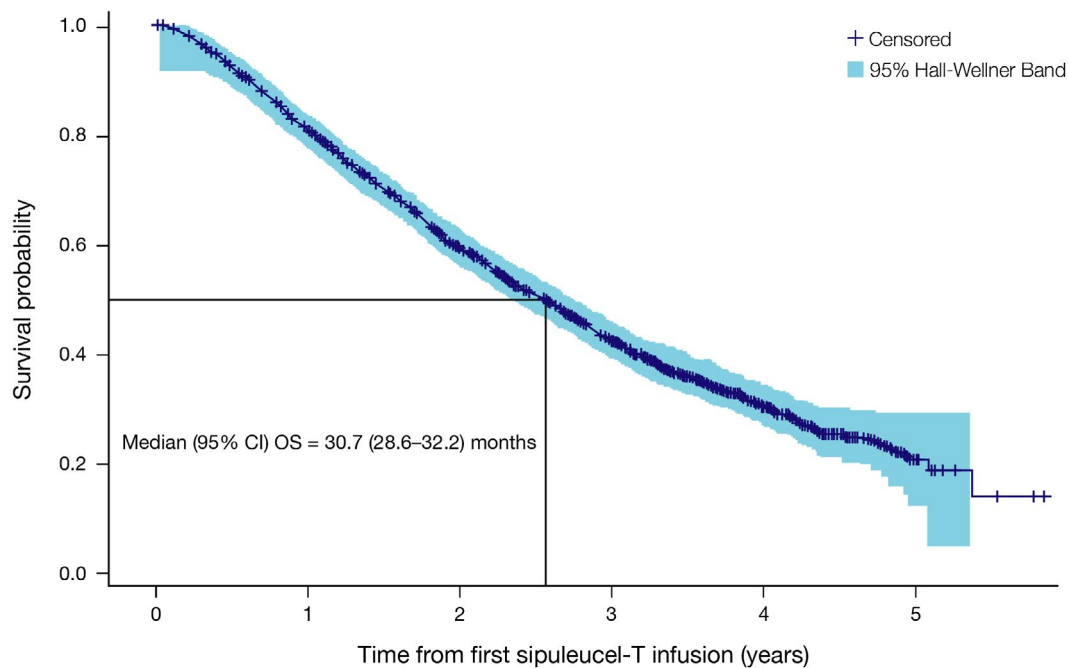


Figure 1. OS in PROCEED as a Kaplan-Meier plot with a 95% Hall-Wellner band. CI indicates confidence interval; OS, overall survival; PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data.

below .05 (Table 2): age, ethnicity, Eastern Cooperative Oncology Group performance status, time since diagnosis, PSA, alkaline phosphatase, hemoglobin, lymph node only metastases, prior abiraterone/enzalutamide, and prior docetaxel/cabazitaxel.

Cumulative sipuleucel-T product parameters (Supporting Table 3) per unit increase correlated with OS.

Safety

All-grade SAEs, regardless of causality, were reported in 260 patients (13.7%); the most common SAEs were disease progression (28 patients), cerebrovascular accident (16 patients), chills (13 patients), syncope (12 patients), and device-related infection (10 patients; Table 3). Seventy-four patients (3.9%) had 1 or more SAEs considered possibly or probably related to the study drug (all grades); the most common were chills (13 [0.7%]), cerebrovascular accident (9 [0.5%]), deep vein thrombosis (4 [0.2%]), device-related infection (4 [0.2%]), pulmonary embolism (4 [0.2%]), and pyrexia (4 [0.2%]). Grade 3 to 5 SAEs, regardless of causality, occurred in 175 patients (9.2%; Table 3). The incidence of grade 4 SAEs was 1.1% (n = 21). Fifty-two patients (2.7%) had grade 5 SAEs, and 22 deaths were due to disease progression. Central venous catheter–related SAEs were reported in 19 patients

TABLE 2. Final Primary Multivariable Analysis of Overall Survival in PROCEED

Baseline Covariate	HR (95% CI)	P ^a
Log PSA (ng/mL)	1.22 (1.16-1.27)	<.001
Hemoglobin, per g/dL increase	0.87 (0.83-0.91)	<.001
ECOG performance status, >0 vs 0	1.22 (1.05-1.42)	.009
Log ALP (U/L)	1.60 (1.42-1.81)	<.001
Age (y), >median vs ≤median	1.30 (1.12-1.50)	<.001
Race, white vs all others	1.64 (1.30-2.06)	<.001
Time since diagnosis (y), >median vs ≤median	0.72 (0.62-0.83)	<.001
Lymph node only metastases, yes vs no	0.79 (0.63-0.99)	.044
Visceral metastases, any vs none	1.30 (0.95-1.78)	.098
Prior docetaxel/cabazitaxel, yes vs no	1.54 (1.25-1.90)	<.001
Prior abiraterone/enzalutamide, yes vs no	1.53 (1.16-1.27)	<.001

Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data; PSA, prostate-specific antigen.

^aMultivariable Cox modeling.

(1.0%); 13 were grade 3 or 4 with no grade 5 SAEs. Of these 19 patients, 2 and 5 had 1 and 2 sipuleucel-T infusions, respectively.

The overall incidence of adjudicated CVEs (excluding TIAs) in PROCEED was 2.8% (n = 54), and the rate per 100 person-years was 1.2 (95% CI, 0.9-1.6; Supporting Table 4). In the SEER-Medicare data analyses of men with PC at diagnosis who were metastatic at

TABLE 3. Overall Summary of All-Grade SAEs and Grade 3 to 5 SAEs Occurring in 3 (0.2%) or More Patients (in the All-Grade List) Regardless of Causality (n = 1902) in PROCEED

SAE	No. (%)	
	All Grades	Grades 3-5
Any SAE	260 (13.7)	175 (9.2)
Disease progression	28 (1.5)	25 (1.3)
Cerebrovascular accident	16 (0.8)	11 (0.6)
Chills	13 (0.7)	0 (0)
Syncope	12 (0.6)	7 (0.4)
Device-related infection	10 (0.5)	7 (0.4)
Acute kidney injury	8 (0.4)	7 (0.4)
Deep vein thrombosis	8 (0.4)	2 (0.1)
Pulmonary embolism	8 (0.4)	7 (0.4)
Anemia	7 (0.4)	2 (0.1)
Dyspnea	7 (0.4)	6 (0.3)
Chest pain	6 (0.3)	2 (0.1)
Myocardial infarction	6 (0.3)	5 (0.3)
Pyrexia	6 (0.3)	2 (0.1)
Subdural hematoma	6 (0.3)	6 (0.3)
TIA	6 (0.3)	1 (0.1)
Cerebral hemorrhage	5 (0.3)	5 (0.3)
Pneumonia	5 (0.3)	3 (0.2)
Cerebral infarction	4 (0.2)	4 (0.2)
Congestive cardiac failure	4 (0.2)	3 (0.2)
Dehydration	4 (0.2)	3 (0.2)
Device-related sepsis	4 (0.2)	3 (0.2)
Intracranial hemorrhage	4 (0.2)	2 (0.1)
Nausea	4 (0.2)	1 (0.1)
Spinal cord compression	4 (0.2)	4 (0.2)
Vomiting	4 (0.2)	4 (0.2)
Asthenia	3 (0.2)	1 (0.1)
Atrial fibrillation	3 (0.2)	1 (0.1)
Back pain	3 (0.2)	2 (0.1)
Bacteremia	3 (0.2)	1 (0.1)
Confusional state	3 (0.2)	1 (0.1)
Constipation	3 (0.2)	2 (0.1)
Fall	3 (0.2)	3 (0.2)
Hematuria	3 (0.2)	1 (0.1)
Hypotension	3 (0.2)	2 (0.2)
Infusion-related reaction	3 (0.2)	2 (0.2)
Presyncope	3 (0.2)	1 (0.1)

Abbreviations: PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data; SAE, serious adverse event; TIA, transient ischemic attack.

follow-up and in a castrated state (n = 11,972), the CVE incidence (excluding TIAs) was 2.8%, and the rate per 100 person-years was 1.5 (95% CI, 1.4-1.7; Supporting Table 5).

Subgroup analyses of CVEs (excluding TIAs) showed higher CVE rates in older patients, African Americans, patients with more advanced PC, and those with preexisting conditions associated with CVEs (Supporting Table 6). Nine patients had a TIA (3 concurrent with another CVE and 6 in isolation). Thus, 60 PROCEED patients (3.2%) had CVEs, including TIAs, and the rate per 100 person-years was 1.3 (95% CI, 1.0-1.7; Supporting Table 4). The observed median time to a CVE (including TIAs) from the last sipuleucel-T infusion was

TABLE 4. Proportion of Patients Receiving an Overall Survival-Prolonging ACI After Sipuleucel-T Treatment

Posttreatment ACI	Safety Population (n = 1902)	Patients Who Died During PROCEED (n = 1255)
No. of posttreatment ACIs, No. (%)		
0	419 (22.0)	287 (22.9)
1	565 (29.7)	329 (26.2)
2	462 (24.3)	326 (26.0)
3	319 (16.8)	216 (17.2)
4	126 (6.6)	87 (6.9)
5	11 (0.6)	10 (0.8)
Specific posttreatment ACI, No. (%)		
Abiraterone	1036 (54.5)	663 (52.8)
Enzalutamide	831 (43.7)	514 (41.0)
Docetaxel	739 (38.9)	553 (44.1)
Cabazitaxel	309 (16.2)	236 (18.8)
Radium 223	90 (4.7)	61 (4.9)

Abbreviation: ACI, anticancer intervention; PROCEED, PROVENGE Registry for the Observation, Collection, and Evaluation of Experience Data.

321 days (10.5 months; interquartile range, 79-689 days or 2.6-22.6 months). For patients with a CVE (including TIAs), the number and percent of patients with CVE onset within ≤ 30 , 31-60, 61-180, and > 181 days of the most recent sipuleucel-T infusion were 10 (16.7%), 4 (6.7%), 9 (15.0%) and 37 (61.7%), respectively. No appreciable differences in the CVE $\pm$ TIA incidence or rate were observed between patients with or without a central venous catheter (Supporting Table 7).

Protocol-Specified, Exploratory Analysis: ACIs

Three hundred thirty-eight patients (17.8%) received an OS-prolonging ACI (abiraterone, enzalutamide, docetaxel, cabazitaxel, or radium 223) before sipuleucel-T. Approximately one-third of the patients (32.5%) did not receive any OS-prolonging ACI at 1 year, and 17.4% did not at 2 years after sipuleucel-T treatment. Of these patients, 9.5% and 7.4% had received an ACI before sipuleucel-T; thus, most of these patients had sipuleucel-T as first-line mCRPC therapy. Among patients in the lowest baseline PSA quartile (≤ 5.27 ng/mL), 44.1% and 25.8% did not receive an ACI at 1 and 2 years, respectively. Of these, 94.3% and 95.0% received sipuleucel-T before any other ACI.

During PROCEED, 1483 of all patients (78.0%) received 1 or more OS-prolonging ACIs, and 48.3% received 2 or more lines of treatment after sipuleucel-T (Table 4). The most commonly used OS-prolonging ACIs after sipuleucel-T treatment were abiraterone (1036 [54.5%]), enzalutamide (831 [43.7%]), and docetaxel

(739 [38.9%]; Table 4). Having sipuleucel-T as the only OS-prolonging treatment in PROCEED was reported in 22.0% of the patients ($n = 419$).

Similar patterns of ACI use were observed in patients who died during PROCEED ($n = 1255$), with 968 patients (77.1%) receiving 1 or more OS-prolonging ACIs and 50.9% receiving 2 or more lines of treatment after sipuleucel-T (Table 4). The most common OS-prolonging ACIs reported in those who died were abiraterone (52.8%), docetaxel (44.1%) and enzalutamide (41.0%; Table 4). Sipuleucel-T was the only OS-prolonging ACI prescribed in PROCEED for 22.9% of these patients ($n = 287$).

DISCUSSION

Since the conduct of the phase 3 IMPACT trial¹ with sipuleucel-T (2003-2007), mCRPC treatments¹⁷⁻²² and guidelines²⁻⁷ have rapidly evolved. The PROCEED study (2011-2017), which includes the largest mCRPC patient population treated with sipuleucel-T and prospectively followed in a real-world setting, offers interesting observations about patients with mCRPC, sipuleucel-T use, and the use of other ACIs since IMPACT. The baseline characteristics of PROCEED patients reveal clinical practice changes (Table 1). Although the median age was similar, the median baseline PSA level was much lower in PROCEED versus IMPACT (15.0 vs 51.7 ng/mL); this is noteworthy because a previous analysis of IMPACT showed a much greater OS benefit from sipuleucel-T versus a placebo in patients with lower baseline PSA levels.⁸ Most PROCEED patients had a good performance status, although in comparison with IMPACT, the performance status was somewhat worse (likely because randomized clinical trials have more stringent eligibility criteria). The Gleason score was also higher in PROCEED. PROCEED enrolled a higher proportion of African American patients than IMPACT (11.6% vs 6.7%), and this is notable because this population is often underrepresented in clinical trials. Visceral metastases, an IMPACT exclusion criterion, were reported in 4.7% of PROCEED patients. Furthermore, PROCEED spanned a period of unprecedented progress in mCRPC management as 4 life-extending therapies became available: abiraterone acetate,^{17,18} enzalutamide,^{19,20} cabazitaxel,²¹ and radium 223.²² Thus, in PROCEED, the median OS (30.7 months) likely, in part, reflects use of these life-prolonging drugs with sipuleucel-T in contrast to the IMPACT (median OS, 25.8 months¹) era, in addition to the use of sipuleucel-T in patients with lower PSA levels.

PROCEED provides further evidence of sipuleucel-T safety and tolerability in a real-world setting. Particularly in an elderly patient population, the safety profile of a treatment deserves careful consideration in decision making. Importantly, the SAE incidence in PROCEED was low and was comparable to that documented during IMPACT.¹ A previous analysis of pooled data from 4 phase 3 trials reported CVE rates (excluding TIAs) of 3.5% (sipuleucel-T) and 2.6% (placebo).¹⁴ The causal relationship of sipuleucel-T with CVEs is unclear. Men with mCRPC are typically elderly with multiple comorbidities that increase the risk of cardiovascular events and CVEs. In PROCEED, a CVE rate of 2.8% was reported. Incidentally, the CVE rate was 2.8% in a SEER-Medicare database analysis with more than 10,000 patients with metastatic PC in a castrated state. Furthermore, subgroup analyses by baseline factors in PROCEED demonstrated that older patients and those with baseline CVE factors had higher rates of CVEs (Supporting Table 6), and this was consistent with published findings.²³⁻²⁵ Moreover, although central venous catheter use (which varied greatly by site) for leukapheresis was high in PROCEED, overall, this practice did not increase CVE risk (Supporting Table 7).

PROCEED also offers confirmation of correlative findings noted in prior phase 3 studies. Patients in the lowest baseline PSA quartile ($PSA \leq 5.27$ ng/mL) had significantly longer OS (median survival, 47.7 months) than those in higher PSA quartiles. Similar findings were seen in the post hoc analysis of IMPACT, which demonstrated a greater OS benefit in lower baseline PSA quartiles versus higher baseline PSA quartiles and also suggested that sipuleucel-T was superior to a placebo in each quartile.⁸ Likewise, similar correlations with immune parameters and OS were seen in both PROCEED and IMPACT; in vitro indicators of immune activation and product potency (cumulative APC activation, APC count, and total nucleated cell count in the product) were significantly correlated with OS (Supporting Table 3).^{26,27}

PROCEED also exhibited 10 baseline characteristics that were independent predictors of OS in PROCEED (Table 2). The examined covariates were selected on the basis of those previously observed to be clinically and statistically relevant in this population. Our findings, though broadly consistent with the Halabi model,²⁸ also differ in terms of which significant predictors were identified, potentially because of the treatment being received (chemotherapy in the population used for

the Halabi nomogram and sipuleucel-T for the current study), the data coming from a clinical trial versus a registry, the time periods during which the various studies informing these analyses were conducted and the changes in available therapies and PSA levels guiding treatment, and so on. One notable observation is the emergence of race as a statistically significant predictor, and this potentially reflects the relatively high enrollment of African Americans in PROCEED (12%). Further research is warranted to explore these findings.

Another notable finding in PROCEED is that a substantial number of patients experienced a long interval between sipuleucel-T and subsequent therapy with abiraterone, enzalutamide, docetaxel, cabazitaxel, or radium 223. Approximately one-third and one-sixth of the patients had not received any of these agents 1 and 2 years, respectively, after sipuleucel-T. For most of these patients, sipuleucel-T was their first OS-prolonging mCRPC therapy; having a long treatment-free interval after sipuleucel-T may reflect patient selection as well as the clinical benefit of sipuleucel-T. Interestingly, 22% of the overall PROCEED population received sipuleucel-T as their only OS-prolonging treatment for mCRPC. The reasons for this are unclear. However, the long median time to death from PC of 42.7 months observed provides further evidence for the early use of sipuleucel-T for mCRPC followed by other ACIs, as recommended by the National Comprehensive Cancer Network and other guidelines.^{2-4,7}

PROCEED has several limitations. Although OS was prospectively determined, there was no comparator group, so a survival benefit could not be determined. Nonetheless, this observation gives an accurate picture of expected OS with sipuleucel-T plus other life-prolonging drugs that were not available when IMPACT was conducted. Similar reasoning applies to SAE and CVE risk in that there was no placebo arm; hence, the results are descriptive.

PROCEED provides a real-world portrait of the safety profile of sipuleucel-T and defines the expected OS after sipuleucel-T in patients with mCRPC in the modern era of 5 additional life-prolonging agents. This information may be useful in powering future combination trials with sipuleucel-T, and studying the sequencing of therapies in this large population may shed light on optimal treatment approaches.

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CONFLICT OF INTEREST DISCLOSURES

Celestia S. Higano has served in an advisory role for Aptevo, Asana, Astellas, Bayer, Blue Earth Diagnostics, Churchill Pharma, Clovis Oncology, Dendreon, Endocyte, Ferring, Medivation, Orion Corporation, and Pfizer; she has also participated in sponsored research for Aptevo, Bayer, Aragon Pharma, Astellas, AstraZeneca, Dendreon, Genentech, Hoffman-LaRoche, Medivation, Sanofi, and Pfizer, and her spouse was in a leadership role for CTI Biopharma. Andrew J. Armstrong has received grants and personal fees from Dendreon, Pfizer/Astellas, Janssen, Bayer, and Sanofi-Aventis during this study as well as grants from Novartis, Gilead, Bristol-Myers Squibb, and Genentech/Roche outside the submitted work. A. Oliver Sartor has served as a consultant for and received personal fees from Advanced Accelerator Applications, Astellas, AstraZeneca, Bavarian-Nordic, Bayer, Bellicum, Blue Earth Diagnostics, Celgene, Constellation, Dendreon, EMD Serono, Endocyte, Johnson & Johnson, Bristol-Myers Squibb, Myovant, Pfizer, Progenics, Sanofi, Teva, and Hnova during this study; he has also received grants from AstraZeneca, Bayer, Constellation, Dendreon, Endocyte, Johnson & Johnson, Bristol-Myers Squibb, Progenics, Sanofi, Innocrin, Invitae, Merck, Roche, and Sotio. Philip W. Kantoff has received personal fees from Astellas, Bayer, Bellicum, BIND Biosciences, Bavarian Nordic Immunotherapies, DRGT, Genentech/Roche, Ipsen Pharmaceuticals, Janssen, Metamark, Merck, Millennium/Prometrika, MTG, Omnitara, OncoCell MDx, OncoGenex, Progenity, Sanofi, Tarveda Pharmaceuticals, Thermo Fisher, GE Healthcare, Context Therapeutics, New England Research Institutes, SEER Biosciences, and Placon; he also has investment interests in DRGT, Tarveda Pharmaceuticals, Context Therapeutics, SEER Biosciences, and Placon. Christopher M. Pieczonka has received personal fees as a consultant for Dendreon, Bayer, Janssen, and Pfizer and as an investigator for Dendreon, Bayer, Janssen, Pfizer, Merck, AstraZeneca, Taiho, Innocrin, and Myovant outside the submitted work. David F. Penson has received personal fees from Dendreon and Janssen as well as a grant from the Vanderbilt University Research Center. Neal D. Shore has served as a consultant for and received personal fees from Ferring, Bayer, Amgen, Janssen, Dendreon, Tolmar, Astellas, Pfizer, AstraZeneca, Genentech/Roche, Myovant Sciences, Merck, Bristol Myers Squibb, and Nymox outside the submitted work. Raoul S. Concepcion has served in an advisory role for Dendreon and received personal fees outside the submitted work. David I. Quinn has been involved in payments to the University of Southern California for trial conduct with Dendreon; he has also acted as an advisor for and received personal fees from Dendreon, Bayer, Janssen, Pfizer, Astellas, Genzyme, Clovis, and AstraZeneca. Vahan Kassabian has served as a consultant or speaker for Dendreon, Amgen, Astellas, Pfizer, Janssen, Bayer, UroGPO, Tolmar, and Genomic Health outside the submitted work and is a shareholder of UroGPO. Matt Harmon reports stock ownership in Amgen. Robert C. Tyler has been an employee of Janssen, Dendreon, Medivation, Pfizer, and Innocrin. Nancy N. Chang was a full-time employee of Dendreon at the time of the analyses and drafting of this manuscript. Hong Tang was a full-time employee of Dendreon at the time of the analyses and drafting of the manuscript; is a nonexecutive director of OnQuality Pharmaceuticals; and owns stock in BeiGene, Nektar, Sangamo Therapeutics, Tesaro, Verastem, Editas Medicine, and CVS Health Corporation. Matthew R. Cooperberg has received personal fees from Dendreon in relation to a PROCEED trial steering committee and has served in an advisory or consultancy role for Bayer, MDx Health, and Myriad Genetics; he has also participated in a registry steering committee for Astellas. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Celestia S. Higano: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, visualization, writing—original draft, and writing—review and editing. **Andrew J. Armstrong:** Conceptualization, investigation, methodology, project administration, resources, supervision, writing—original draft, and writing—review and editing. **A. Oliver Sartor:** Conceptualization, data curation, formal analysis, investigation, methodology, supervision, writing—original draft, and writing—review and editing. **Nicholas J. Vogelzang:** Investigation, writing—original draft, and writing—review and editing. **Philip W. Kantoff:** Conceptualization, investigation, and writing—review and editing. **David G. McLeod:** Writing—original draft and writing—review and editing. **Christopher M. Pieczonka:** Investigation and writing—review and editing. **David F. Penson:** Investigation, methodology, and writing—review and editing. **Neal D. Shore:** Formal analysis, investigation, and writing—review and editing. **Jeffrey Vacirca:** Data curation, investigation, project administration, resources, software, supervision, validation, and visualization. **Raoul S. Concepcion:** Investigation and writing—review and editing. **Ronald F. Tutrone:** Data curation, investigation, and writing—review and editing. **Luke T. Nordquist:** Investigation and writing—review and editing. **David I. Quinn:** Investigation and writing—review and editing. **Vahan Kassabian:** Investigation, validation, visualization, and writing—review and editing. **Mark C. Scholz:** Investigation, supervision, and writing—review and editing. **Matt Harmon:** Data curation, methodology, software, visualization, and writing—review and editing. **Robert C. Tyler:** Conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, and writing—review and editing. **Nancy N. Chang:** Visualization, writing—original draft, and writing—review and editing. **Hong Tang:** Funding acquisition, resources, supervision, and writing—review and editing. **Matthew R. Cooperberg:** Conceptualization, methodology, supervision, visualization, and writing—review and editing.

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Phase I Study of DSTP3086S, an Antibody-Drug Conjugate Targeting Six-Transmembrane Epithelial Antigen of Prostate 1, in Metastatic Castration-Resistant Prostate Cancer

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abstract

PURPOSE Six-transmembrane epithelial antigen of the prostate 1 (STEAP1) is highly expressed in prostate cancers. DSTP3086S is a humanized immunoglobulin G1 anti-STEAP1 monoclonal antibody linked to the potent antimitotic agent monomethyl auristatin E. This study evaluated the safety and activity of DSTP3086S in patients with metastatic castration-resistant prostate cancer.

METHODS Patients were enrolled in a 3 + 3 dose escalation study to evaluate DSTP3086S (0.3 to 2.8 mg/kg intravenously) given once every 3 weeks followed by cohort expansion at the recommended phase II dose or weekly (0.8 to 1.0 mg/kg).

RESULTS Seventy-seven patients were given DSTP3086S once every 3 weeks, and seven were treated weekly. Two patients in the once-every-3-weeks dose escalation had dose-limiting grade 3 transaminitis. Grade 3 hyperglycemia and grade 4 hypophosphatemia were dose-limiting toxicities in one patient treated at 1.0 mg/kg weekly. Initial cohort expansion evaluated dosing at 2.8 mg/kg once every 3 weeks (n = 10), but frequent dose reductions led to testing of 2.4 mg/kg (n = 39) in the expansion phase. Common related adverse events (> 20%) across doses (once every 3 weeks) were fatigue, peripheral neuropathy, nausea, constipation, anorexia, diarrhea, and vomiting. DSTP3086S pharmacokinetics were linear. Among 62 patients who received > 2 mg/kg DSTP3086S once every 3 weeks, 11 (18%) demonstrated a ≥ 50% decline in prostate-specific antigen; two (6%) of 36 with measurable disease at baseline achieved a radiographic partial response; and of 27 patients with informative unfavorable baseline circulating tumor cells ≥ 5/7.5 mL of blood, 16 (59%) showed conversions to favorable circulating tumor cells < 5. No prostate-specific antigen or RECIST responses were seen with weekly dosing.

CONCLUSION DSTP3086S has acceptable safety at the recommended phase II dose level of 2.4 mg/kg once every 3 weeks. Antitumor activity at doses between 2.25 and 2.8 mg/kg once every 3 weeks supports the potential benefit of treating STEAP1-expressing metastatic castration-resistant prostate cancer with an STEAP1-targeting antibody-drug conjugate.

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ASSOCIATED CONTENT

Data Supplements

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

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INTRODUCTION

Treatment options with clinical benefit for metastatic castration-resistant prostate cancer (mCRPC) have expanded significantly with the addition of abiraterone,^{1,2} enzalutamide,³ radium-223,⁴ and cabazitaxel.⁵ The long-term benefit for these agents, however, remains limited and is associated with significant toxicity.^{2,3,6,7} Needed are well-tolerated, targeted treatments with improved clinical benefit for patients whose tumors express the therapeutic target.

Six-transmembrane epithelial antigen of the prostate 1 (STEAP1) is a multitransmembrane protein believed to

act as an ion channel or transporter protein.⁸ As a cell surface protein frequently expressed in prostate cancer, with limited expression in nonprostate tissues,⁹⁻¹¹ STEAP1 is an ideal candidate for antibody-derived therapies in patients with mCRPC.

DSTP3086S is an antibody-drug conjugate (ADC) that contains the humanized immunoglobulin G1 anti-STEAP1 monoclonal antibody MSTP2109A linked through a protease labile linker, maleimidocaproyl-valine-citrulline *p*-aminobenzyloxycarbonyl, to a potent antimitotic agent, monomethyl auristatin E (MMAE). After antigen-specific binding of the ADC, the complex

is internalized, and MMAE is released intracellularly, resulting in inhibition of cell division and cell death.¹²⁻¹⁴ Nonclinical efficacy studies in prostate cancer xenografts provided a rationale for investigating DSTP3086S in patients with mCRPC.¹¹

METHODS

Study Design and Patient Selection

This phase I, multicenter, open-label, 3 + 3, dose-escalation study was designed to evaluate the safety and identify the recommended phase II dose (RP2D) of DSTP3086S in patients with mCRPC. Secondary and exploratory objectives included assessment of the antitumor activity of DSTP3086S in association with STEAP1 expression and of the predictive value of measuring circulating tumor cell (CTC) counts during treatment. The study protocol was approved by institutional review boards before patient recruitment and conducted in accordance with International Conference on Harmonization E6 Guidelines for Good Clinical Practice. Each patient provided signed informed consent before study enrollment.

Study eligibility criteria, including paraffin-embedded tissue screening for STEAP1 expression, are described in the Data Supplement (online only). In the initial dose-escalation stage, patients received intravenous DSTP3086S (supplied by Genentech, South San Francisco, CA) at 0.3 to 2.8 mg/kg once every 3 weeks, with dosing calculated by weight and eventually capped during the 2.4 mg/kg expansion for patients with a body mass index > 35 kg/m² because of excess toxicity seen in morbidly obese patients at higher dose levels. After completing the once-every-3-weeks dose escalation, a weekly schedule was evaluated at 0.8 and 1 mg/kg.

The RP2D was determined on the basis of cumulative safety data obtained at the time of cohort expansion. Dose-expansion cohorts were enrolled at RP2D to further characterize safety, tolerability, pharmacokinetics (PK) variability, and signals of clinical activity in 49 patients with STEAP1-expressing tumors (immunohistochemistry [IHC] 3+, predominantly strong staining; IHC 2+, predominantly moderate staining; IHC 1+, predominantly weak staining; IHC 0, very weak or no staining in > 90% of tumor cells). Patients enrolled in the expansion phase were required to have an STEAP1 IHC score of 2+ or 3+ in an archival or a pretreatment tissue biopsy specimen. A second expansion cohort enrolled chemotherapy-naïve patients who had progressed on abiraterone and/or enzalutamide and received daily prednisone concurrent with DSTP3086S.

Safety Assessment

Safety was assessed on the basis of reports of adverse events (AEs) and included clinical laboratory testing, vital signs, physical examinations, and ECG. Patients were assessed for AEs at each study visit and as necessary throughout the study. AEs were graded in severity

according to the National Cancer Institute CTCAE (version 4.0). Dose-limiting toxicities (DLTs) were defined as grade ≥ 3 nonhematologic or grade ≥ 4 hematologic toxicities attributed to treatment that occurred in the first cycle (for exceptions and additional details, see the Data Supplement). Patients with DLTs could continue treatment at a lower dose if toxicities resolved to grade < 2. The maximum tolerated dose was defined as the highest dose at which zero or one of six patients experienced a DLT. PK and immunogenicity assessments are described in the Data Supplement.

Clinical Activity

Preliminary efficacy measures included post-therapy prostate-specific antigen (PSA) changes shown by waterfall plots, disease progression according to Prostate Cancer Clinical Trials Working Group criteria,¹⁵ and radiographic response according to RECIST version 1.0.¹⁶ Per the Prostate Cancer Clinical Trials Working Group, treatment beyond PSA progression in the absence of radiographic or clinically progressive disease was allowed.¹⁵ Exploratory measures of activity included changes in CTC counts from unfavorable ≥ 5 cells to favorable ≤ 4 cells/7.5 mL of blood per US Food and Drug Administration clearance for Cell-Search (Menarini Silicon Biosystems, Huntingdon Valley, PA).¹⁷⁻²² STEAP1 IHC was performed as described in the Data Supplement.

Statistical Analysis

This study was designed to obtain preliminary safety, PK, and activity information in the treated populations. As such, the sample sizes in the various dose-escalation and dose-expansion cohorts did not reflect explicit, formal power and type I error considerations. Rather, sample sizes were based on an estimation framework either for the ability to identify AEs with various assumed underlying prevalence or for their ability to initially assess antitumor activity and evaluate benefits and risks in this patient population. For safety analysis, all patients who received DSTP3086S were included. Patients were considered for evaluation for response if the baseline PSA was detectable, they had measurable disease as assessed by computed tomography/magnetic resonance imaging by RECIST version 1.0, or they had baseline CTCs $\geq 5/7.5$ mL of blood.

RESULTS

Patient baseline characteristics for each schedule are listed in Table 1. A total of 84 patients were enrolled, including 77 on the once-every-3-weeks dose schedule of whom 28 were enrolled in the dose escalation (0.3 to 2.8 mg/kg), 10 in an initial expansion at 2.8 mg/kg, and 39 at 2.4 mg/kg in two expansion cohorts. The median number of DSTP3086S dose administrations in the once-every-3-weeks cohort was four (range, one to 25). AEs led to dose delays in 29 patients (38%), dose reductions in 12 (16%), and dose discontinuations in 17 (22%). Peripheral neuropathy was the most

TABLE 1. Patient Demographics and Disease Characteristics

Characteristic	DSTP3086S Cohort, No. (%)	
	Once Every 3 Weeks	Weekly
No. of patients	77	7
Median age, years (range)	68 (43-88)	67 (47-75)
ECOG performance status		
0	23 (30)	3 (43)
1	53 (69)	3 (43)
2	1 (1)	1 (14)
Sites of metastatic disease		
Bone	69 (90)	5 (71)
Bone only	5 (7)	0 (0)
Soft tissue	50 (65)	6 (86)
Lung	15 (20)	1 (14)
Liver	11 (14)	2 (29)
Lymph node	42 (55)	6 (86)
Prior systemic therapies (selected)		
Docetaxel	43 (56)	3 (43)
Cabazitaxel	8 (10)	1 (14)
Abiraterone	52 (68)	6 (86)
Enzalutamide	35 (45)	3 (43)
Median baseline prognostic factors (range)		
PSA, ng/mL	89 (0.4-8,471)	21 (0.3-274)
Hgb, g/dL	12 (8-15)	11 (10-13)
Alkaline phosphatase, U/L	134 (43-668)	98 (53-277)
LDH, U/L	236 (117-2,023)	212 (192-631)
Albumin, g/dL	4.1 (1.9-4.7)	4.1 (3.2-4.6)
Baseline CTCs/7.5 mL of blood		
Median (range)	6 (0-446)	1 (0-908)
≥ 5	38 (49)	2 (29)

Abbreviations: CTC, circulating tumor cell; ECOG, Eastern Cooperative Oncology Group; Hgb, hemoglobin B, LDH, lactate dehydrogenase; PSA, prostate-specific antigen.

common AE that led to treatment discontinuation. Dose reductions occurred after one to nine cycles of DSTP3086S treatment in the three highest dose cohorts, including 50% of patients at 2.8 mg/kg (Fig 1).

Of the seven patients enrolled in the weekly dose schedule, four were enrolled at 0.8 mg/kg, and three were enrolled at 1.0 mg/kg; no expansions were performed in the weekly schedule. The median number of DSTP3086S dose administrations in the weekly cohort was seven (range, one to 32); one patient (14%) had a dose reduction, three patients (43%) had dose delays, and one patient (14%) discontinued treatment because of AEs.

Safety

In the once-every-3-weeks dose escalation, DLTs included grade 3 transaminitis in one patient each at 2.25 mg/kg and

2.8 mg/kg. The maximum tolerated dose was not reached, and the RP2D for DSTP3086S was determined to be 2.4 mg/kg once-every 3 weeks on the basis of tolerability after an initial expansion at 2.8 mg/kg once every 3 weeks was deemed not tolerable and required frequent dose reductions (Fig 1).

The most common treatment-related AEs, defined as having occurred in > 20% patients (15 of 77) over all once-every-3-week dose levels, were fatigue (56%), peripheral neuropathy (51%), nausea (38%), constipation (35%), decreased appetite (34%), diarrhea (26%), and vomiting (25%). Table 2 lists related AEs that occurred in ≥ 10% patients in the once-every-3-weeks dose cohort. AEs reported at a maximum intensity of grade ≥ 3 in ≥ 5% of patients over all once-every-3-weeks dose levels (regardless of attribution to study drug) were hyperglycemia (eight

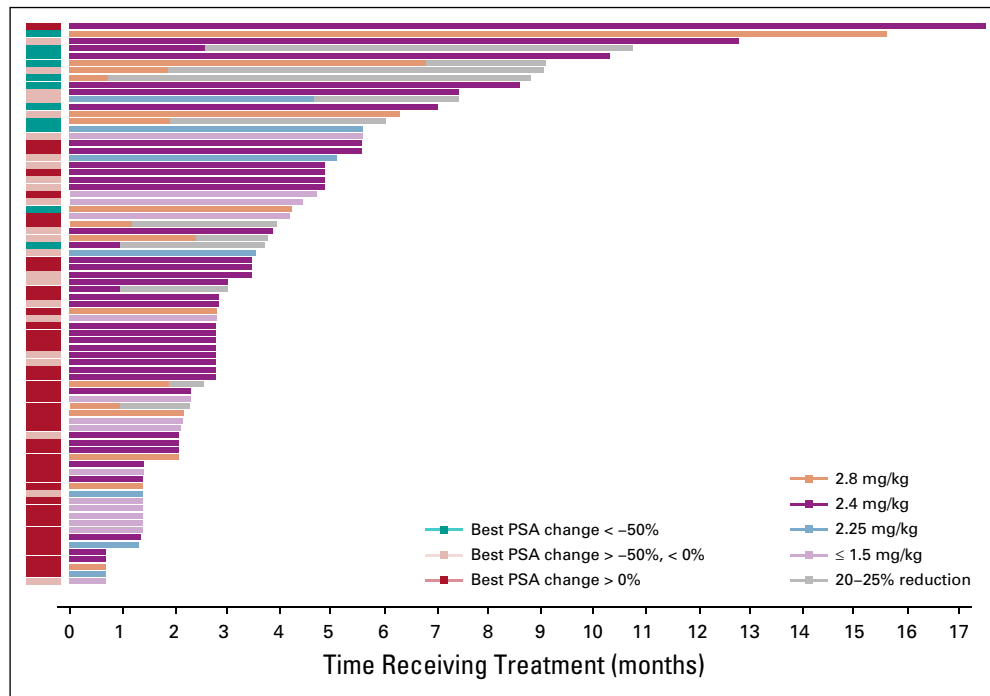


FIG 1. Time on treatment by dosing cohort and corresponding best prostate-specific antigen (PSA) changes in the once-every-3-weeks dose cohort. Dose modifications are represented by changes in color.

patients; 10% [includes one event of blood glucose increased]); anemia and fatigue (five patients each; 7%); and back pain, neutropenia, and pulmonary embolism (four patients each; 5%). Treatment-emergent grade ≥ 3 AEs

reported in at least two patients are listed in the Data Supplement. Grade ≥ 3 AEs that the investigator considered to be related to the study drug were reported in 34% of patients (26 of 77) on the once-every-3-weeks dose

TABLE 2. Most Common Related Adverse Events (Any and Grade 3/4) That Occurred in 10% or More Patients in the Once-Every-3-Weeks Dose Cohort

Adverse Event	Grade, No. (%)									
	DSTP3086S									
	≤ 1.5 mg/kg (n = 15)		2.25 mg/kg (n = 7)		2.4 mg/kg (n = 39)		2.8 mg/kg (n = 16)		Total (N = 77)	
	Any	3/4	Any	3/4	Any	3/4	Any	3/4	Any	3/4
Overall	10 (67)	2 (13)	5 (71)	3 (43)	38 (97)	9 (23)	16 (100)	10 (63)	69 (90)	24 (31)
Fatigue	4 (27)	—	2 (29)	—	25 (64)	—	12 (75)	3 (19)	43 (56)	3 (4)
Peripheral neuropathy*	1 (7)	—	2 (29)	1 (14)	26 (67)	2 (5)	10 (63)	—	39 (51)	3 (4)
Nausea	3 (20)	1 (7)	1 (14)	—	15 (39)	—	10 (63)	—	29 (38)	1 (1)
Constipation	3 (20)	—	2 (29)	—	14 (36)	—	8 (50)	1 (6)	27 (35)	1 (1)
Appetite decreased	2 (13)	—	1 (14)	—	16 (41)	—	7 (44)	—	26 (34)	—
Diarrhea	2 (13)	—	2 (29)	—	10 (26)	—	6 (38)	—	20 (26)	—
Vomiting	2 (13)	—	—	—	10 (26)	—	7 (44)	—	19 (25)	—
Dyspnea	—	—	1 (14)	—	8 (21)	—	5 (31)	1 (6)	14 (18)	1 (1)
ALT increased	1 (7)	—	—	—	9 (23)	2 (5)	1 (6)	—	11 (14)	2 (3)
AST increased	1 (7)	—	1 (14)	1 (14)	6 (15)	—	1 (6)	—	9 (12)	1 (1)
Pain in extremity	—	—	2 (29)	—	5 (13)	—	1 (6)	1 (6)	8 (10)	1 (1)

NOTE. None of the most common related adverse events that occurred in $\geq 10\%$ of patients were grade 5. See the Safety section for a description of related grade 5 adverse events and the Data Supplement for a complete list of grade ≥ 3 -related adverse events in the once-every-3-weeks dose cohort.

*Includes the Medical Dictionary of Regulatory Activities preferred terms peripheral sensory neuropathy, peripheral motor neuropathy, neuropathy peripheral and muscular weakness, hypoesthesia, gait disturbance, and paresthesia and peripheral sensorimotor neuropathy.

schedule (Data Supplement). The most frequently reported grade ≥ 3 -related AE was neutropenia (four patients; 5%).

Serious AEs are listed in the Data Supplement. Drug-related serious AEs occurred in nine patients at the once-every-3-weeks dose levels, including two fatal events: one as a result of sepsis (at 2.25 mg/kg) and one as a result of sepsis and respiratory failure after initial hospitalization for hyperglycemia (at 2.4 mg/kg). Thirteen patients (17%) had a glucose value consistent with grade ≥ 3 hyperglycemia while in the study, with eight (10%) of the 13 reported as grade ≥ 3 AEs. Of note, fasting glucose levels, which are used when making the CTCAE determinations, were not required for this study.

In the weekly cohort, one patient treated with 1.0 mg/kg developed grade 3 hyperglycemia and grade 4 hypophosphatemia, which were considered DLTs. AEs commonly experienced by the patients who received weekly treatment are listed in the Data Supplement. Treatment-emergent grade ≥ 3 AEs for patients on the weekly dose schedule are listed in the Data Supplement. One of seven patients developed nonfatal serious AEs that included dehydration, hyperglycemia, hypomagnesemia, and hypophosphatemia that led to treatment discontinuation.

Peripheral neuropathy-related AEs, regardless of attribution to study drug (identified using the broad Standardized Medical Dictionary for Regulatory Activities Queries for peripheral neuropathy), were reported in 46 patients (60%) on the once-every-3-weeks dose schedule after a median of 2.8 months of treatment. For patients on the weekly dose schedule, peripheral neuropathy-related AEs were reported in two (29%). Overall, grade 3 peripheral sensory neuropathy was reported in three patients, with one also having grade 3 peripheral motor neuropathy. Overall, nine

patients (12%) on the once-every-3-weeks dose schedule and none of the weekly cohort discontinued DSTP3086S treatment because of a peripheral neuropathy-related AE. The majority of peripheral neuropathy AEs were reported as ongoing at the end of the reporting period for the study, which ended 30 days after a patient's last dose.

PK and Immunogenicity Assessments

Linear PK (0.3 to 2.8 mg/kg) were observed for total antibody (Tab) and antibody-conjugated MMAE (acMMAE [RP2D of 2.4 mg/kg listed in Table 3]). For the once-every-3-weeks regimen, the mean acMMAE maximum concentrations occurred immediately after the infusion, increased with dose, and ranged from 94 to 993 ng/mL. The acMMAE PK showed a multi-exponential decline, with half-life values ranging from 4.6 to 6.4 days. The acMMAE PK was similar to the Tab, with a trend of faster clearance for acMMAE than for the Tab analyte. Unconjugated MMAE levels increased with DSTP3086S dose, and systemic exposure of unconjugated MMAE was consistently low across all time points (approximately 100-fold less than the exposure to acMMAE) and exhibited formation-rate-limited kinetics (Data Supplement). Minimal accumulation was observed for the acMMAE, Tab, and unconjugated MMAE analytes upon repeated dosing on the once-every-3-weeks schedule, and steady state seemed to be reached within the first dose in cycle 1.

For the tested weekly regimen of 0.8 and 1.0 mg/kg, dose-proportional maximum concentrations and areas under the curve were observed. On the basis of the limited weekly dosing data, faster clearance was observed for the weekly regimen compared with the once-every-3-weeks regimen. Therefore, no significant accumulation of acMMAE was observed, even when the drug was administered weekly.

One (1%) of the 75 tested patients who were evaluable for postdose anti-DSTP3086S antibodies was confirmed positive for antidrug antibodies. No differences were observed in the PK profiles, safety features, or efficacy outcomes for this patient (data not shown).

Clinical Activity

For patients on the once-every-3-weeks dosing schedule, a waterfall plot of the best PSA percent change from baseline is shown in Figure 2. In aggregate, 11 (14%; 95% CI, 7% to 24%) of 77 patients met the response criteria of a confirmed PSA reduction of $\geq 50\%$. After restricting to patients treated with DSTP3086S at doses > 2 mg/kg ($n = 62$), PSA responses were obtained in one (14%; 95% CI, 0% to 58%) of seven at the 2.25 mg/kg, five (13%; 95% CI, 4% to 27%) of 39 at the 2.4 mg/kg, and five (31%; 95% CI, 11% to 59%) of 16 at the 2.8 mg/kg dose levels. PSA changes relative to baseline for patients with PSA responses are shown in the Data Supplement.

Of the 46 patients with evaluable disease per RECIST at baseline, two (4%) had a partial response (one confirmed)

TABLE 3. Pharmacokinetic Parameters for DSTP3086S Tab, acMMAE, and Unconjugated MMAE Analytes in Cycle 1 at 2.4 mg/kg

DSTP3086S 2.4 mg/kg Once Every 3 Weeks (n = 36), Mean (% CV)	
Parameter	
C_{max}	
Tab, $\mu\text{g/mL}$	56 (23)
acMMAE, ng/mL	879 (20)
Unconjugated MMAE, ng/mL	5.8 (55)
$AUC_{0-\infty}$	
Tab, day $\times \mu\text{g/mL}$	313 (26)
acMMAE, day $\times \text{ng/mL}$	2,423 (20)
Unconjugated MMAE, day $\times \text{ng/mL}$	44 (50)
CL	
Tab, mL/day/kg	8.3 (32)
acMMAE, mL/day/kg	17.5 (23)

Abbreviations: acMMAE, antibody-conjugated monomethyl auristatin E; AUC, area under the curve; CL, clearance; C_{max} , maximum concentration; CV, coefficient of variation; MMAE, monomethyl auristatin E; Tab, total antibody.

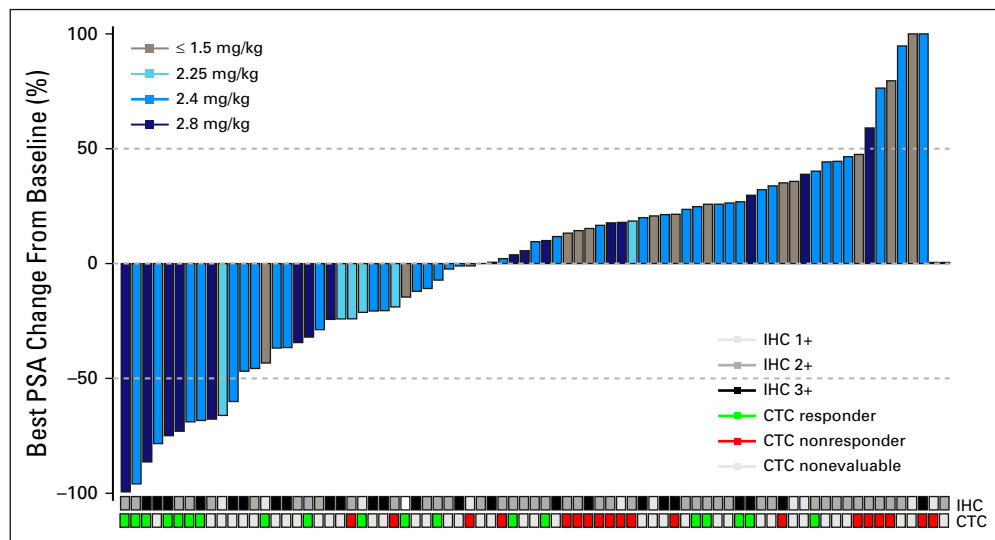


FIG 2. Best response by DSTP3086S once-every-3-weeks dose cohort. Waterfall plot showing best prostate-specific antigen (PSA) change from baseline and corresponding six-transmembrane epithelial antigen of the prostate 1 immunohistochemistry (IHC) and circulating tumor cell (CTC) conversion status. Dashed lines indicate $\pm$ 50% change from baseline.

and 24 (52%) stable disease as best radiographic response. Both patients with partial responses belonged to the subset of 36 evaluable patients per RECIST who received DSTP3086S at doses > 2 mg/kg.

Fourteen patients (18%) remained on study treatment for ≥ 6 months (Fig 1), including two patients with a partial response (Fig 3). One was a 72-year-old man with prostatectomy tumor biopsy tissue that demonstrated IHC 2+ STEAP1 expression. This patient had progressive CRPC after successive treatments with bicalutamide, docetaxel, abiraterone, cabozantinib, and palliative radiation therapy. He received DSTP3086S at a starting dose of 2.8 mg/kg and demonstrated a partial response after cycle 4 (confirmed on subsequent imaging), with a maximum PSA decline of 99%. At cycle 10, DSTP3086S dose was reduced to 2.25 mg/kg because of grade 2 peripheral sensory neuropathy, and the patient discontinued study treatment at cycle 13 as a result of disease progression.

The second patient was a 60-year-old man with prostatectomy tumor biopsy tissue that exhibited IHC 3+ STEAP1 expression. This patient had progressive CRPC after bicalutamide, apalutamide, abiraterone, and docetaxel and received DSTP3086S at a starting dose of 2.8 mg/kg, which was reduced to 2.25 mg/kg at cycle 3 because of grade 3 pulmonary embolism. He demonstrated an unconfirmed radiographic partial response after cycle 4 and a maximum PSA decline of 86% from baseline. He continued on study treatment until cycle 8 and discontinued DSTP3086S as a result of disease progression.

In the weekly cohorts, two patients remained on study treatment for ≥ 6 months. No patients achieved a PSA or RECIST response.

Biomarker Analysis

Among the 134 patients screened for the study, tumor STEAP1 protein expression by IHC was as follows: IHC 0 in

one (1%), IHC 1+ in 35 (26%), IHC 2+ in 65 (49%), and IHC 3+ in 33 (24%). Given that only patients with IHC 2+ or 3+ tumor were eligible for the expansion cohorts, most had high STEAP1-expressing tumors (Fig 2). Of the 11 patients with PSA declines of $\geq 50\%$ from baseline, one (10%) had IHC 1+, five (45%) had IHC 2+, and five (45%) had IHC 3+ tumors. At doses of > 2 mg/kg, one (20%) of five patients with IHC 1+ tumors, five (14%) of 36 with IHC 2+ tumors, and five (24%) of 21 with IHC 3+ tumors had PSA declines of $\geq 50\%$ from baseline.

Of the 77 patients who received DSTP3086 once every 3 weeks, 38 (49%; 95% CI, 38% to 61%) had baseline CTCs $\geq 5/7.5$ mL of blood. CTC conversions from ≥ 5 to < 5 cells/7.5 mL of blood after treatment were observed in 19 (50%; 95% CI, 33% to 67%) of 38 patients and in 16 (59%; 95% CI, 39% to 78%) of 27 patients who received DSTP3086S at doses > 2 mg/kg. By dose level, of the CTC-informative patients, CTC conversions were observed in three (27%; 95% CI, 6% to 61%) of 11 patients treated at doses < 1.5 mg/kg, one (20%; 95% CI, 1% to 72%) of five patients at 2.25 mg/kg, seven (64%; 95% CI, 31% to 89%) of 11 patients at 2.4 mg/kg, and eight (73%; 95% CI, 39% to 94%) of 11 patients at 2.8 mg/kg. Of the 19 CTC converters, the median baseline (pretreatment) CTC count was 31 cells (range, 6 to 304 cells), with 14 (74%) of 19 patients having baseline CTCs $> 10/7.5$ mL of blood. No patients on the weekly dose schedule demonstrated a CTC conversion.

Among the patients treated once every 3 weeks with DSTP3086S, 53 (69%; 95% CI, 57% to 79%) of 77 had baseline CTCs $\geq 1/7.5$ mL of blood, 18 of whom converted to 0 (34%; 95% CI, 22% to 48%) detectable CTCs on DSTP3086S treatment. This represented 18 (45%; 95% CI, 29% to 62%) of 40 patients treated with DSTP3086S > 2 mg/kg once every 3 weeks v zero (0%; 95% CI, 0% to 25%) of 13 patients who received DSTP3086S ≤ 1.5 mg/kg once every 3 weeks.¹⁸

DISCUSSION

ADCs are designed to deliver potent cytotoxic agents directly to tumors that overexpress the target antigen while improving the therapeutic index by reducing normal tissue exposure.²³ DSTP3086S is a novel ADC that targets the STEAP1 antigen frequently expressed in prostate cancer (73% IHC 2+/3+ in patients screened for this trial). In this study, the RP2D of 2.4 mg/kg once every 3 weeks showed preliminary evidence of antitumor activity in patients with progressive mCRPC, including those with prior exposure to microtubule inhibitors. Patients enrolled in the study were enriched for high STEAP1-expressing tumors because they were considered to be the most likely to benefit from DSTP3086S treatment. Antitumor activity was assessed by

PSA changes, imaging, and novel CTC-based measurements to broadly investigate potential clinical benefit. Although DSTP3086S would require refinement to optimize its therapeutic index for further clinical development, the phase I data support the feasibility of targeting STEAP1 in mCRPC. As such, the data may be a valuable guide for novel therapeutic modalities, such as improved ADCs, chimeric antigen receptor T cells, and immune cell-recruiting bispecific antibodies that target STEAP1.

Overall, there was a general concordance between measures of antitumor activity (ie, PSA changes, CTC conversions, RECIST changes; [Figs 1 to 3](#)). Clinical activity was evident at dose levels > 2 mg/kg as shown by $\geq 50\%$ declines in PSA in 18% of patients, although only two

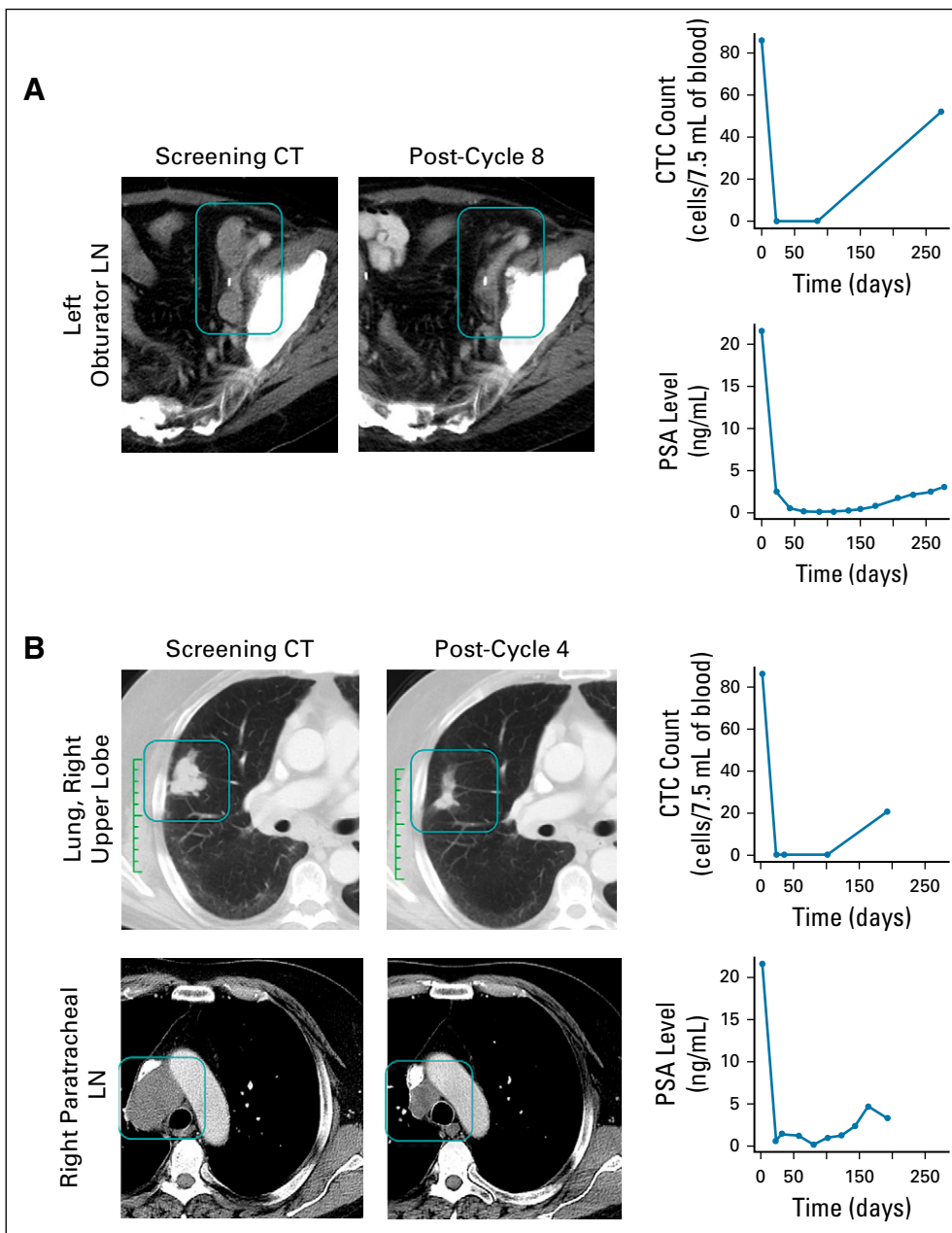


FIG 3. Patient vignettes. (A) A 72-year-old man with six-transmembrane epithelial antigen of the prostate 1 immunohistochemistry 2+ prostate cancer. This patient received DSTP3086S at 2.8 mg/kg and demonstrated a partial response after cycle 4 that was confirmed on subsequent imaging and a maximum prostate-specific antigen (PSA) decline of 99%. The patient discontinued study treatment at cycle 13 as a result of disease progression on the basis of a rising PSA level. (B) A 60-year-old man with six-transmembrane epithelial antigen of the prostate 1 immunohistochemistry 3+ prostate cancer. This patient received DSTP3086S at 2.8 mg/kg, which was reduced to 2.25 mg/kg at cycle 3 because of grade 3 pulmonary embolism. He demonstrated a maximum PSA decline of 86% and an unconfirmed radiographic partial response after cycle 4. Study treatment continued until cycle 8 and was discontinued as a result of disease progression. CT, computed tomography; CTC, circulating tumor cell; LN, lymph node.

patients who received the highest tested dose of DSTP3086S 2.8 mg/kg once every 3 weeks achieved a partial radiographic response. This clinical activity was also noted in heavily pretreated patients.

Half of the patients who received DSTP3086S once every 3 weeks had informative baseline CTCs $\geq 5/7.5$ mL of blood, where CTC conversion to favorable < 5 cells/7.5 mL of blood after treatment was observed in 50% of patients across all dose levels, with an increasing conversion rate of 64% in the 2.4 mg/kg cohort and 73% in the 2.8 mg/kg cohort. A biomarker panel containing CTC conversions has been shown to be a surrogate for survival at the individual-patient level in trials with novel anti-androgens, such as abiraterone acetate (28% of CTC-informative patients converted) and enzalutamide (24% of CTC-informative patients converted).^{18,21} Although PSA declines and imaging responses with STEAP1-ADC treatment were not common, half of the patients with evaluable CTCs had CTC conversions, some coupled with prolonged disease stability. This suggests activity for STEAP1-ADC that is reflected by CTC conversion rather than by PSA or imaging responses and warrants further investigation. In general, the number of prior treatments (either docetaxel or androgen receptor directed) correlated with worse response to DSTP3086S. A limited number of chemotherapy-naïve patients enrolled in the initial 2.4 mg/kg expansion cohort. Because of an overlapping mechanism of action and toxicity between systemic taxanes and MMAE delivered by DSTP3086S, an additional 17 patients were enrolled to assess DSTP3086S in those who had received abiraterone and/or enzalutamide but were chemotherapy naïve; notably only one PSA response was observed. This suggests that prior chemotherapy exposure is not the only factor that potentially limits DSTP3086S activity.

The PK of DSTP3086S was linear across all doses assessed, driven mainly by the anti-STEAP1 antibody, and is consistent with the behavior observed with other ADCs. Dosing on a weekly schedule did not improve overall drug

safety, tolerability, or efficacy compared with once every 3 weeks. Fatigue, peripheral neuropathy, and GI symptoms were the most frequent related AEs observed. Dosing at 2.8 mg/kg required more dose reductions compared with 2.4 mg/kg dosing. Therefore, 2.4 mg/kg was selected as the RP2D.

The relationship between exposure and safety events (eg, neuropathy) is unclear given the small number of patients treated at different doses. The development of peripheral neuropathy with repeated dosing, a known AE associated with microtubule inhibition, is likely mediated by the MMAE therapeutic payload.²⁴⁻²⁷ Hyperglycemia was reported as an AE in 13% of patients in the study. The mechanism for a potential association between DSTP3086S and hyperglycemia remains unclear, although possibly related to MMAE given reports of hyperglycemia with other ADCs conjugated to MMAE.²⁸⁻³⁰

Evaluation of STEAP1 IHC scores suggests a potential association between STEAP1 expression and DSTP3086S clinical activity. However, even with high tumor STEAP1 expression (IHC 3+), the majority of patients did not achieve PSA responses, and the underlying reasons behind intrinsic resistance to DSTP3086S are unknown. It is unknown whether acquired loss of STEAP1 expression after DSTP3086S treatment could explain resistance after an initial response. One effort to better understand STEAP1 expression in patients with CRPC subsequently treated with DSTP3086 was anti-STEAP1-desferrioxamine-⁸⁹Zr-based positron emission tomography imaging.³¹

In summary, DSTP3086S demonstrated an acceptable safety profile, with evidence of antitumor activity confirming that the targeting of STEAP1-expressing mCRPC tumors with an ADC is feasible. Although DSTP3086S would require optimization for further clinical development, these data may inform development of novel ADCs, chimeric antigen receptor T cells, and immune cell-recruiting bispecific antibodies that target STEAP1.

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

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.19.00646>.

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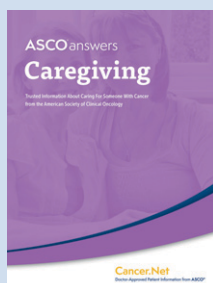
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Phase I Study of DSTP3086S, an Antibody-Drug Conjugate Targeting Six-Transmembrane Epithelial Antigen of Prostate 1, in Metastatic Castration-Resistant Prostate Cancer**

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A Phase Ib/IIa Study of the Pan-BET Inhibitor ZEN-3694 in Combination with Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer

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ABSTRACT

Purpose: ZEN-3694 is a bromodomain extraterminal inhibitor (BETi) with activity in androgen-signaling inhibitor (ASI)-resistant models. The safety and efficacy of ZEN-3694 plus enzalutamide was evaluated in a phase Ib/IIa study in metastatic castration-resistant prostate cancer (mCRPC).

Patients and Methods: Patients had progressive mCRPC with prior resistance to abiraterone and/or enzalutamide. 3+3 dose escalation was followed by dose expansion in parallel cohorts (ZEN-3694 at 48 and 96 mg orally once daily, respectively).

Results: Seventy-five patients were enrolled ($N = 26$ and 14 in dose expansion at low- and high-dose ZEN-3694, respectively). Thirty (40.0%) patients were resistant to abiraterone, 34 (45.3%) to enzalutamide, and 11 (14.7%) to both. ZEN-3694 dosing ranged from 36 to 144 mg daily without reaching an MTD. Fourteen patients (18.7%) experienced grade ≥ 3 toxicities, including three

patients with grade 3 thrombocytopenia (4%). An exposure-dependent decrease in whole-blood RNA expression of BETi targets was observed (up to fourfold mean difference at 4 hours post-ZEN-3694 dose; $P \leq 0.0001$). The median radiographic progression-free survival (rPFS) was 9.0 months [95% confidence interval (CI), 4.6–12.9] and composite median radiographic or clinical progression-free survival (PFS) was 5.5 months (95% CI, 4.0–7.8). Median duration of treatment was 3.5 months (range, 0–34.7+). Lower androgen receptor (AR) transcriptional activity in baseline tumor biopsies was associated with longer rPFS (median rPFS 10.4 vs. 4.3 months).

Conclusions: ZEN-3694 plus enzalutamide demonstrated acceptable tolerability and potential efficacy in patients with ASI-resistant mCRPC. Further prospective study is warranted including in mCRPC harboring low AR transcriptional activity.

Introduction

Prostate cancer is the most common malignancy and second leading cause of death among men in the United States (1). Androgen-signaling blockade with either androgen receptor (AR) antagonism or CYP17 inhibition improves long-term survival in both metastatic castration-resistant prostate cancer (mCRPC) and metastatic castration-sensitive disease (2–5). However, treatment resistance is universal, and cross-resistance between AR antagonists and CYP17 inhibitors limits the clinical utility of these agents when used sequentially (6–10).

Multiple mechanisms of therapeutic resistance to AR pathway inhibitors have been described, including amplification of the AR gene and its enhancers, upregulation of intratumoral androgen synthesis, generation of ligand-independent AR splice variants, activation of alternative oncogenic signaling pathways including MYC, transdifferentiation to an AR-independent, neuroendocrine phenotype, and cooption of alternative steroid hormone receptors including the glucocorticoid receptor (GR; refs. 11–16). A broad therapeutic approach capable of affecting expression/signaling of multiple pathways may provide a means to reverse resistance and restore sensitivity to AR-targeting therapy.

Proteins of the bromodomain extraterminal (BET) bromodomain family are epigenetic readers that bind to acetylated histones through their bromodomains to affect gene transcription (17). They preferentially localize at sites of enhancers of various oncogenes to promote tumorigenesis and progression. ZEN-3694 is an orally bioavailable, second-generation, potent pan-BET bromodomain inhibitor (BETi) that leads to downregulation of expression of AR signaling, AR splice variants, MYC, GR, and other oncogenes in multiple CRPC models, and has significant *in vivo* activity as single agents, with evidence of synergy when combined with enzalutamide (18).

We conducted a first-in-human phase Ib/II dose-escalation/expansion study of ZEN-3694 in combination with enzalutamide in patients with mCRPC and prior progression on one or more androgen-signaling inhibitor (ASI).

Patients and Methods

Patient population

Patients had histologically confirmed mCRPC with progression at study entry by Prostate Cancer Working Group 2 (PCWG2)

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Translational Relevance

Bromodomain extraterminal inhibitors (BETi) demonstrate *in vivo* activity in enzalutamide-resistant prostate cancer models via downregulation of bypass signaling pathways including MYC. Clinical translation of BETi as a therapeutic strategy in metastatic castration-resistant prostate cancer (mCRPC) has heretofore been limited by significant toxicity including risk of thrombocytopenia. In this phase Ia/Ib study of the pan-BETi, ZEN-3694, in combination with enzalutamide in 75 patients with abiraterone- and/or enzalutamide-resistant mCRPC, the combination was well-tolerated without reaching an MTD. Less than 5% of patients experienced a grade ≥ 3 thrombocytopenia. Robust, dose-dependent, and sustained downregulation of expression of BETi target genes including *MYC* was observed using a whole-blood RNA assay. Encouraging efficacy was observed including a median radiographic progression-free survival of more than 10 months in those with prior progression on enzalutamide monotherapy. Clinical benefit was particularly pronounced in high-risk subgroups including those with an aggressive variant clinical phenotype as well as those with lower androgen receptor transcriptional activity in baseline tumor biopsies. A randomized study is planned with ZEN-3694 at the recommended phase II dose of 96 mg orally once daily in combination with enzalutamide in mCRPC with prior progression on enzalutamide or abiraterone.

criteria (19). Patients were required to have progression on prior abiraterone and/or enzalutamide treatment prior to study entry, no prior docetaxel for the treatment of mCRPC, serum testosterone < 50 ng/dL with maintenance of androgen deprivation therapy during study treatment, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function including absolute neutrophil count $> 1.5 \times 10^9/L$, platelet count $> 100,000$, total bilirubin $< 1.5 \times ULN$, and creatinine clearance > 60 mL/minute. Patients with uncontrolled hypertension or New York Heart Association class II or higher congestive heart failure were excluded.

Study approval was obtained from the ethics committees at the participating institutions and regulatory authorities. All patients gave written informed consent. The study followed the Declaration of Helsinki and Good Clinical Practice guidelines (NCT02711956).

Study design and treatment schedule

This was a phase Ib/II, multicenter, open-label, combination dose-escalation study of ZEN-3694 in combination with the standard dose of enzalutamide, 160 mg daily. Lead-in treatment period with enzalutamide monotherapy (day -14 to day -1) was required in subjects not already receiving enzalutamide at the time of study enrollment. Patients continued treatment until radiographic progression by PCWG2 criteria, unequivocal clinical progression, or unacceptable toxicity. PSA progression alone was not used as a criterion for treatment discontinuation.

The starting dose of ZEN-3694 was 36 mg orally once daily. A 3+3 dose-escalation schema was utilized up to a maximum administered dose of 144 mg daily. Dose expansion was subsequently performed in two cohorts in parallel: (i) low dose, ZEN-3694 at 48 mg daily ($N = 14$), and (ii) high dose, ZEN-3694 96 mg daily ($N = 26$).

A formal interim analysis was not planned; however, interim data were reviewed on an ongoing basis. The final planned analyses were performed after 75 patients were enrolled and the database was locked on February 6, 2020.

The primary study endpoint was safety and the recommended phase II dose of ZEN-3694 in combination with enzalutamide. Secondary endpoints included pharmacokinetics assessment of ZEN-3694 and enzalutamide, PSA50 response ($\geq 50\%$ decline in PSA from baseline confirmed ≥ 4 weeks later) rate, duration of PSA50 response, and radiographic progression-free survival (rPFS). Soft-tissue radiographic progression and responses were assessed according to RECIST v1.1 criteria. Progression of bone metastases was assessed using PCWG2 criteria. *Post hoc* analyses were performed to assess composite progression-free survival (PFS), defined as first occurrence of radiographic or clinical progression or death, as well as PSA PFS by PCWG2 criteria. Correlative endpoints included pharmacodynamics assessment of ZEN-3694 in combination with enzalutamide and relationship between tumor genomic/transcriptional profile, protein expression, and clinical variables with clinical outcomes on treatment.

Safety and efficacy assessments

Clinical and laboratory assessments were conducted at baseline and weekly during cycles 1 and 2 (28-day cycle length), every 2 weeks in cycle 3, and then every 4 weeks thereafter. Tumor response monitoring was performed using whole-body bone scan and cross-sectional imaging of the chest/abdomen/pelvis at baseline and every 2 cycles thereafter. Adverse events were graded using Common Toxicity Criteria version 4.0.

Pharmacodynamic/exploratory assessments

Whole-blood RNA for assessment of BETi target gene expression (*MYC*, *IL8*, *CCR1*, *GPR183*, *HEXIM1*, and *IL1RN*) was collected predose, 2 hours, 4 hours, 6 hours, and 24 hours post-cycle 1, day 1 dose (20). Baseline and on-treatment metastatic tumor biopsies of bone or soft tissue were obtained whenever feasible, and were evaluated by RNA-sequencing (RNA-seq) and IHC for protein expression of AR. Quality of the FASTQ files was verified by FASTQC2, and reads were aligned on BaseSpace (<https://base.space.illumina.com>) using the RNA-Seq alignment App (version 1.1.1) with the default parameters (STAR aligner version 2.5.0b, UCSC hg19 reference genome). Gene expression levels (FPKM) for baseline biopsies were estimated using Cufflinks (version 2.2.1). For the paired biopsies, aligned reads were used as input for DESeq2 (version 1.1.0) to enable pairwise differential gene expression analysis using the default parameters. Gene set enrichment analysis (GSEA) was performed on transcriptional data when available, and previously validated AR, prostate cancer, and MYC transcriptional signatures were additionally applied to the transcriptional data (21, 22). For the BETi signature, significant genes ($P < 0.05$) that were > 2 -fold downregulated upon exposure of $0.5 \mu\text{mol/L}$ I-BET762 for 24 hours in LNCaP prostate cancer cells were selected (23). Archival tumor tissue was obtained whenever feasible for analysis of whole transcriptome and exome sequencing.

Pharmacokinetics assessments

Plasma levels of ZEN-3694, the bioactive first-order metabolite ZEN-3791, and enzalutamide were measured predose and up to 24 hours postdose on days 1 and 15 of cycle. Plasma concentrations were determined using validated LC/MS-MS analysis.

Table 1. Baseline characteristics.

	Study cohort (N = 75) ^a
Median age (range), years	70 (47–89)
ECOG score	
0	42 (56%)
1	33 (44%)
Opioid analgesic use	18 (24%)
Visceral metastases at study entry (%)	21 (28%)
Median PSA, ng/mL (range)	26.99 (0.15–1,701.8)
Median ALP, U/L (range)	82 (33–487)
Median LDH, U/L (range)	188 (98–543)
Median hemoglobin, g/dL (range)	13.2 (6.4–20.2)
Halabi risk category (ref. 24; %)	
Low	50 (67)
Intermediate	16 (21)
High	8 (11)
Unknown	1 (1)
Prior number of systemic cancer treatments (range)	3 (1–7)
Prior resistance to AR-targeted therapy (%)	
Abiraterone	30 (40)
Enzalutamide	34 (45)
Both	11 (15)
Duration of prior AR-targeted therapy (range), months	14.3 (1.0–58.3)
Reason for prior abiraterone or enzalutamide discontinuation	
Radiographic progression	8 (11%)
Radiographic and PSA progression	31 (41%)
Clinical and PSA progression	3 (4%)
PSA progression	33 (44%)
Clinical progression	0

Abbreviations: ALP, alkaline phosphatase; LDH, lactate dehydrogenase.

^aFor data recorded in the clinical database as of the data cut-off date of January 7, 2020.

Results

Study population and patient disposition

A total of 75 patients were enrolled from December 2016 to April 2019 across seven investigational sites. Baseline characteristics of the enrolled patients are shown in **Table 1**. At study entry, 30 (40.0%) patients had previously experienced disease progression on abiraterone, 34 (45.3%) on enzalutamide, and 11 (14.7%) on both. Twelve (16%) patients experienced prior primary resistance to first-line AR-targeted therapy, defined in *post hoc* fashion as treatment duration of less than 6 months. Forty-two (56%) patients had evidence of radiographic and/or clinical progression at study entry.

The median duration of treatment was 3.5 months (range, 0–34.7+). As of date of data cutoff, seven patients (9%) remain on treatment without progression, with duration of therapy ranging from 15.0+ to 34.7+ months. Forty-eight patients (64%) discontinued for disease progression; nine patients (12%) discontinued for adverse events, and 11 (16%) withdrew from study.

Safety results

The proportion of patients who experienced grade ≥3 treatment-related adverse event was 18.7% (*n* = 14). The most common grade ≥3 adverse events (≥2 patients) included nausea (*n* = 3; 4%), thrombocytopenia (*n* = 3; 4%), anemia (*n* = 2; 2.7%), fatigue (*n* = 2; 2.7%), and hypophosphatemia (*n* = 2; 2.7%). There were no clinically significant bleeding events observed on treatment.

The most commonly reported ZEN-3694–related adverse events (any grade severity, occurring in ≥10% of patients, in order of incidence) were visual symptoms (described as a transitory perception of brighter lights and/or light flashes, with or without visual color tinges, as well as trouble navigating in dim light; 67%), nausea (45%), fatigue (40%), decreased appetite (25%), dysgeusia (20%), thrombocytopenia (15%), and weight decreased (11%; **Table 2**). Visual symptoms were grade 1 in all cases, resolved 60–90 minutes after dosing, were successfully mitigated with implementation of dosing before bedtime, and resulted in no functional consequences upon repeat eye exams throughout study participation.

Dose reductions and/or treatment discontinuation due to adverse events were required in 24 of 75 (32%) of patients. The percentage of patients requiring dose reduction and/or discontinuation ranged from 10% to 35% for doses from 36 to 96 mg/day, in contrast to 75% and 100% at ZEN-3694 dose levels of 120 and 144 mg/day, respectively (Supplementary Table S1). The class of adverse events leading to dose reduction and/or discontinuation were related to gastrointestinal (GI) toxicities in 83% of occurrences.

Determination of MTD and recommended phase II dose

In the dose escalation, 35 patients were enrolled across dose levels ranging from 36 to 144 mg daily. The MTD was not reached. One patient experienced a dose-limiting toxicity at the 96 mg/day dose level (grade 3 nausea necessitating missing >25% of scheduled doses in cycle 1). On the basis of the aggregate of pharmacodynamics data indicating dose exposure–dependent downregulation of BETi target gene expression with a plateau of effect at doses above 96 mg/day, the high percentage of patients requiring dose interruptions/reductions at doses above 96 mg/day, and a comparable pharmacokinetics/pharmacodynamics effect with preclinical models treated at efficacious doses, 96 mg/day was chosen as the recommended phase II dose of ZEN-3694 for dose expansion (*N* = 26). An additional dose-expansion cohort of 48 mg/day (*N* = 14) was also enrolled, to better characterize the exposure–effect relationship.

Pharmacokinetics analyses

The AUC_{0–24} and the C_{max} of combined ZEN-3694 (parent compound) + ZEN-3791 (active metabolite), on day 1 and day 15 of cycle 1, are shown in **Fig. 1A** and **B**, respectively. Less than dose proportional increase in exposure was observed at doses higher than 96 mg daily. The estimated T_{max} and half-life of ZEN-3694 + ZEN-3791 were 2 and 5–6 hours, respectively. The ratio of ZEN-3791 metabolite to parent compound, ZEN-3694, was increased on day 15 compared with day 1, likely related to enzalutamide-mediated induction of CYP3A4 metabolism (**Fig. 1C**). The observed plasma concentrations of ZEN-3694 + ZEN-3791 were similar to ZEN-3694 monotherapy pharmacokinetics reported previously (24). Likewise, there was no significant impact of ZEN-3694 on enzalutamide and desmethyl enzalutamide concentrations (**Fig. 1D**).

Pharmacodynamics analyses

Pre- and up to 24-hour postdose whole-blood RNA analyses were available from 69 patients enrolled on study. There was a dose-dependent two- to fourfold decrease in the whole-blood mRNA levels of the BETi target genes *MYC*, *IL8*, *CCR1*, *GPR183*, and *IL1RN* (**Fig. 2A**) upon treatment with ZEN-3694, which was sustained for at least 8 hours. Decrease in expression of BETi target genes appeared to plateau at ZEN-3694 dose levels ≥96 mg. There was a direct correlation between cumulative exposure to ZEN-3694 + ZEN-3791 (AUC_{0–2} for *MYC* and *GPR183*, and AUC_{0–4} for *CCR1*, *IL1RN*, and

Table 2. Summary of all grades treatment-related adverse events by dose level of ZEN-3694.

	36 mg QD <i>n</i> = 4	48 mg QD <i>n</i> = 21	60 mg QD <i>n</i> = 6	72 mg QD <i>n</i> = 6	96 mg QD <i>n</i> = 31	120 mg QD <i>n</i> = 4	144 mg QD <i>n</i> = 3	Total <i>N</i> = 75 (%)
Blood creatinine increased			2		3			5 (6.7)
Constipation		1			3			4 (5.3)
Decreased appetite		2	2	1	10	3	2	20 (26.7)
Diarrhea				1	5			6 (8)
Dizziness				1	3			4 (5.3)
Dysgeusia		2	0	0	10	1	3	16 (21.3)
Dyspepsia		1			2			3 (4)
Fatigue	1	8	1	2	13	3	1	29 (38.7)
Nasal congestion					3			3 (4)
Nausea		7	2	3	17	3	2	34 (45.3)
Photopsia		1			3			4 (5.3)
Photosensitivity		2			3			5 (6.7)
Rash					3			3 (4)
Rash maculopapular		3			1		1	5 (6.7)
Taste disorder			1	1	3			5 (6.7)
Thrombocytopenia		1	1	2	6		1	11 (14.7)
Vision blurred					2	1		3 (4)
Visual symptoms ^a	3	12	4	6	17	4	2	48 (64)
Vomiting		1			3	1		5 (6.7)
Weight loss and abnormal weight loss	1			1	3	1	2	8 (10.7)

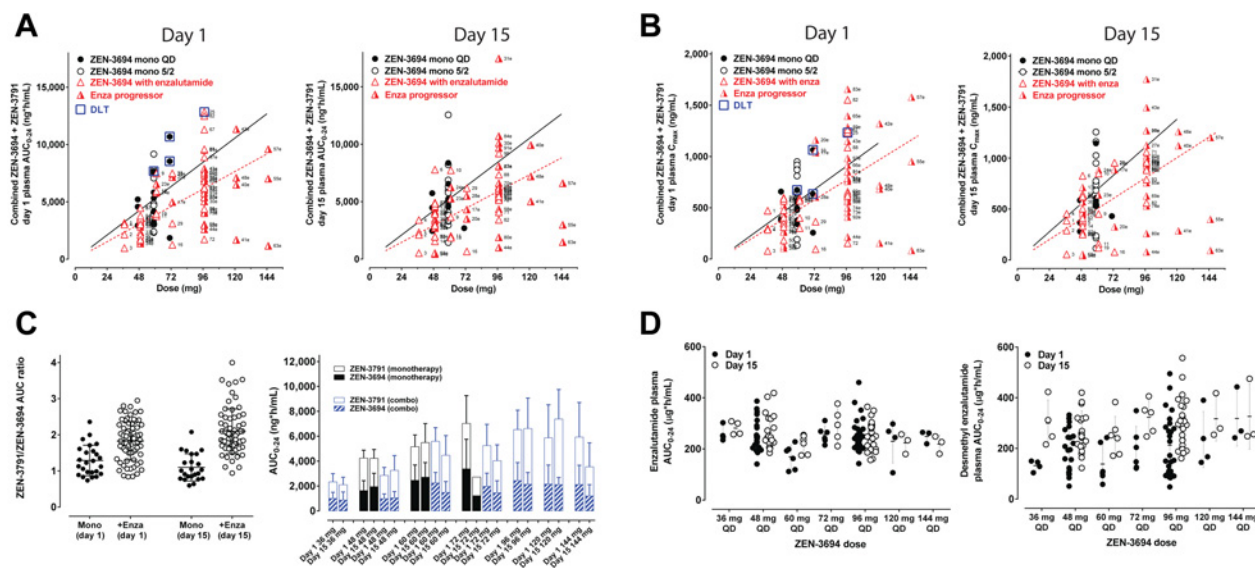
Abbreviation: QD, every day.

^aVisual symptoms defined as a transitory perception of bright lights and/or light flashes with or without visual color tinges.

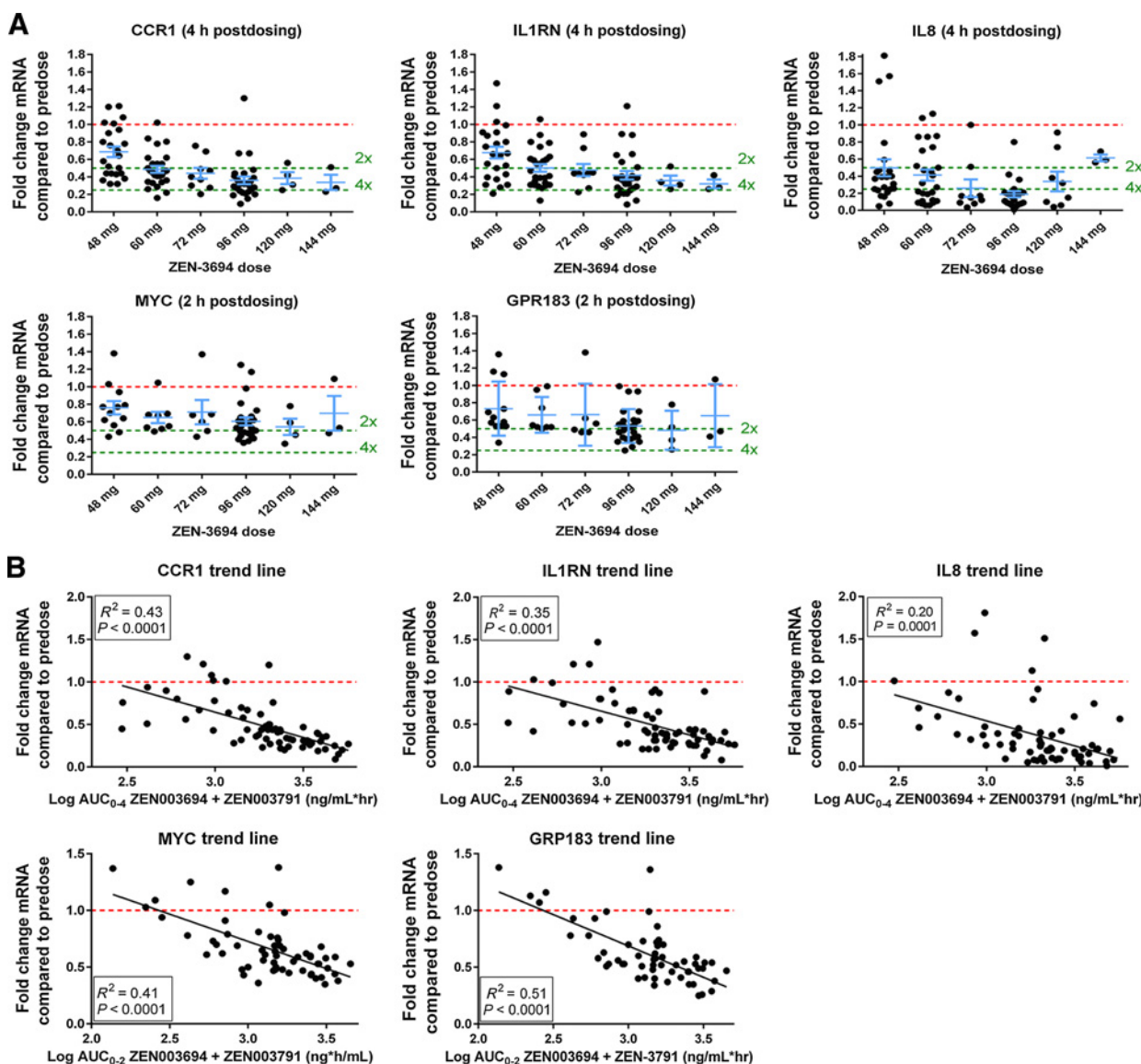
IL8) with downregulation of whole-blood mRNA levels of the BETi target genes (R^2 ranging from 0.20 to 0.51; $P \leq 0.0001$; Fig. 2B).

Four patients had evaluable paired metastatic tumor biopsies obtained at baseline and on-treatment (median duration of treatment 8 weeks prior to on-treatment biopsy). Time after the last ZEN-3694 +

enzalutamide dosing prior to the biopsy ranged from 3.5 to 24 hours. The limited sample size precluded ability to perform statistical analyses of change in expression by dose level. However, on GSEAs, looking at changes between on-treatment versus pretreatment samples, there were strong indications of downregulation of expression of MYC and

**Figure 1.**

Pharmacokinetics analyses. **A** and **B**, AUC from 0 to 24 hours (AUC₀₋₂₄) and maximum serum concentration, respectively, of ZEN-3694 + ZEN-3791 (first-generation active metabolite) serum concentration on day 1 and day 15 of cycle 1 (red triangles). Overlaid AUC₀₋₂₄ data from the monotherapy (mono) trial of ZEN-3694 (23) are shown for dose levels 48 and 72 mg daily (black circles). **C**, Ratio of ZEN-3791 (first-generation active metabolite) versus ZEN-3694 (parent compound) from the prior monotherapy trial (23) and in combination with enzalutamide (enza) on day 1 and day 15 of cycle 1. **D**, Steady-state serum concentration of enzalutamide and desmethyl enzalutamide following 14 day lead-in of enzalutamide (day -14 to day -1), by ZEN-3694 dose level. QD, every day.

**Figure 2.**

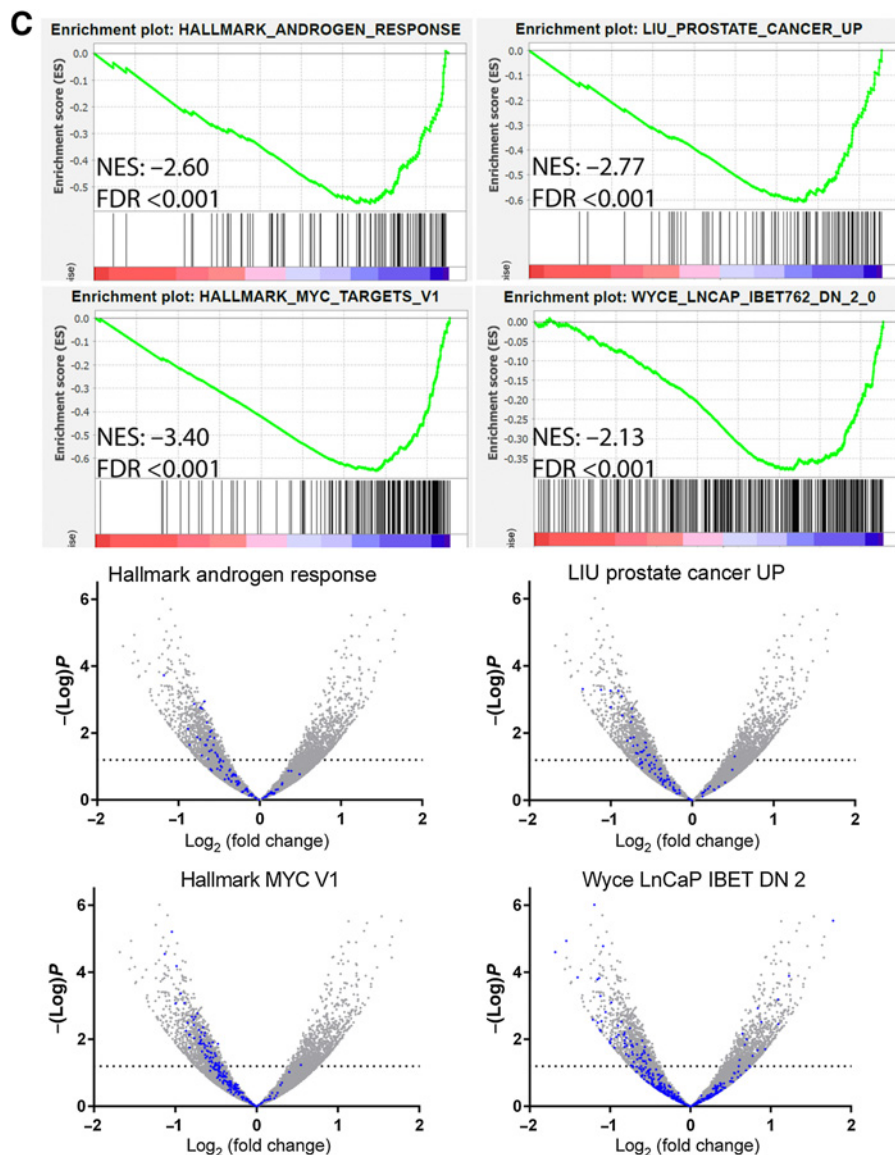
Pharmacodynamics assessments. **A**, Fold-change from baseline in whole-blood RNA expression of BETi target genes *CCR1*, *IL1RN*, *IL8*, *MYC*, and *GPR183* by ZEN-3694 dose level. **B**, Correlation between fold change from baseline in whole-blood RNA expression of BETi target genes and AUC₀₋₂₄ of ZEN-3694 + ZEN-3791 indicates strong pharmacokinetics-pharmacodynamics relationship. (Continued on the following page.)

AR signaling on-treatment compared with baseline biopsies, as well as downregulation of BET-dependent genes previously identified in LnCaP cells treated with the I-BET762 BETi (Fig. 2C; ref. 23).

Efficacy analyses

The median rPFS in the overall cohort was 9.0 months [95% confidence interval (CI), 4.6–12.9], with 7.8 months for patients that had progressed on abiraterone (95% CI, 4.9–10.6) and 10.1 months for patients that had progressed on enzalutamide (95% CI, 4.4–12.9; Fig. 3A). Composite median radiographic or clinical PFS was 5.5 months (95% CI, 4.0–7.8) in the overall cohort, and 5.5 months (95% CI, 4.4–7.8) and 5.1 months (95% CI, 3.2–10.1) in those with prior progression on abiraterone and enzalutamide, respectively

(Fig. 3B). Thirteen (17%) and four (5%) patients remained on treatment for greater than 12 and 24 months without progression, respectively (Fig. 3C). In patients with radiographic progression at the time of study entry, the median rPFS was 7.8 months (95% CI, 4.4–10.6; Fig. 3D) and composite PFS was 4.8 months (95% CI, 3.5–7.7). An analysis of the subset of patients with primary resistance to prior first-line AR-targeted therapy ($N = 12$), defined by progression within 6 months of treatment initiation, demonstrated an on-treatment median rPFS of 10.6 months (95% CI, 7.5–not reached; Fig. 3E). Using a more stringent cutoff of primary resistance of progression within 16 weeks of prior first-line AR-targeted therapy ($N = 5$), likewise demonstrated prolonged median rPFS (median rPFS, 22.4 months; 95% CI, 7.8–not reached) and composite PFS (median

**Figure 2.**

(Continued.) **C**, GSEA of change from baseline in gene expression by RNA-seq in paired metastatic tumor biopsies. Downregulation of MYC signaling pathway was observed in on-treatment versus baseline tumor biopsy.

PFS, 10.6 months; 95% CI, 4.0, not reached) in this subset of patients (Supplementary Fig. S1A and S1B).

Of the four exceptional responders who remained on treatment for greater than 24 months duration, three had radiographic progression at study entry, two had progressed on prior enzalutamide, and one of the four patients experienced an objective radiographic response on enzalutamide + ZEN-3694 (Supplementary Table S2).

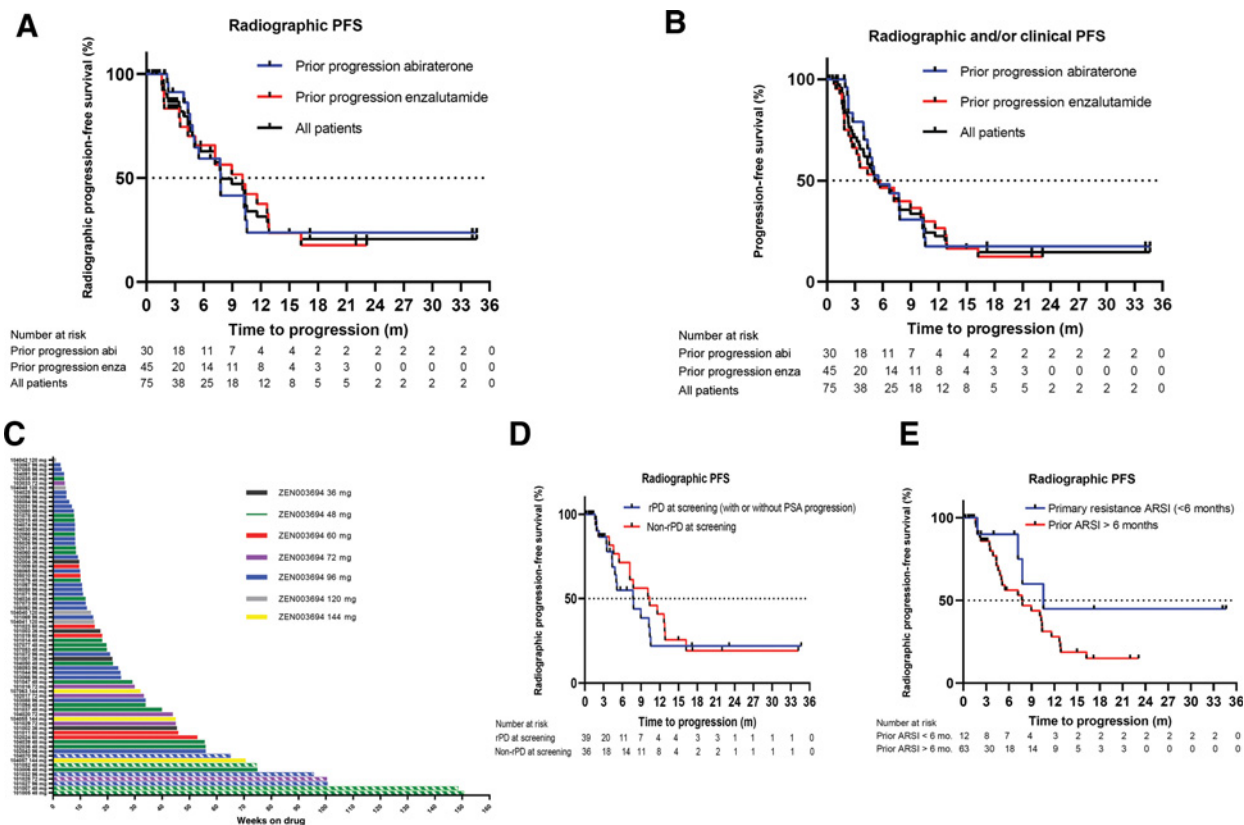
Six patients (8%) experienced a greater than 50% decline from baseline in serum PSA by PCWG2 criteria (PSA50 response), including two patients with prior progression on enzalutamide monotherapy. All PSA responses were confirmed on repeat measurement. Four patients (5.3%) experienced a greater than 90% decline in serum PSA from baseline on study treatment. PSA50 responses were sustained in the majority of cases with median duration of PSA50 response of 21.1 months (95% CI, 19.0–23.2). The median PSA PFS was 3.2 months (95% CI, 3.2–5.1) in the overall study cohort and 3.2 months (95% CI, 2.8–6.4) in those with PSA-only progression at study entry. There were

no substantial differences with respect to rPFS, composite PFS, or PSA PFS noted between 48- and 96-mg dose-expansion cohorts.

In addition, in a subset of patients ($n = 21$), there was a transient increase of >2 ng/mL and 25% above baseline in serum PSA within the first 12 weeks of treatment with subsequent plateau in serum PSA level (Supplementary Fig. S2A). Patients with transient PSA increase as defined above appeared to derive sustained clinical benefit with median rPFS of 10.1 months (95% CI, 5.6–11.7). In contrast, patients whose serum PSA consistently rose beyond the 12-week timepoint ($n = 21$) experienced a median rPFS of 7.2 months (95% CI, 3.9–9.0; Supplementary Fig. S2B).

Predictors of prolonged clinical benefit with ZEN-3694 + enzalutamide

Exploratory analyses were performed with available genomic and transcriptional data from baseline tumor biopsies to evaluate association with subsequent time to progression (TTP) on treatment.

**Figure 3.**

rPFS and duration of treatment. **A**, Kaplan-Meier curve demonstrating rPFS by PCWG2 criteria in all evaluable study participants (black curve), patients with prior enzalutamide (enza) progression (blue curve), or prior abiraterone (abi) progression (green curve). **B**, Kaplan-Meier curve demonstrating composite PFS (time to first clinical or radiographic progression). **C**, Swimmer plot showing duration of treatment, with color labels by ZEN-3694 dose level (hashed line, treatment ongoing). **D** and **E**, Kaplan-Meier curves showing rPFS in subsets of patients with radiographic progression or primary resistance to prior ASI, respectively.

Interestingly, patients whose baseline metastatic tumor biopsies ($N = 13$) harbored lower canonical AR transcriptional activity, as assessed by 5-gene score (25) as well as the HALLMARK_ANDROGEN_RESPONSE signature, experienced a longer median TTP (median TTP 19 vs. 45 weeks; **Fig. 4A** and **B**). In support of the notion that tumors with lower canonical AR activity might be more responsive to BET inhibition, we observed a trend toward prolonged TTP among patients meeting clinical criteria for aggressive variant prostate cancer [e.g., low serum PSA <10 ng/mL with concomitant high disease burden (visceral metastases and/or >10 bone metastases); ref. 26]. The median TTP in patients with aggressive variant disease was 11.6 months (95% CI, 7.2–12.8) versus 5.5 months (95% CI, 2.3–10.6, $P = 0.24$) in those without aggressive variant clinical features at baseline (**Fig. 4C**).

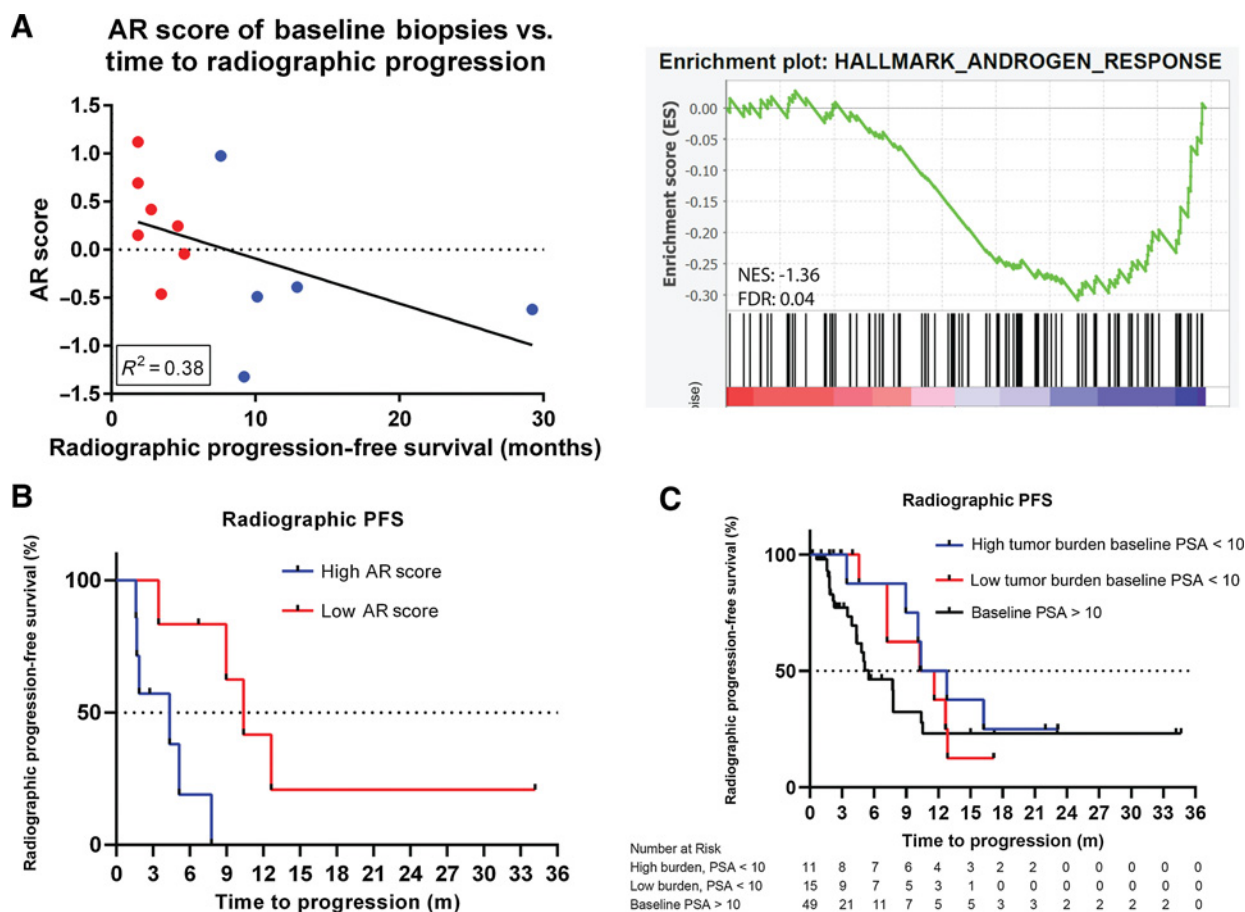
Discussion

Our results demonstrate that the pan-BETi, ZEN-3694, has acceptable tolerability and encouraging preliminary efficacy data in combination with enzalutamide in patients with mCRPC. The median rPFS in the overall cohort was 9 months, and more than 10 months in those with prior progression on enzalutamide monotherapy. ZEN-3694 + enzalutamide treatment led to a two- to fourfold reduction in the expression of BET target genes including *MYC*, which was sustained throughout the 24-hour dosing interval. On the basis of the aggregate

of the safety, efficacy, and evidence of robust downregulation of expression of BET-dependent target genes, ZEN-3694 at 96 mg daily has been selected as the recommended phase II dose to move forward in further clinical development in combination with enzalutamide. The clinical and pharmacodynamics data provide clinical evidence that BET inhibition may be able to abrogate resistance mechanisms and resensitize patients to ASIs.

The prolonged PFS observed in this study in relevant subsets, including those with radiographic progression at study entry, primary resistance to prior AR-targeted therapy, as well as those with prior progression on enzalutamide monotherapy, is consistent with an additive or potentially synergistic interaction between enzalutamide and ZEN-3694. The baseline characteristics of the study cohort are representative of other studies in the post-ASI mCRPC setting, including nearly one-third of patients with intermediate- or high-risk disease by Halabi prognostic model (27), and a quarter of whom required opioid analgesics at study entry. These features argue against the possibility of enrichment of better than average-risk group contributing significantly to the prolonged PFS observed on treatment. Taken together, the data support a randomized study to evaluate for the magnitude of benefit of ZEN-3694 in combination with enzalutamide.

With the caveat of cross-trial comparisons, the median PFS observed with ZEN-3694 + enzalutamide in this study compares favorably with outcomes observed with sequential AR targeting in

**Figure 4.**

AR signaling score and clinical outcomes. **A**, Lower AR activity level in baseline tumor biopsies is correlated with longer time on study ($R^2 = 0.38$) using either the 5-gene AR score (left) or the HALLMARK_ANDROGEN_RESPONSE (right) signatures. For the hallmark signature, baseline gene expression of biopsies from patients with radiographic progression prior to 24 weeks versus greater than 24 weeks were compared (FDR = 0.04). **B**, Kaplan-Meier curve showing significant increase in time to median rPFS in patients with lower AR signaling compared with patients with higher AR signaling score (median rPFS 10.4 months in tumors with low AR score versus 4.3 months in tumors with high AR activity). **C**, Patients with high tumor burden and lower baseline PSA levels (<10 ng/mL; blue curve) demonstrate longer PFS than patients with higher baseline PSA (>10 ng/mL) levels.

mCRPC with abiraterone followed by enzalutamide, or vice versa, in prior studies. In the prospective SWITCH phase II cross-over study, the median PFSs of second-line enzalutamide and abiraterone were 3.5 and 1.7 months, respectively (6). Similarly, median PFSs with second-line AR-targeting therapy have been less than 8 months in most retrospective series (9). Caution should be applied to overinterpretation of these cross-trial comparisons, and a randomized trial will be necessary to assess the individual contribution of ZEN-3694 added to enzalutamide in mCRPC.

The PSA50 response rate with the combination of ZEN-3694 plus enzalutamide was less than 10% in the study, and median PSA PFS was less than 4 months. Although this may reflect lack of additive benefit of ZEN-3694 in combination with enzalutamide, decline in serum PSA and PSA PFS may not be the best metrics to gauge efficacy of BETis including ZEN-3694. In fact, a subset of patients experienced transient early rises in serum PSA levels by week 8 of treatment, which were associated with longer TTP. In addition, tumors harboring lower AR activity at baseline appeared to derive more clinical benefit from treatment. Finally, those with low serum PSA in relation to metastatic disease burden, a clinical profile consistent with small-cell/neuroen-

docrine prostate cancer, may also have longer rPFS compared with those with higher baseline serum PSA levels. Although these observations are hypothesis generating and require prospective validation, it raises the intriguing possibility that BETis may restore dependency on AR signaling in tumors that are less reliant on AR prior to BETi or that BETi is blocking important AR-independent survival mechanisms, such as MYC, which have been shown to be critical for BETi effects in CRPC (13, 28, 29). AR-independent mCRPC is becoming more prevalent with the earlier application of ASIs, and is associated with shortened survival and unmet need to develop novel therapeutic approaches (14).

The acceptable toxicity profile of ZEN-3694 in combination with enzalutamide stands in contrast to the results observed with several other recent BETis reported in the literature, which have been limited by thrombocytopenia and GI toxicities (30, 31). In this study, there was substantially less thrombocytopenia observed. GI toxicities were not as prevalent or severe as prior studies and were manageable with early institution of antiemetics and dose reductions, if necessary. The reasons underlying the potentially more favorable toxicity profile observed in this study, as compared with other BETis, may relate to

patient factors such as excluding prior chemotherapy for mCRPC. Furthermore, it is possible that a pharmacokinetics interaction between ZEN-3694 and enzalutamide may have accelerated production of the first-generation active metabolite, ZEN-3791, which may have a more favorable toxicity profile. The differential toxicity compared with other BETis does not appear to relate to differences in potency, given the robust downregulation of BETi target genes observed in this study.

There were several limitations of the study, including the limited number of baseline and on-treatment paired biopsies, precluding the ability to identify a consistent predictive biomarker with a high degree of statistical confidence. The nonrandomized nature of the dose expansion portion of the study also limits our ability to draw definitive conclusions regarding the potential additive benefit of ZEN-3694, although evidence of contribution is provided by favorable comparison with contemporary controls from other studies as outlined above. AR-V7 splice variant status in circulating tumor cells, a validated resistance mechanism to AR-targeted therapy that may be downregulated with BETi treatment, was not reliably captured in this study in a sufficient number of patients to permit evaluation. Finally, there did not appear to be a relationship between dose level and efficacy outcomes, potentially related to fairly broad interpatient variability in ZEN-3694 exposure, limited sample size, and limited single-agent activity of ZEN-3694.

With the shift in application of potent AR-targeted therapy in earlier castration-sensitive settings, there is an increasing medical need to develop therapies that reverse therapeutic resistance and restore dependency on AR signaling. The preliminary data provided by the phase Ib/II study of ZEN-3694 plus enzalutamide provides strong justification to further investigate it in a prospective, randomized study.

Disclosure of Potential Conflicts of Interest

R. Aggarwal reports grants from Zenith Epigenetics during the conduct of the study, grants and personal fees from Janssen, Merck, and AstraZeneca, and personal fees from Dendreon and Clovis Oncology outside the submitted work. M.T. Schweizer reports grants from Zenith Epigenetics (research funds to institution) during the conduct of the study, Janssen (research funds to institution), AstraZeneca (research funds to institution), Madison Vaccines (research funds to institution), Pfizer (research funds to institution), and Hoffmann-La Roche (research funds to institution), and personal fees from Resverlogix (consulting fee) outside the submitted work. D.M. Nanus reports personal fees from Genentech Roche (DSMB) outside the submitted work. A. Pantuck reports grants from UCLA (clinical trial contract/grant) during the conduct of the study. E. Campeau reports personal fees and other from Zenith Epigenetics Ltd. (salary paid by Zenith Epigenetics Ltd.) during the conduct of the study and outside the submitted work, as well as has a patent for Combination Therapy for the Treatment of Prostate Cancer pending (all patent rights were transferred to Zenith Epigenetics Ltd.). M. Snyder reports personal fees and other from Zenith Epigenetics (employment) during the conduct of the study and outside the submitted work, as well as reports employment with Zenith Epigenetics. S. Lakhota reports personal fees and other from Zenith Epigenetics (paid salaried employee of Zenith, lead clinical development for Zenith) during the conduct of the study and outside the submitted work, as well as has a patent on the combination of ZEN-3694 + enzalutamide for the treatment of prostate cancer, owned by Zenith Epigenetics. F.Y. Feng reports personal fees from Janssen Oncology (advisory board), Sanofi (advisory board), and Bayer (consultant), grants and other from Zenith Epigenetics (research funding from Zenith Epigenetics), other from PFS Genomics (founding member, ownership interests), and personal fees from Celgene (advisory board), Blue Earth Diagnostics (advisory board), Genentech (consultant), Myovant Sciences (consultant), Roivant Sciences (consultant), and Astellas Pharma (consultant) outside the submitted work. E.J. Small reports personal fees and other from Fortis Therapeutics (consulting and stock), personal fees from Harpoon Therapeutics (consulting), Janssen (consulting), BeiGene (consulting), Tolero (con-

sulting), and Teon Therapeutics (consulting) outside the submitted work. W. Abida reports grants from Zenith Epigenetics (research funding to institution) during the conduct of the study, grants from Clovis Oncology (research funding to institution) and GlaxoSmithKline (research funding to institution) outside the submitted work, and personal fees from Clovis Oncology, Janssen Biotech, MORE Health, ORIC pharmaceuticals, and Daiichi Sankyo, grants from AstraZeneca (research funding to institution), J. Alumkal reports grants from Zenith Epigenetics (research support to institution), NCI (research support to institution) during the conduct of the study, and Aragon Pharmaceuticals (research support to institution), and Gilead Sciences (research support to institution) outside the submitted work, and grants and personal fees from Astellas (consulting fees and research support to institution) and Janssen Biotech (consulting fees and research support to institution) outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

R. Aggarwal: Conceptualization, formal analysis, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **M.T. Schweizer:** Conceptualization, formal analysis, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **D.M. Nanus:** Formal analysis, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **A. Pantuck:** Conceptualization, formal analysis, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **E. Heath:** Conceptualization, data curation, software, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **E. Campeau:** Data curation, software, formal analysis, visualization, writing-original draft, writing-review and editing. **S. Attwell:** Conceptualization, data curation, software, formal analysis, supervision, investigation, methodology, writing-original draft, project administration, writing-review and editing. **K. Norek:** Conceptualization, software, supervision, validation, investigation, visualization, methodology. **M. Snyder:** Conceptualization, resources, data curation, software, formal analysis, validation, visualization, methodology, writing-original draft, project administration, writing-review and editing. **L. Bauman:** Conceptualization, resources, data curation, software, formal analysis, supervision, validation, visualization, methodology, writing-original draft, writing-review and editing. **S. Lakhota:** Conceptualization, resources, supervision, funding acquisition, writing-review and editing. **F.Y. Feng:** Conceptualization, data curation, software, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **E.J. Small:** Conceptualization, software, formal analysis, funding acquisition, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **W. Abida:** Conceptualization, data curation, software, formal analysis, supervision, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing. **J. Alumkal:** Conceptualization, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing.

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Clinical Cancer Research

A Phase Ib/Ila Study of the Pan-BET Inhibitor ZEN-3694 in Combination with Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer

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Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019

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ASSOCIATED CONTENT

Appendix

Data Supplement

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

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h2>abstract

PURPOSE Germline testing (GT) is a central feature of prostate cancer (PCA) treatment, management, and hereditary cancer assessment. Critical needs include optimized multigene testing strategies that incorporate evolving genetic data, consistency in GT indications and management, and alternate genetic evaluation models that address the rising demand for genetic services.

METHODS A multidisciplinary consensus conference that included experts, stakeholders, and national organization leaders was convened in response to current practice challenges and to develop a genetic implementation framework. Evidence review informed questions using the modified Delphi model. The final framework included criteria with strong (> 75%) agreement (Recommend) or moderate (50% to 74%) agreement (Consider).

RESULTS Large germline panels and somatic testing were recommended for metastatic PCA. Reflex testing—initial testing of priority genes followed by expanded testing—was suggested for multiple scenarios. Metastatic disease or family history suggestive of hereditary PCA was recommended for GT. Additional family history and pathologic criteria garnered moderate consensus. Priority genes to test for metastatic disease treatment included *BRCA2*, *BRCA1*, and mismatch repair genes, with broader testing, such as *ATM*, for clinical trial eligibility. *BRCA2* was recommended for active surveillance discussions. Screening starting at age 40 years or 10 years before the youngest PCA diagnosis in a family was recommended for *BRCA2* carriers, with consideration in *HOXB13*, *BRCA1*, *ATM*, and mismatch repair carriers. Collaborative (point-of-care) evaluation models between health care and genetic providers was endorsed to address the genetic counseling shortage. The genetic evaluation framework included optimal pretest informed consent, post-test discussion, cascade testing, and technology-based approaches.

CONCLUSION This multidisciplinary, consensus-driven PCA genetic implementation framework provides novel guidance to clinicians and patients tailored to the precision era. Multiple research, education, and policy needs remain of importance.

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INTRODUCTION

The role of germline testing (GT) for prostate cancer (PCA) has increased, with growing precision treatment implications and expanded testing options.^{1,2} A primary driver for GT is now precision therapy for

metastatic disease where genetic results inform options and strategies for targeted treatment, therapeutic planning, and clinical trials.¹⁻⁴ Approximately 12% to 17% of men with metastatic PCA harbor germline mutations, primarily in DNA repair genes, such as

BRCA2, *CHEK2*, *BRCA1*, *ATM*, *PALB2*, and the DNA mismatch repair (MMR) genes,⁵ which are increasingly informing options for poly (ADP-ribose) polymerase (PARP) inhibitors, immune checkpoint inhibitors, platinum chemotherapy, and clinical trials.^{1-4,6} In early-stage disease, emerging data suggest that men with germline *BRCA2* mutations, and possibly *ATM* mutations, have higher rates of upgrading of prostate biopsies while on active surveillance (AS).⁷ GT results are considered increasingly in PCA early detection discussions, particularly for men with *BRCA2* mutations for which data support higher rates of PCA detection, younger age at diagnosis, and more clinically significant disease.⁸⁻¹⁰ Many of the genes that are important for PCA therapy, management, and early detection are associated with hereditary cancer syndromes.¹¹ Pathogenic variants in *BRCA1* and *BRCA2* are associated with hereditary breast and ovarian cancer (HBOC). DNA MMR genes—*MLH1*, *MSH2*, *PMS2*, *MSH6*, and *EPCAM*—are associated with Lynch syndrome.¹¹⁻¹⁶ These and other hereditary cancer syndromes confer risks for multiple cancers that must be addressed for men and their kindred.^{8,16}

As PCA GT has increased, new practice and implementation challenges have emerged in three major areas: expanded options for multigene panels, with a resultant lack of clarity regarding optimized panel use and priority genes to test; variability in guidelines regarding GT indications and genetically based management that incorporates emerging data; and a shortage of genetic services.^{1,17-21} Testing options have expanded rapidly, which include focused, guideline-based, comprehensive, and reflex panels.^{17,18} Panels include genes with strong, limited, and unknown risk for PCA and that yet confer risks for multiple cancers.¹⁸ There is a need for clarity on panel choice and priority genes to test in men with metastatic PCA, nonmetastatic PCA, and men at high risk for PCA that balances the benefits of expanded testing (eg, identifying actionable mutations) with considerations (eg, higher rates of variants of uncertain significance [VUS]).^{3,8,10}

Uniform guidance is also needed regarding GT indications and genetically based PCA management that incorporates rapidly emerging, sometimes conflicting, data. Current National Comprehensive Cancer Network (NCCN) guidelines have variability regarding GT on the basis of pathologic—stage and Gleason/Grade Group—and family history (FH) criteria.^{3,8,9} Management guidance is also needed in multiple areas with consideration of gene-specific outcomes, such as treatment of metastatic disease with variable responses by DNA repair mutations^{1-4,6}; AS discussions that consider strong data for *BRCA2*, but limited data for *BRCA1* and *ATM*⁷; and broader consideration of genes for PCA early detection.^{1,2,11} In particular, strategies for PCA early detection need clarification regarding age to begin screening on the basis of genetic status.^{8,9}

Furthermore, the rising need for PCA GT has created a critical shortage of genetic counseling (GC) services.^{1,19}

Health care providers, such as oncologists and urologists, increasingly are ordering PCA GT to expedite testing for management.^{20,21} Concerns include limited guidance on optimal pretest informed consent, optimal panel testing strategies for comprehensive genetic evaluation, inclusion of personal history and FH, and balancing timely GT with appropriate referral to GC to address patient and family needs.^{1,20,21} As referral of all men to GC for PCA GT is not sustainable, health care and genetic providers need implementation strategies that incorporate alternate genetic evaluation models for the timely and responsible delivery of PCA GT for men and their families.^{1,19}

The 2019 Philadelphia Prostate Cancer Consensus Conference was convened to address challenges in PCA germline evaluation and implementation with attention to evolving genetic and precision medicine data. This meeting was a follow-up to the 2017 Philadelphia Consensus Conference, which focused on the role of GT for inherited PCA risk.¹⁸ The 2019 conference had the following 3 goals: to define optimal GT strategies that incorporate expansion of panel testing options and evolving genetic data, to propose consistent PCA GT indications and management, and to propose alternate genetic evaluation models to address the GC shortage. An expert, consensus-driven genetic implementation framework was developed for health care and genetic providers to streamline GT for PCA in the precision medicine era.

METHODS

Overarching Questions Addressing Implementation Gaps

The following questions were primary drivers of the conceptual framework:

1. Which men should be considered for germline PCA genetic testing?
2. Which panels should be considered and which genes should be prioritized for testing?
3. What PCA-specific recommendations should be considered on the basis of genetic results?
4. What is optimal informed consent for PCA GT?
5. What collaborative strategies may facilitate PCA genetic evaluation between health care and genetic providers?
6. What post-test disclosure strategies are most appropriate on the basis of genetic results?
7. What barriers must be addressed to enhance PCA GT?

Consensus Conference Participants

The Consensus Conference included 97 participants spanning the fields of urology, medical oncology, radiation oncology, clinical genetics, genetic counseling, primary care, pathology, implementation science, population science, epidemiology, and basic science. Patient stakeholders and advocates were active participants. Members of several national organizations, which included NCCN representatives, also participated. Academic and

community practices were represented, and panelists were from multiple regions of the United States, as well as Europe and Australia. The final voting panel included 76 participants (Table 1).

Consensus Process

The modified Delphi model was followed that incorporated elements of the Delphi process as previously published.^{18,22,23} Literature was provided to panel members before the meeting. Multiple expert presentations summarizing evidence relevant to genetic implementation were delivered. Evidence review is summarized in the Data Supplement.

Evidence Review

Thematic topics included: genetic contribution to PCA risk/aggressiveness²⁴⁻⁵⁴; germline mutations by PCA clinical and molecular characteristics^{5,55-66}; PCA clinical multigene testing data^{60,61,67}; germline mutations in diverse populations^{5,24,30,49,61,68-74}; PCA genetic testing capabilities and considerations^{17,75-81} (Fig 1); implementation of GC^{1,3,8,9,17,76,82-93}; NCCN PCA genetic testing guidelines and current variability^{3,8,9}; GT for PCA precision medicine in the metastatic setting^{2,4,6,56,58,94-99}; germline implications for AS of early-stage PCA^{7,35,99,100,101}; and germline implications for PCA early detection.^{8-10,102} Table 2 provides a summary of genetic data for PCA risk and aggressiveness. Full evidence summary is provided in the Data Supplement.

Strength of Consensus

Votes were cast anonymously using a Web-based polling platform. Strength of consensus was $\geq 75\%$ agreement for strong consensus, 50% to 74% agreement for moderate consensus, and $< 50\%$ agreement for lack of consensus.^{22,23}

Development of PCA Genetic Evaluation and Management Framework

A conceptual framework for PCA genetic evaluation and management was developed (Fig 2). Criteria that achieved strong consensus were designated as "Recommend" and those with moderate consensus were designated as "Consider" in the final framework.

RESULTS

Key premises

The following are guiding principles for clinical genetic evaluation:

Premises based on prior literature and Consensus Conference expert guidance:

- In-person GC is a gold standard of genetics practice.^{2,76,82-84}
- Patients' psychosocial needs or preferences should dictate the mode of counseling.^{1,82-84}
- Full FH is important to collect during the genetic evaluation process:^{1,82-84}

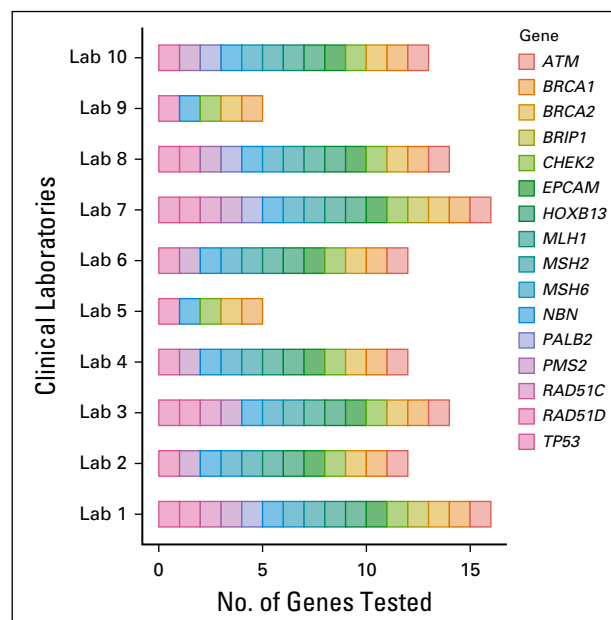


FIG 1. Variability in prostate cancer–specific multigene panels. Genetic testing registry: As of August 2019. Available at: <https://www.ncbi.nlm.gov/gtr/>. Courtesy of Saud AlDubayan, MD.

Premises based on consensus voting:

- Men should engage in informed decision making for genetic testing (Recommend).
- Building collaborations between health care and genetics providers is important for optimal genetic evaluation (Recommend).

1. Which Men Should Be Considered for Germline PCA Genetic Testing?

Gaps addressed. NCCN guidelines (NCCN Prostate Version 4.2019 and NCCN Breast/Ovary Version 3.2019) at the time of the 2019 Consensus meeting had varying indications for PCA GT.^{3,8} Data regarding clinical, pathologic, and FH features were summarized (Data Supplement).

Criteria for testing. Any one of the following criteria may prompt GT:

- **Men with metastatic PCA** (castration resistant or castration sensitive; Recommend).
- **Men with nonmetastatic PCA**—one of the following:
 - Ashkenazi Jewish ancestry (Consider).
 - Advanced disease (T3a or higher; Consider).
 - Intraductal/ductal pathology (Consider).
 - Grade Group 4 (Gleason sum 8) or above (Consider).
- **FH criteria:**
 - **PCA FH criteria:**
 - Men with one brother or father or two or more male relatives with one of the following:
 - Diagnosed with PCA at age < 60 years (Recommend).

- Any of whom died of PCA (Recommend).
- Any of whom had metastatic PCA (Recommend).
- **FH of other cancers:**
 - Two or more cancers in HBOC or Lynch spectrum in any relatives on the same side of the family (especially if diagnosed at age < 50 years; Consider).

Additional considerations. FH consistent with hereditary PCA achieved a strong recommendation for GT. Additional FH criteria were expanded to consider 2 or more cancers in the HBOC or Lynch spectrum to account for limitations in self-reported FH. Genes corresponding to specific cancers are listed in Table 2. Of note, an unremarkable FH does not necessarily negate consideration of GT, particularly for treatment decisions in the metastatic setting.

All pathologic criteria achieved moderate agreement. Universal screening for Lynch syndrome in PCA is not current practice; however, if immunohistochemistry is performed on a prostate specimen revealing loss of the DNA MMR genes, and particularly MSH2, the recommendation is to proceed with GT to determine if the patient has Lynch syndrome given the significant cancer risks and potential treatment implications. Panelists noted that many centers do not report intraductal/ductal pathology or immunohistochemistry for Lynch syndrome markers, which must be addressed with pathologists.

Although multiple unique questions were posed specifically regarding GT for African American men, none met consensus agreement as a result of limited data. Until additional research is completed, testing guidelines as described herein should be applied in under-represented populations.

2. Which Panels Should Be Considered and Which Genes Should Be Prioritized for Testing?

Gaps addressed. Guidance on the use of various gene panels adapted to clinical scenarios is needed given the rapid expansion of panel options and the inclusion of genes with limited association to PCA risk or PCA treatment implications (Fig 1). Furthermore, NCCN guidelines vary regarding genes to test,^{3,8} necessitating consensus prioritization of genes for testing (Data Supplement).

Panels considered. Focused—guidelines-based—panels (approximately 5 to 6 genes), PCA-specific panels (approximately 10 to 15 genes), comprehensive cancer panels (approximately 80 genes), and reflex panels (initial set of genes tested followed by broad gene testing) were considered. Benefits and limitations of various panels were also considered (Data Supplement).

Genes considered. *BRCA1*, *BRCA2*, *HOXB13*, *CHEK2*, *ATM*, *NBN*, *MSH2*, *MSH6*, *MLH1*, *PMS2*, *PALB2*, *BRIP1*, *TP53*, and Fanconi anemia genes were considered.

TABLE 1. Characteristics of Voting Consensus Participants

Participant Characteristic	No. (%)
Primary area of specialty/work (combination of academic and community settings)	
Urology	29 (38)
Medical oncology	13 (17)
Genetic counseling/implementation science	10 (13)
Radiation oncology	5 (7)
Primary care, pathology, and other	9 (12)
Population science/epidemiology	4 (5)
Patient/patient advocate	6 (8)
Geographic region of practice or work	
Northeast United States	26 (34)
Mid-Atlantic United States	14 (18)
Southeast United States	4 (5)
Midwest United States	15 (20)
Southcentral United States	4 (5)
Northwest United States	6 (8)
Southwest United States	3 (4)
Europe, Australia, and Other	4 (5)
Type of region of work	
Urban	55 (71)
Suburban	15 (19)
Rural	2 (3)
Other	5 (6)

TABLE 2. Genetic Contribution to PCA Risk, Aggressiveness, and Proposed Clinical Implications

Gene	Strength of Association for PCA Susceptibility ^a	Risk for Aggressive Disease ^a	Prevalence in Metastatic PCA ^b	Testing for Hereditary Cancer Syndromes and Other Associated Cancers Based on Personal History or FH	Cancer Screening Guidelines for Non-PCAs	PCA-Specific Clinical Impact of Germline Testing: Consensus Conference Summary			
						Implications for PCA Early Detection/PCA Risk Assessment	Implications for AS Decision Making	Metastatic Treatment Options	Clinical Trial Options
<i>ATM</i>	+	++	++	Breast, pancreas	x	+/+++	+	++	+++
<i>BRCA1</i>	++	+/-	+	HBOC syndrome; breast (male and female), ovarian, pancreas, melanoma	x	++		+++	+++
<i>BRCA2</i>	+++	+++	+++	HBOC syndrome; breast (male and female), ovarian, pancreas, melanoma	x	+++	++	+++	+++
<i>HOXB13</i>	+++	-	-	Hereditary PCA		++			
<i>CHEK2</i>	++	+	++	Breast, colon	x				++
<i>MSH2/MSH6</i>	++	+	+	Lynch syndrome; colorectal, ovarian, uterine, gastric, small bowel, pancreas, upper tract urothelial, kidney, sebaceous carcinoma	x	++		++	+++
<i>MLH1/PMS2</i>	+	+/-	+	Lynch syndrome; colorectal, ovarian, uterine, gastric, small bowel, pancreas, upper tract urothelial, kidney, sebaceous carcinoma	x	+		++	+++
<i>NBN</i>	+/-	+/-	+	Breast	x				+
<i>PALB2</i>	-	+	+	Breast, pancreas	x				++
<i>RAD51C-D; BRIP1; Fanconi anemia genes</i>	-	-	+	ovarian (<i>RAD51C/D, BRIP1</i>)	x				++

Abbreviations: AS, active surveillance; FH, family history; HBOC, hereditary breast and ovarian cancer; PCA, prostate cancer.

^aEvidence from case-control, familial, cohort, or clinical studies: strong (+++); moderate (++) ; low (+); conflicting data (+/-); not established (-).

^bHigh prevalence ($\geq 4\%$; +++); moderate prevalence (1% to $< 4\%$; ++); low prevalence ($< 1\%$; +); not reported (-).

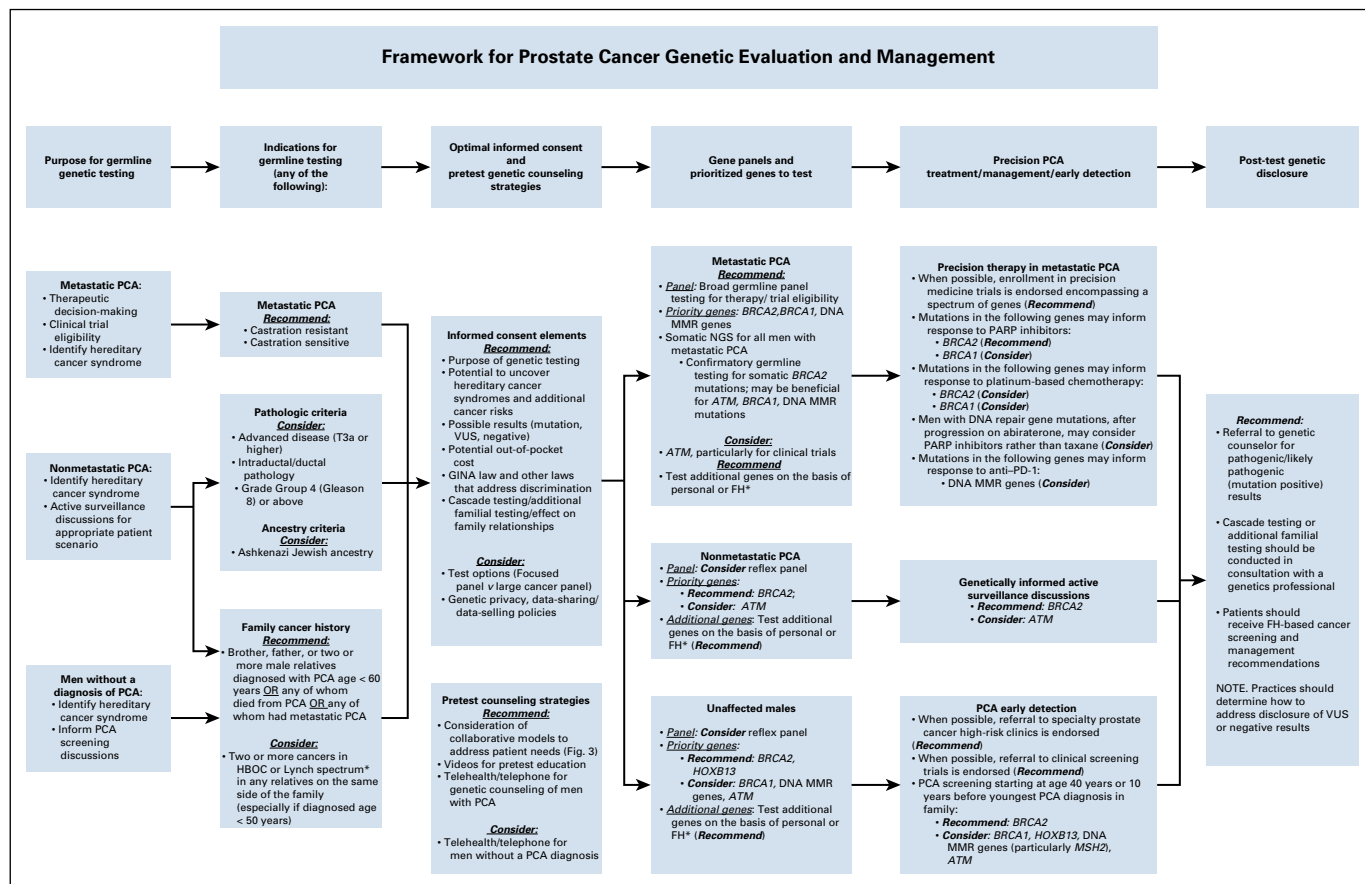


FIG 2. Framework for prostate cancer (PCA) genetic evaluation and management. (*) See Table 2 for personal history or family history (FH) of cancers indicating genes to test. GINA, Genetic Information Nondiscrimination Act; HBOC, hereditary breast and ovarian cancer; MMR, mismatch repair; NGS, next-generation sequencing; PARP, poly (ADP-ribose) polymerase; PD-1, programmed death 1; VUS, variant of uncertain significance.

Panels and genes prioritized for testing:

- **Metastatic PCA:**
 - Comprehensive (large) panel testing for therapy/ clinical trial eligibility (*Recommend*).
 - **Priority germline testing:**
 - *BRCA2/BRCA1* (*Recommend*).
 - DNA MMR genes (*Recommend*).
 - *ATM* (*Consider*).
 - Test additional genes on the basis of personal or FH (*Recommend*).
 - **Somatic testing:**
 - Somatic next-generation sequencing for all men with metastatic PCA (*Recommend*).
 - Confirmatory germline testing for somatic mutations:
 - *BRCA2* (*Recommend*).
 - *BRCA1*, DNA MMR genes, *ATM* (*Consider*).
 - Test additional genes on the basis of personal or FH (*Table 2*; *Recommend*).
- **Nonmetastatic PCA:**
 - Reflex testing may be optimal (*Consider*).
 - Priority genes particularly to inform AS:
 - *BRCA2* (*Recommend*).
- **Men without a diagnosis of PCA meeting FH testing criteria:**
 - Reflex testing may be optimal (*Consider*).
 - Priority genes for risk assessment:
 - *BRCA2* (*Recommend*).
 - *HOXB13* (*Recommend*).
 - *BRCA1*, *ATM*, DNA MMR genes (*Consider*).
 - Test additional genes on the basis of personal or FH (*Table 2*; *Recommend*).

Additional considerations. For men with metastatic PCA, broader panel testing may be appropriate, particularly if considering treatment or clinical trial options (*Table 2*, *Fig 2*, and *Data Supplement*). Reflex testing may be considered for all patients, but especially for men with nonmetastatic disease considering AS or men without PCA for early detection, which allows for initial testing of genes that inform management (*Data Supplement*). Reflex testing also allows for testing of additional genes to account for personal cancer or FH at a later time for comprehensive

genetic evaluation and may also be more amenable to collaborative genetic evaluation models (see below).

Among MMR genes, *MSH2* has the strongest association to PCA; however, it is recognized that *MLH1*, *PMS2*, *MSH6*, and *EPCAM* also need to be tested to establish the diagnosis of Lynch syndrome. Full MMR testing also may be important for treatment consideration or clinical trials in the metastatic setting; therefore, full Lynch syndrome testing is recommended as indicated.

In addition, confirmatory GT is recommended for men with somatic *BRCA2* mutations and may be beneficial for somatic mutations in *BRCA1*, MMR genes, and *ATM* to identify hereditary cancer predisposition. Additional GT beyond these genes may also be recommended on the basis of personal and FH. Consultation with a genetics professional is advised.

3. What PCA-Specific Recommendations Should Be Considered on the Basis of Genetic Results?

Gaps addressed. There is a need for consensus agreement on genetically informed PCA treatment, management, and early detection^{1,2} (Data Supplement). An additional challenge is inconsistency in NCCN genetically based PCA early detection recommendations regarding which genes to consider and the age at which to begin screening^{8,9} (Data Supplement).

Genetically based recommendations. Genes considered included *BRCA1*, *BRCA2*, *HOXB13*, *CHEK2*, *ATM*, *NBN*, *MSH2*, *MSH6*, *MLH1*, *PMS2*, *PALB2*, *BRIP1*, *TP53*, and Fanconi anemia genes.

- **Metastatic PCA:** GT to inform precision therapy:
 - Enrollment of men with PCA in precision medicine trials is endorsed (Recommend).
 - Mutations in the following genes may inform response to PARP inhibitors:
 - *BRCA2* (Recommend).
 - *BRCA1* (Consider).
 - Mutations in the following genes may inform response to platinum-based chemotherapy:
 - *BRCA2* (Consider).
 - *BRCA1* (Consider).
 - Men with DNA repair gene mutations, after progression on abiraterone, may proceed with PARP inhibitor rather than taxane (Consider).
 - Germline mutations in the following genes may inform response to anti-programmed death 1 (PD-1) therapy:
 - DNA MMR genes (Consider).
 - NOTE. The US Food and Drug Administration has granted accelerated approval for anti-PD-1 therapy for microsatellite instability-high/MMR-deficient tumors.
- **Nonmetastatic PCA:** to inform AS discussions:
 - *BRCA2* (Recommend).
 - *ATM* (Consider).

• Men without a PCA diagnosis to inform PCA early detection:

- Referral to specialty PCA high-risk clinics and/or early detection trials was endorsed (Recommend).
- PCA early detection starting at age 40 years or 10 years before the youngest PCA diagnosis in family:
 - *BRCA2* (Recommend).
 - *BRCA1*, *HOXB13*, *ATM*, and DNA MMR genes (particularly *MSH2*; Consider).

Additional considerations. In the metastatic setting, a broad spectrum of genes may be important in determining clinical trial eligibility, and emerging data should continue to refine recommendations. *ATM* garnered consideration for testing, primarily for clinical trial eligibility; however, the panel did not feel that there was sufficient data to endorse *ATM* for informing therapy to PARP inhibitors off study because of the limited independent association to PARP inhibitor response at this time (Data Supplement). *ATM* also garnered moderate consensus for informing AS, but there are limited data at this time (Data Supplement).

For anti-PD-1 therapy, the US Food and Drug Administration has granted accelerated approval for tumors that are microsatellite instability-high or MMR deficient. The panel had moderate consensus regarding a definitive recommendation for anti-PD-1 therapy off study for men with germline MMR mutations, with stronger consideration for clinical trials.

Regarding AS discussions, clinicopathologic criteria, age, and overall health must be considered. *BRCA1* did not achieve consensus for inclusion in AS as a result of limited data for PCA aggressiveness (Data Supplement). Polygenic risk score data were reviewed⁷⁷⁻⁸¹ and did not achieve consensus.

4. What Is Optimal Informed Consent for PCA GT?

Gaps addressed. Current practice guidelines do not provide guidance to health care providers regarding optimal informed consent for PCA GT.

Optimal pretest informed consent elements. Ethical considerations of GC were reviewed (Data Supplement). The following elements garnered strong or moderate consensus to discuss with men before GT (Fig 2 and Table 3):

- Recommend discussing: (1) the purpose of GT; (2) the possibility of uncovering hereditary cancer syndromes; (3) potential types of test results; (4) the potential to uncover additional cancer risks; (5) potential out-of-pocket cost; (6) Genetic Information Non-discrimination Act law and other laws that address genetic discrimination; and (7) cascade testing/additional familial testing.
- Consider discussing: (1) multigene panel options; (2) data sharing/data selling policies of genetic laboratories; and (3) the privacy of genetic tests.

TABLE 3. Priority Elements of Informed Consent for Prostate Cancer Germline Testing

Elements of Informed Consent	Description
Purpose of germline testing	For precision therapy, early detection strategies, and/or to identify hereditary cancer syndrome/risk
Possibility of uncovering hereditary cancer syndromes	Based on FH, testing may include BRCA1 and BRCA2 (associated with hereditary breast and ovarian cancer) or DNA mismatch repair genes (associated with Lynch syndrome; Table 2). Other hereditary syndromes may also be identified.
Panel options	Various multigene panels may be considered for testing (focused PCA panel v large cancer panel v reflex testing); benefits and risks of each option must be discussed, such as cancer risks uncovered, higher rates of VUS with larger panels, or availability of guidelines for management (Data Supplement).
Potential types of test results	Three main types of results should be discussed, including mutation (pathogenic/likely pathogenic variant), VUS, negative, along with implications of these results on management.
Potential to uncover additional cancer risks	Multiple gene-specific cancer risks may be identified beyond PCA risk that affects men and their families (Table 2).
Potential out-of-pocket cost	Not all insurance plans cover genetic testing for PCA. Some mandate referral to GC. It is important to check with the insurance plan.
Genetic Information Nondiscrimination Act law and other laws that address genetic discrimination	Discuss coverage for health insurance and most employment scenarios. Discuss the lack of coverage for life insurance, long-term care, and disability insurance.
Cascade testing/additional familial testing	Testing blood relatives for pathogenic variants or additional genetic testing on the basis of family history; worry and anxiety that may result from hereditary cancer testing; effect on family relationships
Data-sharing/data-selling policies of genetic laboratories	Each genetic testing laboratory may have unique data-sharing and data-selling policies that patents must be aware of.
Privacy of genetic tests	Protection of genetic data from data breach or access by third parties must be discussed.

Abbreviations: FH, family history; GC, genetic counseling; PCA, prostate cancer; VUS, variant of uncertain significance.

Additional considerations. These elements of pretest informed consent apply to all men who are considering PCA GT^{76,82-84} (Fig 2). Such GC aids as handouts or videos may be useful to deliver this information. However, informed consent is a process during which patients have opportunities to ask questions^{76,82-84}; therefore, a question-and-answer process must be available before testing. Clinicians without specific training/expertise in GC/GT are urged to refer patients to GC before ordering GT. Furthermore, it is important to remain current on the ethics/informed consent process for GT because of the rapidly evolving nature of precision medicine.

5. What Collaborative Strategies May Facilitate PCA Genetic Evaluation Between Health Care and Genetic Providers?

Gaps addressed. Multidisciplinary guidance on the implementation of collaborative models between health care providers and GC is currently lacking.¹⁰³ There is a need to address alternate GC models for timely GT with attention to appropriate pretest informed consent and comprehensive evaluation.

Alternate genetic evaluation delivery strategies. The following strategies were endorsed (Data Supplement and Fig 3):

- Practices should consider multiple models to address patients' needs (Fig 3), including point-of-care models

with limited or full pretest FH collection as well as traditional model with upfront referral to GC (Recommend).

- Videos may be useful to deliver pretest informed consent (Recommend).
- In point-of-care models, reflex genetic testing may be optimal to enable additional testing on the basis of personal/FH (Consider).
- Telehealth/telephone delivery of GC is a suitable alternative to in-person GC (Recommend for men with PCA; Consider for unaffected males).

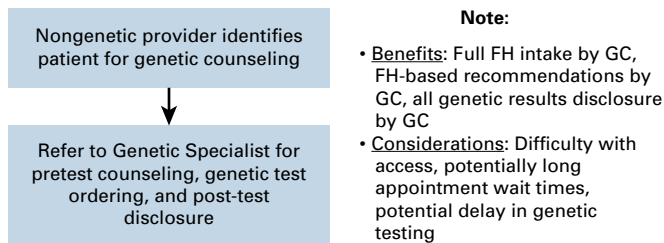
Additional considerations. If limited pretest FH is collected, practices must proactively address the collection of FH in the post-test setting. Reflex testing enables future testing to account for personal/FH. Telehealth/telephone GC was endorsed to address geographic barriers to GC, although patient outcomes data in males are lacking. Key process questions for practices to consider when implementing point-of-care versus traditional GC models were discussed (Data Supplement).

6. What Post-Test Disclosure Strategies Are Most Appropriate Based on Genetic Results?

Gaps addressed. Joint guidance from oncologists, urologists, and genetic counselors for referral to GC is currently lacking.

A

**Traditional model:
Upfront referral to GC**

**B**

**Collaborative/point-of-care/hybrid model:
Pretest engagement by health care provider;
post-test engagement with genetics and/or health care provider**

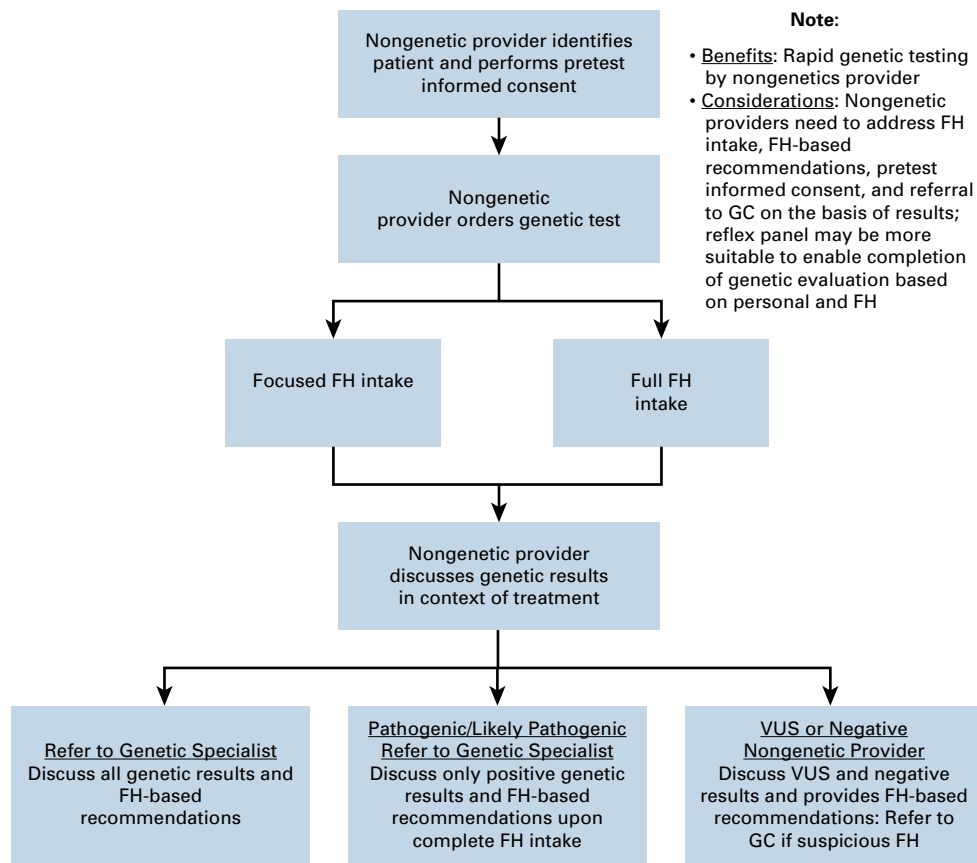


FIG 3. Models of collaboration between genetics and health care practices for prostate cancer genetic evaluation. FH, family history; GC, genetic counseling.

Optimal post-test disclosure strategies:

- Referral to a GC for pathogenic/likely pathogenic results (Recommend).
- Patients should receive FH-based recommendations, either in health care or genetic practices (Recommend).
- Cascade/additional familial testing should be conducted in consultation with a genetic professional (Recommend).

Additional considerations. There was no consensus regarding referral of men with VUS or negative results; therefore, providers will need to determine their ability to discuss VUS results and FH-based recommendations. VUS reclassification to “pathogenic/likely pathogenic” and subsequent management are critical for ordering providers to consider and may support the referral of select men with suspicious VUS to GC. Men with FH of cancers may also warrant referral to GC.

7. What Barriers Must Be Addressed to Enhance PCA GT?

Gaps addressed. Multiple practice, research, and policy gaps pose barriers to PCA GT.

Areas in need of additional attention. The following areas achieved strong or moderate consensus to address:

- Genetic education for providers not formally trained in cancer genetics/genetic counseling (Appendix Table A1, online only, and Data Supplement).
- Barriers to implementation of PCA GT (Appendix Table A2, online only).
- Research priorities (Appendix Table A3, online only).

DISCUSSION

As GT for PCA has rapidly increased, responsible implementation of testing and management are of primary concern.^{1,2,19,23} Current practice challenges that pose barriers to operationalizing PCA GT include the variability in testing indications and genetically based management, the need for guidance on panels and priority genes to test, and guidance regarding alternate evaluation models to address GC demand. The 2019 Philadelphia Prostate Cancer Consensus Conference was a focused attempt to address these critical challenges and practice gaps by developing a first-in-field working framework for PCA genetic evaluation, management, and implementation informed by best evidence and expert guidance.

The strength of the consensus framework is the creation of a unified approach regarding GT indications, genetically informed management and treatment, and the integration of GC. Multiple aspects of the framework had strong evidence and strong expert agreement to deem a definitive action of “Recommend”. The strongest recommendations encompassed testing all men with metastatic PCA or men with FH suggestive of hereditary PCA. Priority genes for testing included *BRCA2*, *BRCA1*, and the DNA MMR genes in metastatic disease to inform treatment or clinical trials; *BRCA2* for AS discussions; and *BRCA2* and *HOXB13* for PCA early detection discussions. This was the first formal, multidisciplinary endorsement for broad panel testing among men with metastatic PCA, recognizing that genetic information may enable men to enroll in clinical trials. Consensus emerged regarding strategies for PCA early detection on the basis of genetic status. For male carriers of *BRCA2*, a recommendation was made to begin PSA screening at age 40 years or 10 years before the youngest PCA diagnosis in a family and is modeled after colorectal cancer guidelines.¹⁶

An important aspect to the genetic evaluation framework was the integration of care processes and GC to account for the increasing need for GC. Strong recommendations were made for optimal pretest informed consent. Recommended strategies to deliver GC included collaborative GC models, videos, and telehealth to facilitate GT through health care practices and to collaborate with GC. Reflex testing

garnered moderate consensus and may be considered, particularly when using collaborative counseling models to enable upfront testing by health care providers, followed by testing additional genes using GC for comprehensive genetic evaluation. In the post-test setting, strong recommendations were made to refer all men with pathogenic mutations to GC, to conduct cascade testing of relatives under the care of genetics professionals, and to determine the delivery of FH-based recommendations.

The panel dealt with many uncertainties in recommendations which garnered moderate consensus. Whereas many genes have a lower level of evidence for PCA risk, aggressiveness, or treatment response, several clinically available multigene panels include lower evidence genes. To indicate these nuances in limited data or moderate consensus, many criteria were designated as “Consider” in the framework. Pathologic criteria for testing, such as disease stage, intraductal/ductal histology, or Grade Group ≥ 4 , garnered moderate consensus and therefore are included as suggestive criteria for testing.^{63,65,66} Ashkenazi Jewish ancestry as a standalone criterion achieved moderate consensus, but may be a stronger consideration for testing for men with higher Gleason score per current NCCN guidelines.⁸ Whereas PCA has been linked with HBOC and Lynch syndrome, a working definition of familial features that increase the likelihood of detecting germline mutations is needed. As such, having two or more relatives with cancers in the HBOC or Lynch syndrome spectrum garnered moderate consensus as standalone criteria and may be considered for GT on the basis of patient preference and insurance coverage.

Priority genes to test also presented challenges, particularly regarding *ATM*, DNA MMR genes, and *HOXB13*. Initial data have reported that men with *ATM* mutations experienced clinical response to PARP inhibitors⁹⁴; however, follow-up studies have reported a limited independent effect of *ATM*.⁹⁹ Similarly, studies in AS had limited association of *ATM* mutations alone with upgrading of biopsies.⁷ Until additional data are available, *ATM* was given a designation of “Consider” for testing, recognizing the potential for clinical trial options for *ATM* carriers. Additional uncertainties were encountered regarding prioritizing MMR genes for GT. Among MMR genes, *MSH2* has the highest reported association to PCA.⁴¹ Although other MMR genes have lower or limited association to PCA, the potential to uncover Lynch syndrome and clinical trial eligibility drove the suggestion to consider full Lynch syndrome testing. *MSH2* status may be more informative for PCA early detection discussions.⁴¹ *HOXB13* has strong association to PCA risk and early-onset disease, though screening outcomes data are limited. Therefore, the consensus panel recommended testing for *HOXB13* and to consider the results in early detection discussions. Overall, *BRCA1*, *HOXB13*, and MMR genes were designated as “Consider”

for beginning screening at age 40 years or 10 years before the youngest PCA diagnosis in the family because of the currently limited screening data.⁹ Data from screening studies, such as IMPACT and the National Cancer Institute (ClinicalTrials.gov identifier: [NCT03805919](https://clinicaltrials.gov/ct2/show/study/NCT03805919)), will be important to reconsider strengthening these recommendations.¹⁰ However, this is the first time that screening strategies based on a larger genetic spectrum have been proposed. Additional research in African American males is

vitaly needed. Future consideration of circulating tumor and cell-free DNA is also warranted.

In conclusion, the 2019 Consensus Conference created the first multidisciplinary PCA genetic implementation framework tailored to the precision medicine era. The framework, which importantly had input from NCCN panel leaders, provides guidance to a spectrum of providers to facilitate timely and responsible PCA GT for the benefit of men and their families.

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APPENDIX

TABLE A1. Priority Topics for Provider Education

Area of Knowledge	Percent Agreement
Recommend	
Purpose of genetic testing	100
Understanding types of results (mutation, VUS, negative)	92
Genetic Information Nondiscrimination Act and other laws that address discrimination	89
Hereditary cancer syndromes (HBOC, Lynch syndrome, HPC) that may be uncovered	86
Test options (focused prostate cancer panel v large cancer panel)	86
Additional cancer risks that may be uncovered	84
Potential out-of-pocket costs for genetic testing for patients	84
Privacy considerations of genetic tests	78
Cascade testing/additional familial testing/effect on family relationships	76
Consider	
Choice of laboratory for testing (pros and cons of test accuracy)	68
Data-sharing/data-selling policies of laboratories	62

NOTE. The Data Supplement provides educational resources for providers or trainees regarding germline testing.
 Abbreviations: HBOC, hereditary breast and ovarian cancer; HPC, hereditary prostate cancer; VUS, variant of uncertain significance.

TABLE A2. PCA Genetic Testing Implementation Barriers

Barrier	Percent Agreement
Recommend	
Increase advocacy and public awareness for PCA genetic testing and impact of genetic results for men and their families	99
Reimburse telehealth and telephone counseling	98
Implement virtual tumor boards, virtual molecular boards, or virtual genetics boards to disseminate genetics and molecular expertise	79
Redefine “actionability” to include familial impact of genetic testing for payer coverage	75
Consider	
Increase lobbying efforts to enhance payer coverage of PCA genetic testing	64
Engage primary care providers in genetic evaluation for PCA	63

Abbreviation: PCA, prostate cancer.

TABLE A3. Research Priorities to Advance PCA Genetics Knowledge and Practice

Priority Area	Percent Agreement
Recommend	
Genetics of PCA in diverse populations of men	93
Clinical outcomes by germline mutation status	93
Precision medicine trials	88
Precision PCA early detection trials	80
Basic science research into metastatic disease biology	76
Consider	
Implementation outcomes research regarding the alternate delivery of genetic counseling	72
Psychosocial outcomes of men undergoing genetic testing through various clinical approaches	63

Abbreviation: PCA, prostate cancer.

Practical Considerations and Challenges for Germline Genetic Testing in Patients With Prostate Cancer: Recommendations From the Germline Genetics Working Group of the PCCTC

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Germline genetic testing is now routinely recommended for patients with prostate cancer (PCa) because of expanded guidelines and options for targeted treatments. However, integrating genetic testing into oncology and urology clinical workflows remains a challenge because of the increased number of patients with PCa requiring testing and the limited access to genetics providers. This suggests a critical unmet need for genetic services outside of historical models. This review addresses current guidelines, considerations, and challenges for PCa genetic testing and offers a practical guide for genetic counseling and testing delivery, with solutions to help address potential barriers and challenges for both providers and patients. As genetic and genomic testing become integral to PCa care, developing standardized systems for implementation in the clinic is essential for delivering precision oncology to patients with PCa and realizing the full scope and impact of genetic testing.

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INTRODUCTION

Genomics is rapidly pushing oncology closer to an actualized version of precision medicine.^{1,2} In the era of poly (ADP-ribose) polymerase inhibition and immunotherapy, genetic testing may yield information that will affect therapeutic choices, in addition to informing the patient about personal and familial risk.³⁻⁵ Multiple guidelines now include germline genetic testing for men with prostate cancer (PCa), although incorporating testing into clinical workflows remains a challenge.^{5,6} This article addresses (1) current guidelines for germline testing, (2) key aspects of testing and counseling, (3) a road map for genetic testing and counseling delivery, (4) challenges of testing and possible solutions, and (5) benefits and limitations of testing.

Germline Genetic Counseling for Men With PCa

Since the landmark article by Pritchard et al⁷ that described a relatively high prevalence of germline mutations in DNA repair genes in men with metastatic PCa, other groups have reported the prevalence of germline mutations in PCa ranging between 7.5% and 19%, with *BRCA2* being the highest overall contributor.⁸⁻¹¹ Consequently, several groups issued recommendations for germline testing (Table 1), which place significant

demands on clinical workflows and resources for genetic counseling. Genetic counselors (GCs) are trained to assess family histories for genetic risk, provide pretest and post-test counseling, order appropriate testing, and interpret test results. Unfortunately, access to genetic providers is limited, with the majority of the small workforce usually centered in urban areas and academic institutions.^{12,13} In 2016, the Genetic Counselor Workforce Working Group estimated a growth of 72% in the workforce between 2017 and 2026, with demand not expected to meet population equilibrium until 2024-2030.¹⁴ This limited access may necessitate other health care providers, including oncologists, urologists, and primary care physicians, to absorb some responsibility for genetic testing. However, these providers may be insufficiently trained in genetics, resulting in inappropriate testing and misinformation.¹⁵⁻¹⁷

The increased number of men with PCa to be tested and the scarcity of GCs suggest a critical unmet need for expanded genetic services through novel approaches outside of historic delivery models.¹⁸ Evolving service models that incorporate phone and video telemedicine can be particularly useful when geography or public health crises, such as COVID-19, make in-person visits challenging.^{19,20} Hybrid service models

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that divide responsibilities between physicians and GCs are also options.²¹ Collaboration between GCs and clinicians is critical to determine which approach best suits a practice, because there is no one-size-fits-all solution.

Delivery of Germline Testing and Counseling

Initiating genetic testing. One of the greatest hurdles is ensuring that appropriate patients are systematically identified for testing. Developing a plan to consistently screen and identify patients based on current guidelines is necessary (Table 1). Assigning screening to a team member or using patient-completed family history questionnaires can facilitate referral and testing processes. Automated electronic medical record (EMR) features can trigger genetic counseling referrals or alert the clinical team based on a diagnosis code for metastatic PCa or family history/pedigree functionality.

After patients are identified, several options for counseling and testing are available:

1. Referral to a geneticist or GC for in-person, telephone-based, or telemedicine counseling services in response to manual referral or automated EMR triggers.
2. Treating clinicians perform pretest consent and order germline genetic testing directly: If genetic counseling services are unavailable, testing is urgent, or workflow supports providers initiating testing, treating providers can perform pretest education, obtain informed consent, and order genetic testing.²¹ Providers should consider any clinical, psychosocial, and financial issues when determining whether to pursue testing within their practice or refer to a remote/telehealth genetic service if they do not have access within the practice.
3. Patient-initiated testing (PIT) platforms: Some commercial genetic testing laboratories, such as Color and Invitae, offer clinical-grade testing that can be initiated by the patient. This process may involve a pretest clinician review and the option for post-test genetic counseling. However, there remain concerns about guidance on test selection, limitations in genetic counseling, lack of follow-up regarding future reclassification of variants, potential for misinterpretation of results, and propagation of misinformation within families. Furthermore, PIT may not include genes important to a patient's personal or family history, potentially creating a false sense of reassurance if testing is negative. Given this, provider-initiated testing is preferred.
4. Direct-to-consumer (DTC) testing platforms: DTC genetic testing has become increasingly popular, likely because of easy access and no medical provider oversight. DTC testing is not comprehensive and should not be considered a substitute for clinical-grade testing. Although 23&Me has Food and Drug Administration approval to report on the three known Ashkenazi Jewish BRCA1/2 founder variants, the National Comprehensive Cancer Network (NCCN)

cautions that any results should be confirmed with a clinical-grade test.²² Providers should be skeptical of any raw data findings from secondary companies, such as Promethease, which are prone to false positives and false negatives.²³

Family cancer history intake. Although all patients with high-risk localized or metastatic PCa should undergo germline genetic testing regardless of family history, accurately evaluating a patient's personal and family history is essential to determine whether patients need a broader germline panel. Furthermore, gathering a family history can help inform personal and family screening recommendations in the event of negative testing. Cancer counseling sessions include a three- to four-generation pedigree with information on maternal and paternal relatives with cancer, age of diagnosis, age/cause of death, and any prior genetic testing.^{22,24} For relatives with PCa, the Gleason grade, metastatic status, and/or cause of death can be useful. Information about ancestry (eg, Ashkenazi Jewish) and consanguinity should be noted. Family history questionnaires can be completed in the clinic or electronically.

Complete family histories ensure that the most informative, cost-effective testing is performed. Although the presence of other cancer types in a family history may be explained by a mutation in a PCa predisposition gene, providers should consider expanded testing for genes related to the observed cancers in a family history when necessary. For instance, hereditary pancreatic cancer and PCa typically occur in the setting of a pathogenic *BRCA2* variant. However, it may be reasonable to include other genes associated with pancreatic cancer, such as *CDKN2A* and *CDK4*.

Somatic next-generation sequencing. Somatic next-generation sequencing tumor testing is increasingly used to guide treatment decision making and can be performed in parallel with germline testing. In addition to detecting tumor-specific mutations, it can sometimes identify potential germline mutations. Most somatic testing platforms are not validated to distinguish germline from somatic-only mutations, even if paired testing with a blood or saliva sample is performed. Thus, a referral to genetics is recommended to determine whether confirmatory or more comprehensive testing is warranted. Providers should consider the variant allele frequency, actionability of the gene, classification of the variant, and tumor type when reviewing somatic variants for possible germline origin.²⁵

Pretest education and informed consent. Pretest education and informed consent discussions should review the purpose of testing; general information about included genes; possible test results (Table 2); medical management implications; review of possible benefits, risks, and limitations (Table 3); and the voluntary nature of testing.^{24,26} Several major medical societies have also published detailed guidelines reviewing the components of pretest counseling and informed consent to help clinicians.²⁴ Clinical teams

TABLE 1. Summary of the Current PCa Genetic Testing Guidelines

Organization	Source	Guidelines	Genes
National Comprehensive Cancer Network	Genetic/familial high-risk assessment: breast, ovarian, and pancreatic version 1.2020 ²²	Testing is clinically indicated in the follow scenarios:	<i>ATM</i> <i>BARD1</i> ^a <i>BRCA1</i> <i>BRCA2</i> <i>BRIP1</i> <i>CDH1</i> ^a <i>CDKN2A</i> ^a <i>CHEK2</i> <i>MSH2</i> <i>MLH1</i> <i>MSH6</i> <i>PMS2</i> <i>EPCAM</i> <i>NBN</i> <i>NF1</i> ^a <i>PALB2</i> <i>PTEN</i> ^a <i>RAD51C</i> <i>RAD51D</i> <i>STK11</i> ^a <i>TP53</i>
	Hereditary cancer testing criteria	1. Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene 2. Individuals meet the criteria below but with previous limited testing (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multigene testing 3. Personal history of cancer • Metastatic or intraductal PCa at any age • High-grade (Gleason score ≥ 7) PCa with: - o Ashkenazi Jewish ancestry; or - o ≥ 1 close relative with breast cancer at age ≤ 50 years or ovarian, pancreatic, or metastatic or intraductal PCa at any age; or - o ≥ 2 close relatives with breast or PCa (any grade) at any age • A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline • To aid in systemic therapy decision making 4. Family history of cancer • An affected or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except individuals who meet criteria only for systemic therapy decision making) There is a low probability ($< 2.5\%$) that testing will have findings of documented clinical utility in the following scenarios: • Men diagnosed with localized PCa with Gleason score < 7 and no close relative with breast, ovarian, pancreatic, or PCa	
National Comprehensive Cancer Network	Prostate cancer, version 1.2020 ⁴⁴	Germline testing is recommended for patients with PCa and any of the following: • High-risk, very-high-risk, regional, or metastatic PCa • Ashkenazi Jewish ancestry • Family history of high-risk germline mutations (eg, <i>BRCA1/2</i>, Lynch mutation) • A positive family history of cancer: - o A strong family history of PCa consists of: brother or father or multiple family members who were diagnosed with PCa (but not clinically localized Grade Group 1) at < 60 years of age or who died from PCa; OR - o ≥ 3 cancers on same side of family, especially diagnoses ≤ 50 years of age: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial cancer	<i>ATM</i> <i>BRCA1</i> <i>BRCA2</i> <i>CHEK2</i> <i>HOXB13</i> <i>MLH1</i> <i>MSH2</i> <i>MSH6</i> <i>PALB2</i> <i>PMS2</i>

(continued on following page)

TABLE 1. Summary of the Current PCa Genetic Testing Guidelines (continued)

Organization	Source	Guidelines	Genes
Expert Panel	Philadelphia Consensus meeting publication, 2017 ⁴⁵	Men meeting any one of the following suggested criteria should undergo genetic counseling and genetic testing: - All men with PCa from families meeting established testing or syndromic criteria for the following: - HBOC (Consensus: 93%) - HPC (Consensus: 95%) - LS (Consensus: 88%) - Men with PCa with two or more close blood relatives on the same side of the family with a cancer in the following syndromes: - Post-consensus discussion included consideration of age cutoff for this criterion. A specific age cutoff will require additional data, and age at diagnosis is important to inquire about in the genetic counseling session with patients. - HBOC (Consensus: 93%) - HPC (Consensus: 86%) - LS (Consensus: 86%) - All men with metastatic castrate-resistant PCa should consider genetic testing (Consensus: 67%). Post-consensus discussion also included consideration of testing men with metastatic, hormone-sensitive PCa to identify germline mutations to inform potential future treatment options and cascade testing in families. Men with tumor sequencing showing mutations in cancer-risk genes should be recommended for germline testing, particularly after factoring in additional personal and family history (Consensus: 77%).	<i>ATM</i> <i>BRCA1</i> <i>BRCA2</i> <i>HOXB13</i> <i>MSH2</i> <i>MLH1</i> <i>PMS2</i> <i>MSH6</i>
AUA	Clinically localized PCa: AUA/ASTRO/SUO guideline, 2017 ⁴⁶	The Panel recommends that clinicians take a detailed family history of cancers and give consideration to patient referral for genetic screening and counseling for men with localized high-risk PCa, particularly in the setting of family history of first-degree relatives with cancers of breast, ovary, pancreas, other GI cancers, and lymphoma.	No genes specified for germline testing

Abbreviations: ASTRO, American Society of Therapeutic Radiation and Oncology; AUA, American Urological Association; HBOC, hereditary breast and ovarian cancer syndrome; HPC, hereditary prostate cancer; LS, Lynch syndrome; PCa, prostate cancer; SUO, Society of Urologic Oncology.

^aThese genes are not currently associated with PCa.

should note the requirements for documentation of informed consent, which differ by state and institutional policies.

Test selection and ordering. Many commercial laboratories offer clinical genetic testing for hereditary cancer syndromes. Testing panels range from targeted, guidelines-based panels to comprehensive, pan-cancer panels that may include preliminary evidence genes. Some major laboratories, such as Ambry Genetics, Invitae, and GeneDx, offer PCa-specific panels that include the following genes: *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, and *TP53*. Genetic testing panels are subject to change, and decisions regarding specific genetic tests should be individualized based on factors such as laboratory reputation and quality, insurance networks, genes offered and customizability of panels, laboratory billing practices, follow-up testing options for family members, turnaround times, and availability of genetic counseling services.

Clinicians should recognize that larger panels increase the probability of detecting variants of uncertain significance (VUS), incidental/secondary findings (pathogenic variants in genes not related to hereditary PCa), and variants associated with syndromes that may be outside of the scope of clinicians treating PCa (Tables 2 and 3). Clinical workflows must ensure that tasks involved with ordering genetic testing include determination of insurance coverage and submission of orders, standardized collection and shipment of samples, and a clear chain of responsibility.

Insurance coverage for germline testing is in flux. Although the cost of genetic testing has decreased, the possible out-of-pocket (OOP) cost for patients can be difficult to discern because of the varying billing policies of laboratories and insurance coverages.²⁷ Although the NCCN hereditary breast and ovarian cancer guidelines (v3.2019) are often the primary source used by payers, including Medicare, to develop coverage policies, most have their own criteria that

TABLE 2. Possible Genetic Test Results^{47,48}

Interpretation	Result	Definition
Positive	Pathogenic	An alteration in the DNA that is associated with increased disease risk.
	Likely pathogenic	An alteration in the DNA that is likely to be associated with increased disease risk. Meets most but not all criteria to be classified as pathogenic.
Uncertain	Variant of uncertain significance	An alteration in the DNA that may or may not be disease causing. Insufficient evidence to classify as either pathogenic or benign.
Negative	Likely benign	An alteration in the DNA that is unlikely to be associated with increased disease risk. Meets most but not all criteria to be classified as benign.
	Benign	An alteration in the DNA that is not associated with increased disease risk.

determine testing coverage. These criteria may not be up to date with current NCCN guidelines, potentially excluding PCa from their criteria completely, and may mandate a consultation with certified GC for approval.

Many, but not all, laboratories work with commercial insurance companies to negotiate coverage into their policies and will provide an estimate of the OOP cost of testing. Not all insurance companies require prior authorization for genetic testing. Laboratory online ordering portals will often indicate whether provider-initiated insurance prior authorization is needed. Typically, all components of the billing process, including submission of insurance prior authorization, are handled by the laboratory. Several commercial laboratories offer a patient-pay or fixed OOP cost, often \$250 or lower, making testing more financially accessible. In addition, patients may qualify for a sponsored testing program at no cost in exchange for de-identified data shared with the sponsoring companies.

Results delivery and follow-up. Methods for delivering test results vary, depending on workflow, availability of genetic counseling services, and provider comfort level and training. Regardless of result type, genetic test reports should be offered to patients for their own records and uploaded into the EMR. Refer to Table 2 for information regarding the following result types. Options for returning results include:

1. Ordering provider refers all patients for post-test counseling, either through referral to a local GC or a telehealth genetic counseling service.

2. Ordering provider refers patients with complex results (eg, positive and/or VUS) for post-test counseling. This type of blended approach to genetic testing has been previously discussed and has received strong consensus across multiple disciplines.^{21,26}

a) Negative results: Clinical teams can disclose results via telephone, patient portal message, a follow-up appointment, or a letter summarizing the results and providing contact information if there are questions. A templated letter can be generated with GC input. Cancer screening recommendations should be based on the family history and should be reviewed with the patient. For example, men with a first-degree relative with PCa remain at increased risk for PCa and should initiate prostate screening at a younger age per routine guidelines. Patients should be encouraged to discuss updates to personal and family history, which may prompt consideration of additional genetic testing or altered screening recommendations.

3. Ordering provider discloses all result types. It is important to note that even in this situation, a referral can be made to genetics for post-test counseling.

a) Positive results: Providers should discuss and document the implications of the results in terms of cancer risks associated with the identified gene mutation, additional cancer screening recommendations, appropriate referrals, and possible implications for treatment. Providers should also recommend cascade testing, which entails genetic

TABLE 3. Pretest Talking Points Regarding the Benefits and Risks/Limitations of Genetic Testing^{27,49}

Benefits	Risks/Limitations
May help explain personal cancer history	May increase anxiety and guilt regarding hereditary cancer risk
May help inform prognosis	Potential for uncertain results: 1) Variants of uncertain significance, or 2) Positive results in lesser established genes and those with no management guidelines currently available
May help inform risks for additional cancers	Genetic discrimination risks (life insurance or long-term care insurance)
May help guide treatment decisions	Financial barriers
May help inform cancer risks for family members	

counseling and testing in at-risk relatives of individuals identified to carry specific genetic mutations or further testing in the family based on family history. Access to the proband's test report will be essential for family members considering testing.

- b) VUS results: It is critical to review the uncertainty of whether the specific gene mutation identified is disease causing or a benign variation. The vast majority of VUS results are later reclassified to negative^{28,29}; thus, they are typically treated as negatives, and screening recommendations are made based on personal and family history. Testing family members for a VUS is typically not recommended unless it is in the context of a variant resolution or research program. When a VUS is reclassified, new reports are customarily issued to the ordering provider, and it is therefore the responsibility of the ordering provider to follow up with patients over the long term concerning any reclassifications. Patients should be encouraged to check in with their providers every few years to see whether there are updates to the classification. It is also important to note the possibility of discrepant variant classifications across laboratories. These discrepancies may cause difficulty determining how to appropriately manage patients and family members. ClinVar is a free, publicly available database that aggregates variant classifications, although a limitation is that entry submissions may not be completely up to date.

Cascade testing. The concept of cascade testing should be introduced as part of pretest counseling. Family letters can facilitate genetic testing for other relatives in the event of a positive result and typically include a short description of the cancer syndrome, the specific mutation identified, information on how to contact a GC in their area, and laboratory/specimen identification for the patient's testing. A number of the genes associated with hereditary PCa, such as *BRCA1/2* and the mismatch repair genes, are associated with additional cancers and may have well-defined risk numbers and screening recommendations for males and females. Targeted testing for the known familial variant can clarify the cancer risks for other relatives, allowing for the initiation of appropriate increased cancer screening and risk-reducing therapies, and consideration of reproductive planning options.²⁷ Ultimately, it is the patient's decision and responsibility to inform at-risk relatives about their genetic test results, which underlies the importance of reviewing cascade testing and providing resources to help facilitate this transfer of critical information.

Additional Considerations

Pathogenic mutations identified in DNA-damage repair genes, such as *BRCA1/2* or mismatch repair genes, have implications for management and treatment.^{3,4} Germline mutations are identified in approximately 12% of patients

with metastatic PCa, but because some are not actionable, it is important to manage expectations concerning outcomes for germline testing.⁷⁻¹¹ Many of the genes included on PCa panels are newly associated with PCa and do not yet have well-defined cancer risks. This increases the possibility of a positive result in a gene associated with low-to-moderate increased cancer risk, which may not have clear screening recommendations. Providers need to be clear about the preliminary nature of findings and that there may not be an immediate impact on cancer screening or treatment options. Patients and their families should be encouraged to participate in registries or research studies to better characterize the risk associated with specific variants over time. Providers can refer patients to a GC for further discussion. Finally, as germline mutations continue to be levied for treatment purposes, providers must be aware of the risk of secondary malignancies and treatment-related adverse effects in some mutation carriers.²⁸⁻³²

Some providers may be concerned about the potential for negative consequences from genetic testing. A number of studies have found that most individuals are unlikely to experience significant psychological distress after receiving genetic test results.^{33,34} Notably, the likelihood of psychological distress, family disruption, and nonadherence to surveillance guidelines was greater in settings without adequate patient education, counseling, informed consent, and follow-up.^{33,35} A recent study of men with PCa undergoing genetic testing found genetic counseling to be beneficial.³⁵

Some patients are hesitant about genetic testing because of concerns about discrimination. The Genetic Information Nondiscrimination Act (GINA), a federal law passed in 2008, protects individuals from genetic discrimination from health insurance companies and employers, with specific limitations on the type of employer and size of the company. Importantly, GINA protections do not extend to life, disability, or long-term care insurance. Some states have passed genetic discrimination laws that extend protection beyond GINA. Information regarding GINA is often included in the consent forms for testing laboratories, and summary handouts could be given to patients with additional questions.

Practical Strategies to Overcome Genetic Service Barriers

ASCO and other major health societies strongly encourage and often provide additional education training for non-genetics providers who are interested in responsibly incorporating genetic services into their practice. Courses on genomic cancer risk assessment for physicians, advanced practice providers, nurses, GCs, and other health care professionals are available through organizations such as City of Hope, American Urological Association, and ASCO.

Alternatives to in-person pretest counseling, such as educational handouts, videos, and presentations, are allowing genetic counseling expertise to be shifted to the post-test setting, prioritizing visits for complex counseling patients and/or abnormal results, and facilitating a hybrid service

delivery model.^{18,36} Data are still emerging regarding the effectiveness of these models and patient satisfaction. Other practical strategies have focused on increasing GC efficiency and patient volumes, leading to the creation of new support roles, such as GC assistants; incorporation of technologies that reduce appointment time, such as online pedigree collection tools; and group genetic counseling sessions.^{37,38} There are now chatbots, such as Genetic Information Assistance, that can converse with patients about family history and the basics of genetic testing and insurance, and determine who qualifies for genetic testing.

Special attention and strategies to minimize disparities in genetics are essential. It has been well documented that socioeconomically disadvantaged individuals, racial/ethnic minorities, and men are less likely to receive genetic services.^{18,39-43} PCa genetic testing provides a unique opportunity for providers and institutions to address possible disparities and consider offering counseling services within

a male-friendly environment. It is imperative that health care providers from all specialties work together to provide equal access to genetic services by minimizing biases, improving patient education and understanding, creating culturally sensitive interfacing materials, and expanding services to underprivileged areas.

In conclusion, as genetic testing becomes integral to the care of patients with PCa, coordinated efforts across multiple disciplines are required to deliver optimal care. Developing creative, scalable strategies to deliver high-quality personalized genetics care for patients with PCa will be paramount to realizing the full scope and impact of genetic testing for individual patients and family members. It is clear that expanding education around the need for testing and developing standardized systems for implementation in the clinic are important directions for genetics care delivery and essential for delivering precision oncology to men with PCa.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Practical Considerations and Challenges for Germline Genetic Testing in Patients With Prostate Cancer: Recommendations From the Germline Genetics Working Group of the PCCTC**

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Genetic Testing in Prostate Cancer

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Abstract

Purpose of Review This review summarizes recent advances in prostate cancer (PCa) genetics.

Recent Findings Upwards of 20% of metastatic castration-resistant prostate tumors (mCRPC) carry homologous recombination (HR) repair gene mutations, of which ~10% are germline (inherited). Another ~5% exhibit microsatellite instability (MSI-H) and/or mismatch repair deficiency (MMRd). Pembrolizumab is approved for tumors with MMRd, thus patients with mCRPC and MMRd are candidates for pembrolizumab. Emerging data indicate that platinum chemotherapy and poly ADP-ribose polymerase inhibitors (PARPi) are effective in PCa exhibiting HR deficiency. NCCN guidelines now recommend germline and somatic tumor testing in specific clinical scenarios due to treatment and family implications.

Summary Genetic testing in PCa patients may inform prognosis, treatment options, and have implications for family counseling. PARPi, platinum chemotherapy, and immune checkpoint inhibitors are promising targeted therapies for PCa with specific molecular features. Therapeutic advances, along with importance to relatives, are driving genetic testing in prostate cancer.

Keywords Prostate cancer · Genetics · BRCA · PARPi · Germline testing

Introduction

Prostate cancer has a significant heritable component. In the past few years, substantial strides have been made in understanding genetic factors influencing prostate cancer susceptibility. Many of the recent discoveries have extended beyond common single-nucleotide polymorphisms (SNPs) to high and moderate penetrance genetic variants, alongside new precision-directed therapeutic implications that are leading to shifts in research and practice.

More than 100 susceptibility loci for prostate cancer have been identified with GWAS (genome-wide association studies), accounting for ~33% of familial prostate cancer risks [1–7]. Many variants identified were high prevalence and

low-penetrance, and were not clinically used to differentiate risk of aggressive from indolent prostate cancer [7]. The germline *HOXB13 G84E* variant was established in 2012 as a susceptibility loci that significantly increased prostate cancer risk through study of families with multiple cases of prostate cancer [8]. Germline testing of unselected prostate cancer patients showed overall low prevalence of germline pathogenic or likely pathogenic variants (hereafter referred as mutations) in *BRCA2*; 1.2% among men were diagnosed before 65 years old [9, 10]. Prior to 2016, clinical germline testing for prostate cancer risk was not pervasive.

The Molecular Landscape of Metastatic Prostate Cancer

Substantial changes came with a Stand Up To Cancer-Prostate Cancer Foundation Prostate Cancer Dream Team study that sequenced metastatic prostate cancer biopsies and provided molecular characterization of later evolutionary stages of tumorigenesis [11]. A notable finding was that alterations in *BRCA2*, *BRCA1*, and *ATM* were observed in 19.3% (29/150) of metastatic tumors—a much higher frequency compared with localized disease [9, 11]. Eight percent (12/150) of patients with metastatic prostate cancer had pathogenic germline alterations [11].

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Prevalence of Germline Mutations in Metastatic Prostate Cancer

In 2016, Pritchard et al. reported a study of germline sequencing in 692 men with metastatic prostate cancer, unselected for family history or age at diagnosis, and found that 11.8% (82/692) had germline DNA repair alterations compared with 4.6% (23/499) among men with localized prostate cancer from the Cancer Genome Atlas (TCGA), and 2.7% (1434/53,105) in persons without a known cancer diagnosis (EXAC) [12••]. A subsequent cross-sectional study by Nicolosi et al. evaluated 3607 men with a personal history of prostate cancer who underwent germline genetic testing between 2013 and 2018. The study found that 4.74% of patients with prostate cancer had *gBRCA2* mutations, 2.88% *gCHEK2*, 2.03% *gATM*, 1.25% *gBRCA1*, 1.12% *gHOXB13*, 0.69% *gMSH2*, and 0.56% *gPALB2* gene mutations [13]. The higher than previously recognized prevalence of DNA repair gene mutations led to changes in clinical testing guidelines.

Emerging data suggest that patients with ductal and intraductal prostate cancer carcinoma have higher risk of having microsatellite instability [14–17] and germline homologous recombination repair mutations [17–20]. Taylor et al. performed whole exome sequencing of prostate cancer tumors from 14 patients with castration-sensitive localized prostate cancer and *gBRCA2* mutations, and showed that these tumors harbor increased genomic instability, and their mutation profiles resemble metastatic tumor [18]. A case study of patients with ductal histology prostate carcinoma showed that 49% (25/51) had DNA repair gene alterations, including 20% (10/51) with germline alterations. Somatic tumor sequencing of this patient cohort reported that 14% (7/51) tumors had mismatch repair gene alterations and 31% (16/51) in homologous recombination repair genes [17].

Collectively, these studies suggest that germline DNA repair mutations are present in substantial percentages in specific populations, (1) prostate cancer patients with metastatic disease, (2) those with a family history suggestive of inherited cancer predisposition, (3) ductal and intraductal histologic subtypes. NCCN guidelines for prostate cancer now recommend offering germline genetic testing to men in these groups (Table 1) [21, 22].

Family Impact of Germline Testing

Germline testing in men with prostate cancer can potentially benefit the patient in informing treatment options, and if a mutation is identified, may also guide screening of other cancers and have family implications for cascade genetic testing (testing of close relatives for the same germline mutation). Early cancer detection strategies and preventive measures may be available to relatives identified to have same germline mutations. Cascade family testing can be valuable for family

Table 1 Family history for prostate cancer patients

Family history criteria
Family history of high-risk germline mutations (e.g., <i>BRCA1/2</i> , Lynch syndrome)
Brother or father or multiple family members diagnosed with prostate cancer (but not clinically localized grade group 1) at < 60 years or who died from prostate cancer
Ashkenazi Jewish ancestry
≥ 3 cancers on same side of family, especially diagnosed at age ≤ 50 years, bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized grade group 1), small bowel, or urothelial

members, but unfortunately cascade family testing is currently underperformed, and strategies to overcome barriers, such as lack of knowledge, family communication, lack of access to genetic services, and cost of testing, are needed.

The NCCN guidelines for Genetic/Familial High-Risk Assessment for Breast and Ovarian Cancer [23] recommend breast cancer screening starting at age 25 years for female relatives and age 36 years for male relatives with deleterious *gBRCA1/2* mutations. *gBRCA1/2* female carriers should discuss with their health care provider risk reduction mastectomy and salpingo-oophorectomy, which is typically recommended between 35, 36, 37, 38, 39, 40 years old, and upon completion of childbearing.

Male relatives with *gBRCA2* and *gBRCA1* mutations may be at increased risk of cancers such as male breast, pancreatic, colon, and prostate. A study of 173 breast-ovarian cancer families with *gBRCA2* mutations showed 4.7- to 8.6-fold increased risks of prostate cancer with cumulative risk of 20–33% in US carriers by the age of 70 years [24]. A study of 913 male *gBRCA1* mutation carriers reported that *gBRCA1* mutation increases the relative risk of prostate cancer by 3.75-fold and results in an 8.6% cumulative risk by age 65 [25].

The IMPACT study (Identification of Men with a Genetic Predisposition to Prostate Cancer: Targeted screening in *gBRCA1/2* mutation carriers and controls) conducted yearly PSA screening in families with known *gBRCA1/2* mutations [26, 27]. The study enrolled 2932 men with no personal history of prostate cancer, 919 *gBRCA1* carriers, 902 *gBRCA2*, 497 *gBRCA2* noncarriers, and 709 *gBRCA1* noncarriers. Preliminary results reported after 3 years of follow-up showed overall 21% positive predictive value (PPV) of PSA > 0.3 ng/ml with 31% PPV in *gBRCA2* carriers and 18% in *gBRCA2* noncarriers; and 23% in *gBRCA1* carriers and 15% in *gBRCA1* noncarriers. PPV of prostate biopsy, initiated when PSA > 3.0 ng/ml, was 39% in *gBRCA2* carriers and 28% in *gBRCA2* noncarriers, but no significant difference was detected between *gBRCA1* carriers and *gBRCA1* noncarriers. *gBRCA2* carriers had higher incidence of prostate cancer diagnosed at younger age and

with more aggressive disease characteristics compared with *gBRCA2* noncarriers. The results for *gBRCA1* carriers were not definitive, and further investigation is needed. The number needed to screen to detect one clinically significant prostate cancer was 60 for *gBRCA2* carriers ages 40–54 years and 13 for carriers ages 55–69 years. Thus, the results from IMPACT suggest annual PSA screening for *gBRCA2* mutation carriers between age 40 and 69, using PSA cutoff of 3 ng/ml [27]. Studies evaluating predictive value of lower PSA cutoff and prostate MRI are ongoing (e.g., www.clinicaltrials.gov, NCT03805919, NCT01990521).

Prognostic Impact of DNA Repair Gene Mutations

Prostate cancer patients may benefit from germline and/or somatic genetic testing to inform disease prognosis and treatment decisions, with somatic testing being potentially more relevant for treatment decisions. Several studies showed that germline *BRCA1/2* mutations are associated with poor prognosis and worse outcomes in prostate cancer. Castro et al. showed that prostate cancer patients with *gBRCA1/2* mutations were more likely to have a Gleason score ≥ 8 , T3/4 stage, nodal involvement, and metastases at the time of diagnosis compared with noncarriers. Moreover, *gBRCA1/2* carriers had shorter cancer-specific survival (CSS) compared with noncarriers (15.7 vs 8.6 years) [28]. *gBRCA1/2* carriers with localized prostate cancer have worse outcomes after conventional treatment with surgery or radiation compared with noncarriers, 5-year metastasis free survival 72% vs 94%, 5 year CSS 76% vs 97% [29]. A retrospective case study by Na et al. found that proportion of men carrying *gBRCA1/2* or *gATM* mutations was significantly higher in men who died from prostate cancer compared with men with localized disease (6.07% vs 1.44%). This study also showed that among patients with lethal prostate cancer rate of *gBRCA1/2* and *gATM* mutations was higher in patients who died younger, 10% among those who died <60 years, 9% for age of death 61–65; 8% 66–70 years, 4% 71–75 years, and 2.97% among those who died >75 years old [30]. The prospective PROREPAIR-B found that *gBRCA2* status is an independent prognostic factor for CSS in metastatic castration-resistant prostate cancer (mCRPC) patients (17.4 vs 33.2 months, $p=0.027$) [31].

Somatic DNA repair gene mutations are present in about 8–10% of localized prostate cancer cases and 20–25% of mCRPC cases, and Marshall et al. reported that presence in localized disease is associated with higher Gleason grade group (≥ 3) and more advanced clinical stage ($\geq$ cT3 disease) at the time of diagnoses [32].

Recommendations for Genetic Testing in Prostate Cancer

Based on these and other studies, NCCN guidelines for Prostate Cancer recommend offering germline testing, ideally with genetic counseling access, to the following groups of prostate cancer patients [22]:

1. Men with high-risk, very-high risk localized prostate cancer
2. Men with metastatic prostate cancer
3. Men with intraductal histology
4. Men with Ashkenazi Jewish ancestry
5. Men meeting family history criteria (see Table 1)

Somatic tumor sequencing should also be considered in prostate cancer patients especially with advanced disease. Sequencing of tumor metastatic biopsies is preferred when available, as tumor clones evolve over time, and primary prostate cancer tissue might miss alterations developed later in the disease course. Men should also be counseled that somatic tumor testing could potentially suggest presence of a germline mutation, and if the case, referral to genetic counseling to discuss dedicated germline testing would be advised. NCCN guidelines for Prostate Cancer recommend that germline and somatic testing panels should include Lynch syndrome associated genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) and homologous recombination genes (*BRCA1/2*, *ATM*, *PALB2*, *CHEK2*) [21, 22]. Other genes might be appropriate for testing in certain scenarios, such as potential enrollment into clinical trials, where significance of newer gene/mutations as biomarkers for new treatments are being explored.

Treatment Implications of Genetic Testing

Advanced Disease

Targeted therapies are being investigated in clinical trials for prostate cancer patients with specific DNA repair gene alterations in tumor and/or germline. At present, the treatment implications of genetic testing are arguably greatest in metastatic disease, as this is the disease space with the majority of therapeutic clinical trials.

Some studies are available in earlier disease states of prostate cancer and more are expected to follow. Patients with homologous DNA repair mutations are candidates for clinical trials using poly ADP-ribose polymerase inhibitors (PARPi) and/or platinum chemotherapy, and novel combinations. There are several ongoing clinical trials evaluating the role of these agents as monotherapy or in various combination therapies in different stages of prostate cancer (e.g., www.clinicaltrials.gov, NCT02975934, NCT02952534, NCT02854436, NCT02987543, NCT03413995). Below is a

summary of current data on targeted therapy in prostate cancer patients with DNA repair gene mutations, i.e., immunotherapy, PARPi, platinum chemotherapy.

Immunotherapy Pembrolizumab received the first tumor agnostic FDA approval in 2017 for metastatic solid tumors with microsatellite instability (MSI-H) and mismatch repair deficiency (MMRd) [33, 34]. About 5% of mCRPC cases are estimated to be MSI-H/MMRd and would qualify for treatment with pembrolizumab [35, 36–38]. In a single institution case series of 1033 prostate tumors undergoing next generation sequencing, 3.1% (32/1033) were found to be MSI-H/MMRd, 78% (25/32) tumors had somatic mutations, and 22% (7/32) were found to have germline Lynch-associated mutations [35]. Somatic and germline testing for MSI-H/MMRd is recommended in certain prostate cancer patient populations (see above) and has direct clinical implications as MSI-H/MMRd patients are eligible for pembrolizumab in second line of mCRPC treatment.

PARPi Patients with DNA repair mutations have higher response rates to PARPi and platinum chemotherapy [39]. The clinical activity of PARPi in prostate cancer was first reported in the TOPARP-A trial (Trial of Olaparib in Patients with Advanced Castrate Resistant Prostate Cancer), which evaluated olaparib in mCRPC patients who failed multiple lines of therapy (98% received prior abiraterone or enzalutamide, 58% cabazitaxel) [40]. TOPARP-A reported that 88% (14/16) of patients with DNA repair mutations had response to olaparib therapy, where response was defined as a reduction in the PSA by 50% (PSA₅₀), a RECIST-defined objective response rate or circulating tumor cell reduction. Only 2 out 32 patients without DNA repair gene alterations responded to olaparib in TOPARP-A trial. As a result of this trial, olaparib received FDA breakthrough therapy designation in January 2016 for patients with *BRCA2*-, *BRCA1*-, or *ATM*-mutated mCRPC who had received prior taxane and either enzalutamide or abiraterone.

The phase 2 TRITON2 (NCT02952534) study evaluated rucaparib in mCRPC patients with homologous recombination gene mutation progressing after 1–2 lines of androgen receptor-directed therapy and 1 prior line of taxane. Preliminary results demonstrated that among *BRCA1/2* carriers 44% (11/25) had radiographic response, and 51% (23/45) had PSA₅₀ response [41]. Based on these results, FDA granted rucaparib breakthrough designation in October 2018 [42].

The phase 2 TOPARP-B is a trial of PARPi in mCRPC patients with DNA damage repair alterations progressing after at least one taxane ($n = 98$) [43]. The overall median progression-free survival (mPFS) was 5.4 months. Subgroup analyses per altered gene indicated following response rates (defined as in TOPARP-A study), *BRCA1/2* 83% (25/30; mPFS 8.1 months); *PALB2* 57% (4/7; mPFS 5.3 months);

ATM 37% (7/19; mPFS 6.1 months); *CDK12* 25% (5/20; mPFS 2.9 months); other (*ATR*, *CHEK1*, *CHEK2*, *FANCA*, *FANCF*, *FANCG*, *FANCI*, *FANCM*, *RAD50*, *WRN*) 20% (4/20; mPFS 2.8 months). The highest PSA₅₀ response rates were observed in the *BRCA1/2* (22/30; 73%) and *PALB2* (4/6; 67%) mutated subgroups.

The first phase 3 randomized clinical trial evaluating PARPi in mCRPC was recently reported [44]. PROfound enrolled mCRPC patients who progressed on abiraterone or enzalutamide and had mutations in homologous recombination DNA repair genes, identified by tumor sequencing; cohort A, patients with *BRCA1/2* and *ATM* mutations; cohort B, patients with mutations in other homologous recombination repair genes. Patients were randomized to olaparib 300 mg BID or physician's choice of enzalutamide or abiraterone. The results showed improved radiographic PFS (rPFS) in the olaparib arm of cohort A (7.39 vs 3.55 months, homologous recombination (HR) 0.34 $p < 0.001$), with objective response rate of 33.3% in olaparib and 2.3% in physician's choice arm of cohort A (OR 20.86 $p < 0.001$). Despite the crossover design, overall survival (OS) was 18.5 months in olaparib arm compared with 15.11 months in abiraterone/enzalutamide arm of cohort A, although statistical significance was not reached at time of initial reporting. There was also rPFS benefit in combined cohorts A and B, 5.82 months in olaparib arm vs 3.52 months in physician's choice arm (HR 0.49 $p < 0.001$). We anticipate that the FDA will approve olaparib for subset of mCRPC patients on the basis of the PROfound trial results.

Table 2 summarizes currently available study results reporting response rates to PARPi in prostate cancer.

Platinum chemotherapy Platinum chemotherapy has been proven to be effective in *BRCA1/2* mutated breast and ovarian cancers [49, 50]. Our single institution retrospective case series showed that 3/3 prostate cancer patients with biallelic inactivation of *BRCA2* had exceptional response to platinum chemotherapy after progressing on several therapies [51]. The findings were supported by a retrospective study that showed 75% (6/8) of mCRPC patients with *gBRCA2* mutation had PSA₅₀ response to platinum chemotherapy compared with 17% (23/133) of mCRPC patients without *gBRCA2* mutations [52].

Localized Disease

In an active surveillance cohort, patients with localized prostate cancer and *gBRCA2*, *gBRCA1*, or *gATM* mutations were more likely to experience grade reclassification compared with non-mutation carriers [53]. Further studies are warranted, but these data suggest that this group of patients will be monitored closely, ideally on a clinical trial, or consider a definitive treatment approach. The role of PARPi in localized prostate

Table 2 Response to PARPi in mCRPC patients stratified by HR gene mutations

Study	Agent used	Response measured by	Number of patients responded to PARPi by mutation status				
			<i>BRCA1/2</i>	<i>ATM</i>	<i>CDK12</i>	Other HRD mut	No HRD mut
PROfound, Hussain et al. [44••]	Olaparib vs abiraterone/enzalutamide	Imaging rPFS (months)	84/162 vs 42/83	~ 3/94	vs ~ 4/48		N/A
TOPARP-A, Mateo et al. [40]	Olaparib	Imaging PSA ₅₀ CTC	8/8	4/5	N/A	2/3	2/33
TOPARP-B, Mateo et al. [43••]	Olaparib	Imaging PSA ₅₀ CTC	24/30	7/19	5/20	8/27	N/A
TRITON2, Abida et al. [41••]	Rucaparib	Imaging	11/25	0/5	0/8	2/8	N/A
		PSA ₅₀	23/45	0/18	1/13	2/9	N/A
NCI study (50) Karzai et al. [45]	Durvalumab + olaparib	Imaging PSA ₅₀	7/11	N/A	N/A	N/A	2/6
GALAHAD, Smith et al. [46]	Niraparib	Imaging PSA ₅₀ CTC	18/29	N/A	N/A	5/21	N/A
KEYNOTE-365, Yu et al. [47] 2019	Olaparib + pembrolizumab	Imaging	N/A	N/A	N/A	N/A	8/28
		PSA ₅₀	N/A	N/A	N/A	N/A	5/41
Retrospective analysis, Marshall et al. [48]	Off-label olaparib	PSA ₅₀	13/17	0/6	N/A	N/A	N/A

Mut, mutations; *CTC*, circulating tumor cell DNA; *PSA₅₀*, decline of prostate-specific antigen by 50% from baseline; *Imaging*, radiographic response measured by RECIST criteria; *rPFS*, radiographic progression-free survival

cancer is being evaluated in several ongoing clinical trials (www.clinicaltrials.gov, NCT03570476, NCT02324998 and NCT03432897).

Biochemical Recurrence

Patients historically classified as having biochemically recurrent (BCR) prostate cancer are now moved to the metastatic group with the use of more sensitive treatment modalities such as PSMA-PET and fluciclovine PET. Advances in imaging has changed the BCR patient population. There is currently no standard of care treatment implications of DNA repair mutations in BCR group, but the use of PARPi is currently being studied in phase 2 clinical trial (NCT03047135), evaluated PSA₅₀ response to olaparib in BCR prostate cancer patients. The study is enrolling patients unselected for DNA repair mutation status with an adaptive plan to enrich study population with DNA repair mutation carriers if response is low in first 20 patients.

Conclusions

There has been significant advancement in prostate cancer genetics in the last 5 years. In metastatic castration-resistant prostate cancer, ~20% of tumors harbor homologous recombination repair gene mutations, and 5% harbor mismatch repair gene mutations; alternations in both pathways have clinical implications. The NCCN Prostate Cancer guidelines recommend germline testing for men with high-risk, very high-risk localized prostate cancer, all metastatic prostate cancer

patients, patients with intraductal histology of prostate cancer, and for patients meeting family history criteria. Somatic tumor testing should also be considered for advanced disease as it may inform treatment decisions.

Patients with homologous recombination-deficient prostate cancer appear to respond to PARPi and platinum chemotherapy, although more individual gene-specific data is needed. The PROFound study, a phase 3 randomized clinical trial of olaparib in mCRPC patients with *BRCA1/2* and *ATM* mutations showed improved rPFS. Patients with MSI-H/MMRd are eligible for immune checkpoint inhibitor therapy in second-line treatment for mCRPC. Both germline and somatic tumor genetic testing are recommended for prostate cancer patients in specific clinical scenarios. Clinical trials are ongoing to evaluate treatment implications of alterations in mismatch repair genes and homologous recombination genes, and we expect new indications and combinations of PARPi and immune checkpoint inhibitors to be explored by these trials. Further investigation is needed to identify individual gene contributions to treatment response prediction and germline risk of prostate and other cancers.

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Compliance with Ethical Standards

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Honing in on PARPi Response in Prostate Cancer: from HR Pathway to Gene-by-Gene Granularity

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SUMMARY

PARP inhibitors (PARPi) are promising in *BRCA2*-altered prostate cancer. Data were presented on PARPi efficacy in prostate cancers with alterations in other DNA damage repair genes which suggest low re-

sponse rates in *ATM*-, *CHEK2*-, *CDK12*-altered tumors and promising results in *PALB2*-, *RAD51B*-, *FANCA*-, and *BRIP1*-altered tumors.

See related article by Abida et al., p. 2487

In this issue of *Clinical Cancer Research*, Abida and colleagues report response to the PARPi rucaparib in patients with metastatic castration resistant prostate cancer (mCRPC) harboring deleterious alterations in non-*BRCA* DNA damage repair (DDR) genes (1). The data provides early evidence that prostate tumors with *ATM*, *CDK12*, and *CHEK2* alterations may have limited response to rucaparib, while tumors with alterations in *PALB2*, *FANCA*, *BRIP1*, and *RAD51B* may benefit from PARP inhibition (1).

Several studies suggest that PARPis are effective in prostate cancer tumors with *BRCA2* alterations (2). The mechanism of action of PARPi in tumors is typically attributed to impaired double-strand DDR-homologous recombination (HR) repair-deficient tumors, but likely involves additional mechanisms such as (i) trapping of the PARP1-enzyme, which regulates several DNA repair processes; (ii) inhibition of base excision, critical to single-strand DNA repair; (iii) activation of error prone nonhomologous end joining repair, important in double-strand DNA repair; and (iv) inhibition of DNA repair protein recruitment (e.g., *BARD1-BCR1* complex; ref. 3). Multiple non-*BRCA* genes mediate HR repair (e.g., *ATM*, *CHEK2*, and others), so many have been included as candidate biomarkers for PARPi sensitivity. However, data to date has been limited by small numbers and technical differences (2).

To begin to address this, Abida and colleagues evaluated response to rucaparib in patients with metastatic castration-resistant prostate cancer and non-*BRCA* DDR gene alterations in the phase II TRITON2 study. Eligibility included patients with disease progression after second-generation androgen receptor-targeted therapy and taxane-based chemotherapy and who were identified to have germline and/or somatic mutations in selected DDR genes (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*). Whole blood was used for germline testing and somatic sequencing was performed on circulating tumor DNA (ctDNA) or on tumor tissue by central or local laboratory. This *ad hoc* analysis included 78

patients whose tumors were found to have alterations in non-*BRCA* DDR genes. Response was defined as partial or complete radiographic response per RECIST criteria or PSA50 response (decline of serum prostate-specific antigen by 50% from baseline). Overall rates of response among patients with *ATM*, *CHEK2*, and *CDK12* alterations were low: 2/49 (*ATM*), 2/12 (*CHEK2*), 1/15 (*CDK12*). Interestingly, the proportion of patients without evidence of radiographic progression (labeled clinical benefit) at 6 and 12 months suggests that rucaparib may stabilize disease in these patients. Responses were observed in 2 of 2 patients with *PALB2*, 1/4 with *FANCA*, 1/2 with *BRIP1*, 1/1 with *RAD51B* mutations, small, but intriguing numbers.

These findings are consistent with previously reported data: 1 of 5 patients with *FANCA*-, 4/7 with *PALB2*-, 2/19 with *ATM*-, and 0/20 with *CDK12* -alterations had RECIST or PSA50 response to PARPi in TOPARP-B trial (2). In the PROfound study, patients with *RAD51B* alterations treated with PARPi had a 6-month median radiographic progression-free survival (rPFS) benefit compared with physician choice therapy arm, and similar rPFS was observed between two arms in patients with *ATM* alterations (2). Similarly 0 of 6 patients with *ATM* alterations had PSA50 response in a retrospective study (2). As a field, we must be careful to draw conclusions from small numbers in each analysis, however, in aggregate, patterns are emerging.

The authors of this manuscript acknowledge several limitations (1). First, there was no requirement for central laboratory confirmation of reported alterations. Some, but not all, sequencing results were confirmed by central laboratory, increasing the chance of false positive results for eligibility. Second, clonal hematopoietic (CH) variants may introduce interference in ctDNA studies and mistakenly attributed to tumor-specific alterations (4). Among genes included for eligibility in this study, alterations in *ATM* are more common in CH and thus may contribute to variant origin misclassification (4). Third, loss of heterozygosity (LOH) and tumor sequencing data were not available for several patients, including the patients with *ATM* alterations who had response to rucaparib. It is possible that non-*ATM* tumor alterations contributed to PARPi responses in these patients even though their eligibility was due to an *ATM* alteration.

This study addresses important knowledge gaps by characterizing response to PARPi in tumors with relatively rare alterations in DDR genes. It is especially timely as we anticipate FDA approval of PARPi in prostate cancer based on the positive phase III PROfound study and other eagerly anticipated trials such as TRITON3, GALAHAD and TALAPRO-1 (2). Understanding the efficacy of PARPi in prostate tumors with non-*BRCA* DDR gene alterations is essential before

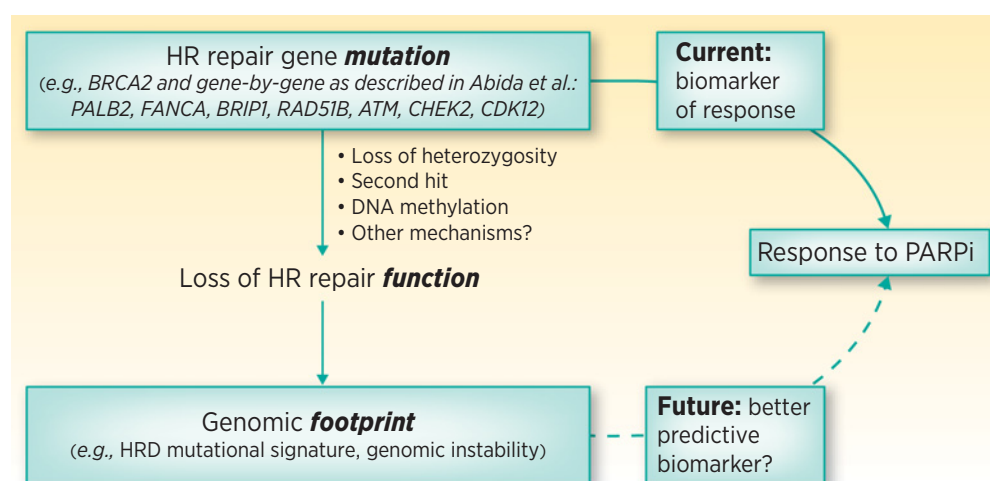
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**Figure 1.**

Predictive biomarkers for PARPi efficacy. Currently, alterations in HR repair genes are used to predict loss of HR repair function and to select prostate cancer patients most likely to respond to PARPi, potentially overlooking other causes of HR function loss. HR repair function loss consequences (i.e., genomic footprint) may be a better predictive biomarker for response to PARPi. HRD, homologous recombination deficiency.

widespread clinical use makes the task more challenging. The data presented by Abida and colleagues may help generate hypotheses about mechanisms of response and resistance, and refine predictive biomarkers for PARPi use for patients with prostate cancer, including in subsequent preclinical and clinical trials.

A better understanding of which patients benefit the most from PARPi and which DDR gene mutations could be the best predictors of response to PARPi will help refine precision oncology in prostate cancer therapy. A notable example is that not all *BRCA2*-mutated tumors respond to PARPi (1, 2) and conversely, in the TOPARP-A study, two patients without evidence of DDR gene mutations achieved response to PARPi, suggesting additional mechanisms of PARPi sensitivity beyond those specifically tested (2). Sensitivity to PARPi is hypothesized to be determined by functional HR deficiency (HRD), such that relying solely on gene mutations to predict PARPi sensitivity may overlook other mechanisms resulting in loss of HR function, for example, DNA hypermethylation. Loss of HR repair function, regardless of the cause, is thought to lead to characteristic genomic changes such as HRD mutational signature and genomic instability. HRD mutational signature is characterized by a more-or-less equal representation of all possible single base substitutions and all 96 mutant nucleotide contexts (5). With the data and specimens from Abida and colleagues and other PARPi studies, examining the downstream consequences of HR loss and the associated genomic footprints with clinical response may facilitate more accurate prediction of response to PARPi in the future (Fig. 1).

We applaud the authors in reporting their findings of response to PARPi in tumors with non-*BRCA* DDR gene alterations. To further strengthen the available data for patients whose tumors carry these and other rare alterations and the response to PARPi and other treatments, a concerted team approach is needed. Assembling greater numbers of patients with rare mutations will allow more robust investigation of clinical response, mutational signatures of specific gene alterations, mechanisms of resistance such as reversion mutations, and opportunities for model systems to dissect mechanisms. This will further refine predictive biomarkers, stratify appropriate patients to PARPi therapy and improve the precision of our targeted therapies.

Disclosure of Potential Conflicts of Interest

E.Y. Yu is a paid consultant for AstraZeneca, Clovis, Merck, and Janssen, and reports receiving commercial research grants from Merck. H.H. Cheng is a paid consultant for AstraZeneca and reports receiving other commercial research support from Clovis Oncology, Janssen, Medivation, Sanofi, and Color Genomics. No potential conflicts of interest were disclosed by the other author.

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Clinical Cancer Research

Honing in on PARPi Response in Prostate Cancer: from HR Pathway to Gene-by-Gene Granularity

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Two Steps Forward and One Step Back for Precision in Prostate Cancer Treatment

Michael T. Schweizer, MD^{1,2}; Heather H. Cheng, MD, PhD^{1,2}; Peter S. Nelson, MD^{1,2,3}; and R. Bruce Montgomery, MD^{1,2,4}

The recent US Food and Drug Administration approval of two poly (ADP-ribose) polymerase (PARP) inhibitors, rucaparib and olaparib, for men with metastatic castration-resistant prostate cancer (mCRPC) and mutations in homologous recombination (HR) repair genes has finally ushered in the era of precision medicine for advanced prostate cancer.¹⁻⁴ These approvals represent the culmination of years of work and are clearly a major step forward for the field. However, the respective labels for rucaparib and olaparib offer stark contrasts, the former restrictive to only *BRCA1*- and *BRCA2*-mutated prostate cancer, and the latter permissive of a larger number of genes directly and indirectly involved in HR repair. The broad approval for olaparib includes several genes that, to date, have not individually been shown to predict for response to PARP inhibition. The unintended consequence of using this permissive biomarker strategy for selecting patients for PARP inhibitor treatment may be that patients who have an unclear chance of benefit are exposed to toxicities and delays in utilizing more effective therapies. In addition, this broad approval could hamper efforts to enroll patients in studies designed to better delineate the ability of relatively rare mutations to predict response to PARP inhibitors.

Rucaparib was granted accelerated approval on the basis of the phase II TRITON2 study.^{1,3} In this trial, patients with mCRPC were eligible if they previously experienced progression on a next-generation androgen receptor–signaling inhibitor (eg, abiraterone, enzalutamide, or apalutamide), received one prior line of taxane-based chemotherapy, and who were identified to have a mutation in at least one gene of a larger panel with roles in HR DNA repair. However, only the group consisting of those with *BRCA1* or *BRCA2* mutations clearly seemed to be predictive of response.⁵ In total, 115 patients with *BRCA*-mutated mCRPC enrolled, with 62 having measurable disease. Within this group, a confirmed objective radiographic response was observed in 27 patients (44%), with a duration of response 6 months or longer in 56% of responders (range, 1.7 to ≥ 24 months).¹

Whereas the final TRITON2 results are still anticipated, results of a subgroup analysis evaluating clinical

outcomes in those with non-*BRCA*-mutated mCRPC enrolled has recently been reported.⁵ Overall, responses in those with *ATM* (n = 49), *CDK12* (n = 15), *CHEK2* (n = 12), or other HR genes (n = 14) were low. The prostate-specific antigen (PSA) response rate (ie, 50% or greater decline in PSA) was observed in only 4% of *ATM*-mutated cases, 7% of *CDK12*-mutated cases, and 17% of *CHEK2*-mutated cases. Radiographic responses in the subset with measurable disease were similarly low in non-*BRCA* HR repair genes. Small numbers of patients with mutations in *FANCA* (n = 4), *NBN* (n = 4), *BRIP1* (n = 2), *PALB2* (n = 2), *RAD51* (n = 1), *RAD51B* (n = 1), and/or *RAD54L* (n = 1) were also reported. Whereas sample size limitations prevent drawing conclusions about the sensitivity of any given gene, it is notable that responses were observed in those with mutations in genes that directly interact with the BRCA complex (ie, *PALB2*, *FANCA*, and *BRIP1*), which contrasts with the low response rates in genes that either sense DNA damage (eg, *ATM*, *CHEK2*) or indirectly regulate *BRCA* expression (eg, *CDK12*). Finally, it is worth acknowledging that relatively few men with *BRCA1* alterations were included in this study (n = 14), and the true response rate within this population also remains poorly defined.⁶

Olaparib was approved on the basis of the phase III PROfound study, which was a randomized, open-label study evaluating olaparib versus physician's choice of enzalutamide or abiraterone in men with mCRPC and deleterious germline or somatic mutations in HR repair genes.⁴ Similar to TRITON2, the PROfound investigators also focused on the subgroup that previously experienced progression on next-generation androgen receptor–directed therapy, and, also similar to TRITON2, enrollment was allowed on the basis of a panel of genes involved in the HR repair pathway. Primary end point was progression-free survival (PFS) in the group with *BRCA1*, *BRCA2*, and/or *ATM* mutations (cohort A). A second cohort consisted of patients with mutations in other HR repair–associated genes (cohort B). Secondary end points were analyzed in a hierarchical fashion to control for trial-wide Type 1 error associated with multiple testing, which occurred in the following order: objective response rate (cohort A),

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PFS (combined cohorts A and B), time to pain progression (cohort A), and overall survival (cohort A).

The primary end point was met, with a PFS of 7.4 months versus 3.6 months ($P < .001$) in the olaparib versus control groups for cohort A. Secondary end points also favored the olaparib group, with an objective response rate in cohort A of 33% versus 2% in control group ($P < .001$), median PFS of 5.8 months versus 3.5 months for combined cohorts A and B ($P < .001$), median overall survival of 18.5 months versus 15.1 months for cohort A ($P = .02$), and median overall survival of 17.5 months versus 14.3 months for combined cohorts A and B ($P = .0063$). These results led the US Food and Drug Administration to approve olaparib for a broad group of patients with mCRPC with somatic or germline alterations in *BRCA1*, *BRCA2*, or any of 12 additional HR repair pathway genes.

Whereas the magnitude of benefit reported for cohort A in PROfound is apparent, the lack of details provided for cohort B leaves more questions than answers. Examining the data more closely, it seems that the observed benefit was largely driven by *BRCA*-mutated patients, which primarily consisted of men with *BRCA2* mutations ($> 90\%$). There is a clear improvement in PFS for the *BRCA*-mutated group ($n = 160$), whereas no difference in PFS was observed in either *ATM* ($n = 86$) or *CDK12*-mutated cases ($n = 89$; Fig 2B and Supplemental Figure S5). Unfortunately, no detailed analysis of outcomes for cohort B— independent of cohort A—are provided, and the small sample size within any given genomic subgroup limits our ability to determine which of these patients may have benefited from olaparib.

The TOPARP-A and -B studies, which preceded PROfound, tested olaparib in a similar patient population.^{7,8} In TOPARP-B, the authors found low PSA and radiographic response rates for *ATM* (5.3% and 8.3%, respectively) and *CDK12*-mutated mCRPC (0% for both).⁸ In addition, the PROfound investigators acknowledged that the benefits of olaparib are most apparent in *BRCA*-mutated mCRPC. Whereas the design of PROfound was likely informed by the initial TOPARP-A experience, which found that four of five patients with *ATM*-mutations responded favorably to olaparib (ie, PSA response and/or favorable changes in circulating tumor cell counts), the biologic and clinical rationale for combining *ATM* and *BRCA1/2* mutations into a single cohort is questionable on the basis of our current knowledge.⁷ Registries capturing clinical and genomics data are ongoing and may provide important insights into the clinical relevance of rare variants⁹; however, additional prospective studies evaluating outcomes for patients with HR repair-associated mutations receiving PARP inhibitors should be conducted on an individual gene basis.

In the case of PROfound, the *BRCA* group seems to have driven the overall effect size observed between the olaparib and control groups. An important concern is that this

experience may motivate the design of future precision medicine trials. The precedent set by the olaparib approval for prostate cancer may incentivize studies that combine molecular subgroups to attain broad indications. This may lead to future study designs that include two groups: one that is expected to benefit (eg, *BRCA2*) and another that is more exploratory and permissive (eg, *ATM/CDK12*). The consequence, intended or not, may be that a P value less than .05 could be reached in the combined group as long as the sample size is sufficient to detect a diluted treatment effect. This approach would ultimately run counter to the idea of precision oncology.

As discussed above, the clinical data supporting the use of PARP inhibitors in non-*BRCA2*-mutated cases remain scant; however, there is a rationale for their routine use in men with mutations in a handful of other HR repair-associated genes. Whereas some data suggest lower response rates in men with *BRCA1*- compared with *BRCA2*-mutated prostate cancer (eg, PSA response rate of 29% v 56% per TRITON2) and no clear difference in PFS was observed in men with *BRCA1* mutations receiving olaparib versus abiraterone/enzalutamide in PROfound, the small number of patients with *BRCA1* mutations included in prospective studies make drawing conclusions regarding differences in activity impossible.^{4,6} Overall, the known biologic role of *BRCA1* in HR repair, along with available clinical data, generally supports the use of both olaparib and rucaparib in these patients. Likewise, there is also evidence that PARP inhibitors may afford benefits to those with *PALB2* mutations, with responses to olaparib documented in approximately one third of *PALB2*-mutated prostate cancers.⁸ In addition, because *PALB2* also plays a critical role in HR repair—directly interacting with the *BRCA* complex—there is a strong biologic rationale for using PARP inhibitors in patients with prostate cancer with inactivating *PALB2* mutations.^{5,8,10,11}

The primary advantage of olaparib's broad approval is that providers will have the latitude to use this drug in men with mutations in less common HR repair genes (eg, *PALB2*) that are likely predictive for response. However, approving olaparib for such a large genomic subgroup could prove detrimental to some patients and the field if not used judiciously. To qualify for olaparib, patients must have already experienced progression on a next-generation hormonal agent (eg, abiraterone or enzalutamide) and owing to the heavily pretreated state of their disease, this population often has rapid disease progression with a short overall survival. On the basis of the published studies, there are limited data to support use of olaparib in the absence of *BRCA1/2* mutations, and without other indications of HR repair deficiency, these patients would be better served by participating in clinical trials or receiving a therapy that is beneficial in unselected patients (eg, taxane-based chemotherapy).¹² Using standard-of-care PARP inhibitors in those with uncertain or little chance of

benefit could mean missing a window of opportunity for more effective therapy. This may result in decreased survival and hamper clinical trial enrollment to the very studies that could define the predictive utility of individual genes. Cumulative experience should matter, and given our

understanding of which genes predict response to PARP inhibitors, the use of rucaparib and olaparib should be primarily limited to those with *BRCA1/2* mutations until the development of additional biomarkers that are more predictive of benefit.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Two Steps Forward and One Step Back for Precision in Prostate Cancer Treatment**

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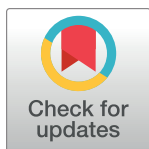
RESEARCH ARTICLE

Impact of mutations in homologous recombination repair genes on treatment outcomes for metastatic castration resistant prostate cancer

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Abstract

Introduction

A significant proportion of patients with metastatic castration-resistant prostate cancer (mCRPC) harbor mutations in homologous recombination (HR) repair genes, with some of these mutations associating with increased tumor susceptibility to poly(ADP-ribose) polymerase (PARP) inhibitors and platinum-based chemotherapy. While mutations in some HR repair genes (e.g., *BRCA1/2*) have been associated with a more aggressive clinical course, prior studies correlating HR mutational status with treatment response to androgen receptor (AR) signaling inhibitors (ARSI) or taxane-based chemotherapy have yielded conflicting results.

Methods

We conducted a single-center retrospective analysis to assess clinical outcomes to conventional, regulatory-approved therapies in mCRPC patients with somatic (monoallelic and biallelic) and/or germline HR repair mutations compared to patients without alterations as determined by clinical-grade next-generation sequencing assays. The primary endpoint was PSA30/PSA50 response, defined as $\geq 30\%$ / $\geq 50\%$ prostate-specific antigen (PSA) reduction from baseline. Secondary endpoints of PSA progression-free survival (pPFS) and clinical/radiographic progression-free survival (crPFS) were estimated using Kaplan-Meier methods.

Results

A total of 90 consecutively selected patients were included in this analysis, of which 33 (37%) were identified to have HR repair gene mutations. Age, race, Gleason score, prior

analysis, decision to publish, or preparation of the manuscript.

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surgery, and receipt of prior radiation therapy were comparable between carriers and non-carriers. There was no evidence that PSA30/PSA50 differed by HR gene mutational status. Median pPFS and crPFS ranged 3–14 months across treatment modalities, but there was no evidence either differed by HR gene mutational status (all $p > 0.05$). There was also no difference in outcomes between those with *BRCA2* or *PALB2* mutations ($n = 17$) compared to those without HR repair mutations.

Conclusion

HR gene mutational status was associated with comparable clinical outcomes following treatment with ARSIs or taxane-based chemotherapy. Additional prospective studies are needed to confirm these findings.

Introduction

DNA damage repair (DDR) pathways play an essential role in maintaining genomic integrity. Individuals harboring germline mutations in DDR genes are more susceptible to cancer development [1]. Germline and somatic DDR mutations are also associated with a more aggressive clinical course in certain cancers: germline *BRCA* mutations have been associated with decreased breast cancer-specific survival [2] and linked to poor outcomes in patients with prostate cancer, including decreased metastasis-free survival in those initially presenting with localized disease [3, 4]. The significance of DDR mutations in prostate cancer has expanded in recent years as studies have demonstrated that their prevalence is higher than previously thought [5, 6].

Importantly, DDR genes specifically involved in homologous recombination (HR) repair may be predictive for response to poly(ADP-ribose) polymerase (PARP) inhibitors in patients with metastatic castration-resistant prostate cancer (mCRPC). Treatment with PARP inhibitors leads to persistent single-strand DNA (ssDNA) breaks through inhibition of base excision repair. These ssDNA breaks then degenerate to double-strand DNA (dsDNA) breaks and, because HR repair deficient cells are unable to efficiently repair dsDNA breaks, PARP inhibitors are synthetically lethal to these cancer cells [7, 8]. Various other mechanisms likely contribute to PARP inhibitor sensitivity in HR repair deficient tumors, including PARP1 trapping and creation of cytotoxic PARP1-DNA complexes at sites of endogenous damage, the promotion of nonhomologous end joining (NHEJ) activity, and inhibition of DNA repair protein recruitment (e.g., *BRCA1*, *BARD1*) [9, 10].

The two-stage TOPARP trials revealed high response rates to olaparib in mCRPC patients with HR repair gene mutations who were no longer responding to standard therapies [11, 12]. More recently, the phase III PROfound trial demonstrated increased radiographic progression-free survival (PFS) and objective responses in mCRPC patients with HR repair gene mutations receiving olaparib compared to enzalutamide or abiraterone [13], although activity in the patients with mutations in non-*BRCA*-mutated HR repair genes remains uncertain [12, 14, 15]. The phase II TRITON2 study found no clear evidence of response to rucaparib in patients with *ATM*, *CDK12*, and *CHEK2* mutations, whereas patients with mutations in genes that directly interact with the *BRCA* complex (e.g. *PALB2*, *FANCA*, *RAD51*, etc.) showed promising radiographic and prostate-specific antigen (PSA) response [15]. Rucaparib has since gained accelerated FDA approval for mCRPC patients with deleterious *BRCA1/2* mutations who were previously treated with novel androgen receptor (AR) targeted therapy and

taxane chemotherapy [16]. Olaparib has received full approval for mCRPC patients who have at least one line of novel AR targeted therapy and have a suspected or known deleterious HR repair mutation across a broad panel [17].

The presence of HR repair gene mutations in cancers has also been associated with enhanced sensitivity to platinum-based chemotherapy. The likely mechanism behind this sensitivity is through the formation of dsDNA breaks via DNA adducts [18].

Cheng, et al. reported that patients with biallelic *BRCA2* inactivation can achieve excellent clinical response with carboplatin even after progression on first-line therapies for mCRPC [19]. Germline *BRCA2* variants were also found to strongly associate with PSA response $\geq 50\%$ in mCRPC patients treated with carboplatin [20].

While significant effort has gone into exploring precision medicine approaches for treating prostate cancer patients with HR repair gene mutations, there are limited reports describing the clinical course of these patients following treatment with standard therapies. Androgen receptor signaling inhibitors (ARSIs), such as abiraterone and enzalutamide, as well as taxane-based chemotherapy, such as docetaxel and cabazitaxel, have been established as standard, regulatory-approved treatment options for patients with mCRPC [21]. Recently, Hussain, et al. reported that somatic HR repair mutations may be associated with improved PSA response and PFS with abiraterone [22]. This contrasted with previous findings of attenuated ARSI response in germline HR gene mutation carriers [23]. Studies examining taxane-based chemotherapy treatment in mCRPC found no significant difference in treatment responses when stratifying by HR gene mutation status [24, 25]. Notably, treatment with cabazitaxel was not evaluated in these reports.

The objective of this paper is to investigate how mutations in genes directly and indirectly involved in the HR repair pathway impact treatment response and long-term outcomes in mCRPC patients treated with abiraterone, enzalutamide, docetaxel, and cabazitaxel. We hypothesized that the presence of HR repair gene mutations will correlate with poor clinical outcomes following treatment with these agents.

Materials and methods

Patients

A retrospective analysis was performed using the institutional Caisis database, which includes prostate cancer patients treated at the University of Washington/Seattle Cancer Care Alliance (UW/SCCA). Prior to data abstraction, this project was reviewed by the Institutional Review Board at the University of Washington and deemed to be minimal risk. As such, the requirement for informed consent was waived. Patient electronic medical records were accessed between 05/2018-02/2020 and were not anonymized to data abstractors. All patient data was de-identified prior to performing statistical analysis.

Our inclusion criteria mandated that patients have pathologically proven prostate cancer and documented mCRPC status, defined as disease progression following surgical/medical castration (i.e. androgen deprivation therapy; ADT) by PSA or radiographic/clinical evidence. Additionally, patients must have previously undergone clinical-grade next-generation sequencing (NGS) of their tumor. An exception was made to include patients with known germline *BRCA2* mutations who did not undergo tumor sequencing, given that these germline cases are most often associated with the loss of the second allele by somatic mutation [6]. The following assays were included: UW-OncoPlex, FoundationOne, Guardant360, GeneTrails, BROCA, Color, BRACAnalysis, and Whole Exome Sequencing (WEC) assay results [5].

We specifically analyzed monotherapy treatments with each of the four agents (abiraterone, enzalutamide, docetaxel, cabazitaxel) that occurred between 2011–2019. Per Prostate Cancer

Working Group 3 (PCWG3) guidelines, we required a minimum 60 days of therapy in order to assess responses and progression endpoints [26]. Patients treated with more than one of the four agents were eligible for analysis in multiple treatment groups if all above inclusion criteria were met. If a patient received multiple courses of the same agent, only the first treatment course was assessed. Confirmation of PSA response/progression was not required since this was not uniformly performed in these non-trial patients. Patients with neuroendocrine or small cell differentiation were excluded unless their treatments occurred prior to pathological confirmation of neuroendocrine/small cell transdifferentiation.

HR repair gene status

Patients were sub-divided into two groups based on the presence or absence of HR repair gene mutations. The HR group contained patients with both somatic and germline mutations in genes involved in HR repair, including those indirectly regulating this pathway [5, 6, 27]. A broad set of genes was included given the recent approval of olaparib across an inclusive set of genes both directly and indirectly involved in HR repair [13, 17]. Monoallelic somatic mutations were considered sufficient for inclusion, given that many assays (e.g., FoundationOne) do not assess for loss of heterozygosity (LOH) or explicitly report germline mutations. Mutations were considered pathogenic if reported as such on the clinical report. Variants of unknown significance or otherwise benign changes were not included in the HR repair mutation cohort.

Data endpoints

The primary objective of this study was to determine the PSA50 and PSA30 response rate for each therapy, which was defined as the proportion of patients achieving $\geq 50\%$ and $\geq 30\%$ PSA reduction from the baseline PSA, respectively. Nadir PSA was recorded as the lowest PSA after starting treatment and prior to initiating a subsequent therapy.

The secondary objectives included determining PSA PFS (pPFS) and clinical/radiographic PFS (crPFS). PSA progression was defined by a PSA increase that was ≥ 2 ng/mL and $\geq 25\%$ above the nadir on two consecutive lab draws. Clinical/radiographic progression was based on the assessment of the treating physician and was determined through chart review. Response Evaluation Criteria in Solid Tumors (RECIST) criteria were not utilized given that most patients were not treated on a clinical trial.

Statistical analysis

Differences in demographic characteristics and baseline laboratory measurements between the two populations were evaluated using Kruskal-Wallis or Fisher's exact tests. Differences in PSA50 and PSA30 between populations were evaluated using Fisher's exact tests separately for each treatment modality. Kaplan-Meier curves were calculated for pPFS and crPFS for each treatment modality, and differences between populations were evaluated using log-rank tests. A p-value < 0.05 was considered statistically significant. All analyses were carried out using R statistical software version 3.6.3.

A secondary analysis estimated probabilities of PSA30/PSA50 using Bayesian logistic regression to adjust for prior receipt of similar therapy. Adjustment for prior similar therapy was examined given numerous studies highlighting varying levels of cross-resistance in these treatment modalities [28–32]. Prior similar therapy was defined as prior receipt of abiraterone or enzalutamide when either ARSI treatment was analyzed and prior receipt of docetaxel or cabazitaxel when either taxane-based chemotherapy was analyzed.

An exploratory analysis compared outcomes specifically for patients with *BRCA2* and *PALB2* mutations to those without HR repair gene mutations. Previous literature has demonstrated that these genes are closely associated with HR repair functional status [33, 34] and appear to be important predictive biomarkers for determining eligibility for DNA damaging agents. PSA30/PSA50 and pPFS/crPFS outcomes were re-evaluated for these comparisons.

Results

Patients

A total of 90 consecutively selected patients were included in this analysis, with HR repair gene mutations identified in 33/90 (37%). Of the 20 patients who underwent dedicated germline testing, 5 (25%) were found to harbor germline HR repair alterations. Mutations were found in 8 unique HR repair genes, with *BRCA2* ($n = 16$) being the most frequently altered (Table 1, S1 Table). A demographic comparison based on HR status showed similarity in age at diagnosis, Gleason score, prior surgery, and receipt of prior radiation therapy between the two patient populations (Table 2). Over 21% of patients with HR repair mutations were non-white in comparison to 7.1% of patients without HR repair mutations, although this finding did not reach statistical significance ($p = 0.07$). Laboratory parameters assessed prior to starting each treatment were also similar between the populations (S2–S5 Tables).

Efficacy outcomes

Best PSA response among patients with/without HR repair gene mutations is depicted in Fig 1 using waterfall plots for each treatment modality. Most patients achieved a PSA reduction from baseline in every treatment group except for patients without HR repair mutations treated with cabazitaxel. There was no evidence that PSA30 or PSA50 differed based on HR status for any treatment modality (Table 3). The frequency of patients achieving PSA50 in the population with HR repair gene mutations was 26% higher in the enzalutamide group and 40% higher in the cabazitaxel group compared to patients with no HR repair gene mutations, though neither result was statistically significant ($p = 0.09$ and $p = 0.07$, respectively). Regardless of HR repair gene mutation status, the PSA30 response rate was $>50\%$ and PSA50 response rate was $>40\%$ for all treatment modalities except cabazitaxel. Adjusting for prior similar therapy did not reveal an association between HR repair gene mutation status and PSA30/PSA50 for any of the treatments (S6 Table).

Kaplan-Meier curves of pPFS and crPFS are provided in Fig 2 by treatment modality. Median pPFS ranged between 2.8–6.5 months and median crPFS ranged between 4.2–14.2 months across treatment groups. There was no evidence that pPFS or crPFS differed based on HR repair gene mutation status for any treatment modality (Table 4).

Exploratory analyses comparing patients with mutations in *BRCA2* or *PALB2* to patients without HR repair mutations did not reveal differences in PSA30/PSA50 or pPFS/crPFS for any treatment (S1 and S2 Figs, S7 and S8 Tables), although the sample size within any molecular subgroup was small.

Discussion

The principal impetus behind this study was to evaluate whether mCRPC patients harboring mutations both directly and indirectly involved in HR repair achieve comparable outcomes to patients without such mutations following treatment with conventional, regulatory-approved treatment regimens. Given the recent FDA approvals of the PARP inhibitors rucaparib and olaparib, as well as interest in developing platinum-based chemotherapy for patients with HR

Table 1. Complete list of HR mutations.

Study ID	Sequencing Assay	Affected HR Gene	Germline alteration?	Bi-allelic mutation?
1	UW-OncoPlex	<i>FANCA</i>	N/A	No
2	WEC	<i>BRCA2</i>	No	Yes
4	UW-OncoPlex	<i>BRCA2</i>	N/A	Yes
9	UW-OncoPlex	<i>MRE11A</i>	N/A	No
14	UW-OncoPlex	<i>BRCA2</i>	No	Yes
20	UW-OncoPlex	<i>BRCA2</i>	No	Yes
24	FoundationOne, Color	<i>BRCA2</i>	Yes	Yes
25	UW-OncoPlex	<i>CDK12</i>	N/A	Yes
27	UW-OncoPlex	<i>BRCA2</i>	N/A	No
28	UW-OncoPlex, WEC	<i>BRCA2</i>	Yes	Yes
31	UW-OncoPlex	<i>BRCA2</i>	N/A	Yes
33	UW-OncoPlex	<i>BRCA2</i>	N/A	No
34	UW-OncoPlex	<i>CDK12</i>	N/A	Yes
36	FoundationOne	<i>ATM</i>	N/A	Yes
38	UW-OncoPlex	<i>PALB2</i>	N/A	Yes
39	UW-OncoPlex	<i>CHD1</i>	N/A	No
43	UW-OncoPlex	<i>BRCA2</i>	N/A	N/A
44	Color	<i>BRCA2</i>	Yes	N/A
48	UW-OncoPlex	<i>CHD1</i>	N/A	Yes
57	FoundationOne	<i>CDK12</i>	N/A	Yes
59	UW-OncoPlex	<i>BRCA2</i>	N/A	Yes
63	BRCAAnalysis	<i>BRCA2</i>	Yes	N/A
69	UW-OncoPlex	<i>CHD1</i>	N/A	Yes
70	UW-OncoPlex	<i>ATM</i>	N/A	No
71	UW-OncoPlex	<i>FANCA</i>	N/A	N/A
72	UW-OncoPlex	<i>CDK12</i>	N/A	N/A
78	Guardant360, FoundationOne, Color	<i>BRCA2</i>	Yes	N/A
79	UW-OncoPlex	<i>CHD1</i>	N/A	Yes
81	FoundationOne	<i>ATM</i>	No	No
82	GeneTrails	<i>FANCA</i>	N/A	N/A
84	UW-OncoPlex	<i>BRCA2</i>	N/A	Yes
86	UW-OncoPlex	<i>MRE11A</i>	N/A	Yes
90	UW-OncoPlex	<i>BRCA2, CHEK2</i>	N/A	Yes

“WEC” denotes the Whole Exome Sequencing assay.

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repair gene mutations, we felt it was imperative to examine whether current conventional mCRPC treatments retain efficacy in this patient population. Our findings of similar PSA response and PFS in patients with HR repair gene mutations treated with ARSIs and taxane-based chemotherapy suggests that current standard mCRPC treatments are still very reasonable options for this patient population.

Our data largely aligns with the results of the recently published PROREPAIR-B study, which found non-significant differences in PSA50, PFS, and cause-specific survival when comparing germline *ATM/BRCA1/BRCA2/PALB2* carriers to non-carriers [35]. In contrast to the PROREPAIR-B study, which reported decreased survival in men with *BRCA2* mutations in a post hoc analysis, we did not observe survival differences in those with *BRCA2* mutations; although, our small sample size limited our statistical power to detect differences in outcomes.

Table 2. Patient characteristics by HR status.

Measure	No HR (N = 57)	HR (N = 33)	P-value
Age, years, median [IQR]	61.1 [55.2, 66.4]	61.0 [53.0, 67.5]	0.8
Race, N (%)			
• White	53 (93.0)	26 (78.8)	0.07
• Black	1 (1.8)	4 (12.1)	
• Asian/Unknown	3 (5.3)	3 (9.1)	
Gleason Score, N (%)			
• 6	2 (3.5)	0 (0.0)	0.6
• 7	20 (35.1)	10 (30.3)	
• 8–10	31 (54.4)	22 (66.7)	
• Unknown	4 (7.0)	1 (3.0)	
Prior Surgery, N (%)			
• No	31 (54.4)	20 (60.6)	0.4
• Yes	26 (45.6)	12 (36.4)	
• Unknown	0 (0.0)	1 (3.0)	
Prior Radiation Therapy, N (%)			
• No	14 (24.6)	12 (36.4)	0.6
• Yes	29 (50.9)	15 (45.5)	
• Unknown	14 (24.6)	6 (18.2)	

P-value for age from Kruskal-Wallis rank sum test and for other measures from Fisher's exact test.

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It does seem plausible that *BRCA1/2* and other proteins directly interacting with the *BRCA* complex may have distinct clinical and biologic relevance compared to those that indirectly regulate HR repair (e.g., *CDK12*, *ATM*, *CHEK2*). Indeed, results from TRITON2, TOPARP-B, and PROfound all suggest that responses to PARP inhibitors are largely observed in those with *BRCA* mutations [12, 13, 15]. These observations support the need to further examine clinical outcomes on an individual gene basis.

The 37% overall HR repair gene mutation rate found within our population is significantly higher than what has been reported in previous studies. It is important to emphasize that our research was not designed to characterize the frequency of HR repair gene mutations within mCRPC patients, but rather to assess clinical response in patients with such mutations. Our population was not cross-sectional and was enriched by our selection criteria. Specifically, our requirement of NGS likely inflated the frequency of HR repair gene mutations found, as NGS was more often performed in patients with significant family history, high-risk tumor histology (e.g., Gleason grade group 4–5 and ductal histology) [5, 36, 37], unique clinical course, or known germline variants.

A major limitation of this study was its small sample size. With 90 total patients and relatively small numbers in each treatment modality, our analyses were underpowered to detect small differences in outcomes. Limited patient numbers also precluded additional sub-analyses, including comparisons of germline versus somatic mutations, monoallelic versus biallelic mutations, and *BRCA1/2*-mutated versus other HR repair gene alterations. We also used a permissive approach for classifying HR repair deficiency. This approach was largely pragmatic in nature and resembles the 'real world' data most practicing oncologists use to make treatment choices given that many NGS platforms do not report LOH events or germline alterations. Until such data becomes more readily reported and operational for providers, our data indicates that standard therapies for mCRPC (i.e. non-DDR-targeted treatments such as ARSIs and taxane chemotherapy) should still be considered for these patients.

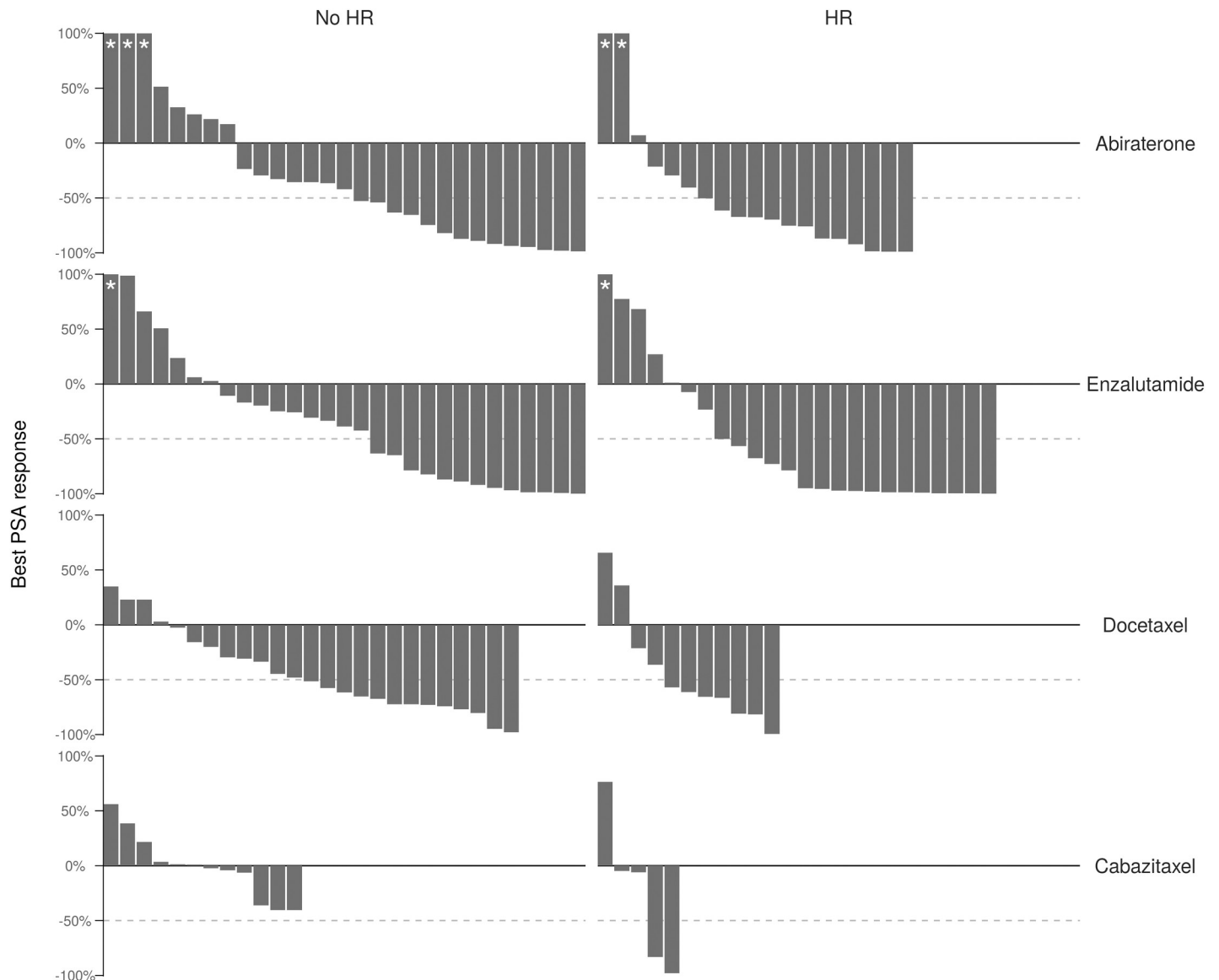


Fig 1. Waterfall plot of best PSA response by treatment and HR status. Maximum percent relative change from baseline during treatment or after completing treatment but prior to subsequent treatment. Maximum percent change greater than 100% is truncated at 100%. Dashed horizontal lines show 50% decrease.

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Table 3. Best PSA response by treatment and HR status.

Treatment	Response	No HR, N (%)	HR, N (%)	P-value
Abiraterone	PSA30	19/29 (66%)	14/19 (74%)	0.8
	PSA50	14/29 (48%)	13/19 (68%)	0.2
Enzalutamide	PSA30	17/29 (59%)	17/24 (71%)	0.4
	PSA50	13/29 (45%)	17/24 (71%)	0.09
Docetaxel	PSA30	17/25 (68%)	8/11 (73%)	1.0
	PSA50	13/25 (52%)	7/11 (64%)	0.7
Cabazitaxel	PSA30	3/12 (25%)	2/5 (40%)	0.6
	PSA50	0/12 (0%)	2/5 (40%)	0.07

PSA50 is 50% decrease in PSA relative to baseline. PSA30 is 30% decrease in PSA relative to baseline. P-values from Fisher's exact test.

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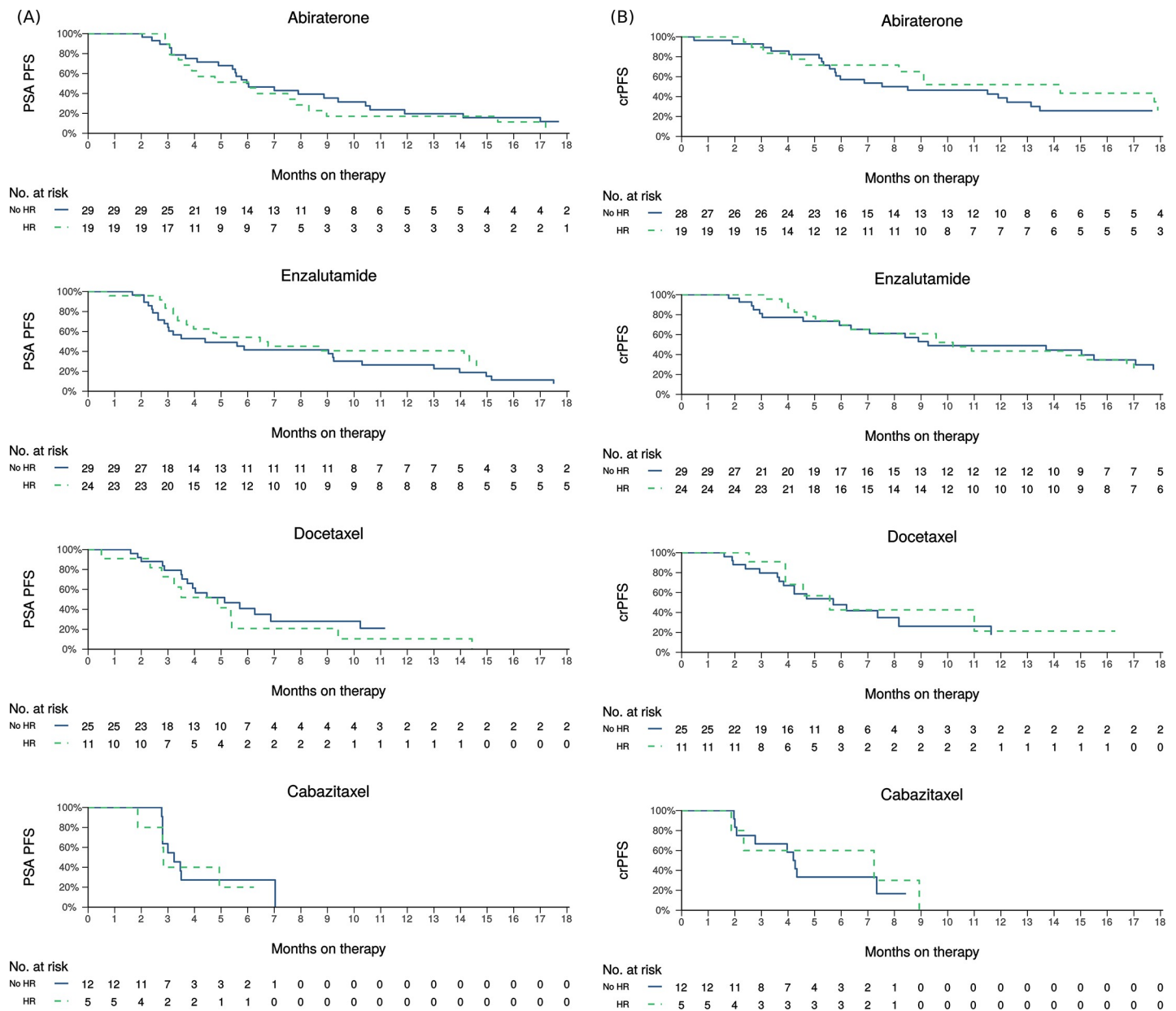


Fig 2. Kaplan-Meier curves of (A) PSA progression-free survival and (B) clinical or radiographic progression-free survival by treatment and HR status.

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The retrospective nature of this study provided its own set of challenges. NGS was performed at variable times during clinical courses, so HR repair gene mutation status may have been unknown at the time of treatment in many patients. While some data suggests that HR repair gene mutations are typically early (i.e. truncal) genomic events, we cannot rule out the possibility that some patient had their HR gene mutational status misclassified [38]. Additionally, when assessing PFS endpoints, we did not require confirmation of PSA or clinical/radiographic progression. No central review was performed, and there were no preset criteria for the evaluation of progression events. PFS outcomes were also dependent on the intervals at which clinical markers for progression were assessed. Whereas a prospective trial could standardize the frequency of clinical evaluations across all patients, ours were entirely provider dependent.

Table 4. Median (A) PSA progression-free survival and (B) clinical or radiographic progression-free survival by treatment and HR status.

A) PSA progression-free survival (pPFS)				
Treatment	HR Status	N	Median pPFS (95% CI)	P-value
Abiraterone	No HR	29	6.0 (5.4, 10.6)	0.4
	HR	19	6.1 (3.9, 9.0)	
Enzalutamide	No HR	29	4.4 (3.0, 10.3)	0.15
	HR	24	6.5 (4.0, 24.0)	
Docetaxel	No HR	25	5.1 (3.7, NA)	0.2
	HR	11	4.9 (3.2, NA)	
Cabazitaxel	No HR	12	3.2 (2.8, NA)	0.7
	HR	5	2.8 (2.8, NA)	
B) Clinical or radiographic progression-free survival (crPFS)				
Treatment	HR Status	N	Median crPFS (95% CI)	P-value
Abiraterone	No HR	28	8.0 (5.8, 13.5)	0.6
	HR	19	14.2 (8.2, NA)	
Enzalutamide	No HR	29	9.3 (6.4, 19.3)	0.5
	HR	24	10.2 (6.2, 19.5)	
Docetaxel	No HR	25	5.7 (4.2, NA)	0.7
	HR	11	5.6 (3.9, NA)	
Cabazitaxel	No HR	12	4.2 (2.8, NA)	0.6
	HR	5	7.2 (2.3, NA)	

P-values from log-rank tests. NA = not achieved.

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Another potential constraint was our exclusion of treatments lasting less than 60 days. Consistent with PCWG3 guidelines, our intent was to only evaluate patients who had received a sufficient duration of treatment to determine if they would achieve any therapeutic response. In this regard, patients who may have been taken off therapy prematurely for rising PSA values or symptoms consistent with clinical progression would not obscure the remainder of the data set. However, if there happened to be an association between HR repair gene status and frequency of early-onset progression events, it could be indicative of a bias that was manufactured through our inclusion criteria.

Future directions should include an effort to more definitively describe treatment responses in mCRPC patients with HR repair gene mutations using larger, prospective trials with standardized clinical outcomes. In addition, more granular outcomes data for each specific HR repair gene are needed to determine which are predictive and prognostic biomarkers.

Conclusion

In our retrospective analysis of patients with mCRPC, HR repair gene mutational status associated with similar PSA response and PFS following treatment with ARSIs and taxane-based chemotherapy. Available data suggests that standard therapies should still be considered for patients with HR repair gene mutations. Additional prospective and larger studies are needed to confirm these findings.

Supporting information

S1 Fig. Waterfall plot of best PSA response by treatment and HR status (BRCA2 or PALB2 vs no HR). Maximum percent relative change from baseline during treatment or after

completing treatment but prior to subsequent treatment. Maximum percent change greater than 100% is truncated at 100%. Dashed horizontal lines show 50% decrease.

(TIF)

S2 Fig. Kaplan-Meier curves of (A) PSA progression-free survival and (B) clinical or radiographic progression-free survival by treatment and HR status (BRCA2 or PALB2 vs no HR). (TIFF)

S1 Table. Specific genetic variants of every patient included in the HR cohort. “WEC” denotes the Whole Exome Sequencing assay.

(PDF)

S2 Table. Baseline lab comparisons at start of abiraterone based on HR status. P-values for continuous measures from Kruskal-Wallis rank sum test and for categorical measures from Fisher’s exact test.

(PDF)

S3 Table. Baseline lab comparisons at start of enzalutamide based on HR status. P-values for continuous measures from Kruskal-Wallis rank sum test and for categorical measures from Fisher’s exact test.

(PDF)

S4 Table. Baseline lab comparisons at start of docetaxel based on HR status. P-values for continuous measures from Kruskal-Wallis rank sum test and for categorical measures from Fisher’s exact test.

(PDF)

S5 Table. Baseline lab comparisons at start of cabazitaxel based on HR status. P-values for continuous measures from Kruskal-Wallis test rank sum and for categorical measures from Fisher’s exact test.

(PDF)

S6 Table. Predicted probabilities of (A) PSA30 and (B) PSA50 adjusted for prior treatment with similar therapy.

(PDF)

S7 Table. Best PSA response by treatment and HR status (BRCA2 or PALB2 vs no HR). PSA50 is 50% decrease in PSA relative to baseline. PSA30 is 30% decrease in PSA relative to baseline. P-values from Fisher’s exact test.

(PDF)

S8 Table. Median (A) PSA progression-free survival and (B) clinical or radiographic progression-free survival by treatment and HR status (BRCA2 or PALB2 vs no HR). P-values from log-rank tests. NA = not achieved.

(PDF)

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Appendix 3

Curricula vitae:

Heather H. Cheng - PI

Evan Y. Yu - co-investigator

Michael T. Schweizer - sub-investigator

Celestia S. Higano – former PI, retired 30Jun2020

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 Member, 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

- 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 Employment:** n/a

7. **Honors/Awards:**

1998 Sigma Xi Society, Princeton, NJ
1998 New Jersey Cancer Commission Research Fellowship
2000 Paul Allen Research Fellowship
2009 UW School of Medicine: Resident Teaching Award (medical student-nominated)
2010 UW Physicians: Honor Your Physician Award (patient-nominated)
2012 ASCO/NCI/EORTC Markers in Cancer Meeting, Merit Award
2014 ASCO Genitourinary Oncology Symposium, Merit Award
2014 ASCO 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 NCI 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 11/03/2020
DEA #FC2472328 expires 08/31/2022

10. **Professional Organizations:**

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

11. **Teaching Responsibilities:**

Courses:

2012-2013 **UWSOM HUBIO 513, 522 and 535, Intro to Clinical Medicine**, Small Group Leader
2014 **UWSOM MEDECK 614, Medical Oncology Clerkship**, Richard Stein, MS4 (Fall 2014).
2014 **UWSOM HUBIO 550, Introduction to Clinical Medicine**, panelist
2014-2016 **UWSOM 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 **UWSOM MEDSCI 540A, Blood and Cancer**, small group leader

Teaching/Committees:

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 Multidisciplinary Clinics and Inpatient Oncology service.
2017 Mentor for NCI Fogarty International Center Fellow Candidate, **Paul Katangole, MD, MS** (Uganda Cancer Institute)
2018-present Primary research mentor, Hematology/Oncology fellow **Alexandra Sokolova, MD**
2018-2019 Primary research mentor, UWSOM **MS1 Darren Pouv** Independent Investigative Inquir
2019-present Heme/Onc fellowship faculty champion for outpatient Genitourinary Oncology Block

2019-present Secondary research mentor, Hematology/Oncology fellow, **Risa Wong, MD**

2020-present Research mentoring committee for UW **MPH candidate, Emiko M. Oshima**

Invited Local/Regional Talks:

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. 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.
7. 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
8. 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
9. 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
10. 05/07/2015 *Prostate Cancer: Progress Made and Research in Progress*. Research Matters Series, Seattle Cancer Care Alliance, Seattle, WA
11. 03/24/2016 *Leveraging DNA Repair Defects for Treatment of Prostate Cancer*. PPCR SPORE Seminar Series, Fred Hutchinson Cancer Research Center, Seattle, WA
12. 06/29/2016 *Emerging Therapies in Cancer: Cancer Genetics*. Seattle Cancer Care Alliance CME lecture for Skagit Valley Hospital, Mount Vernon, WA
13. 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
14. 10/27/2016 *Prostate Cancer Foundation Women’s Networking Forum*. Junior Investigator Panelist at the 2016 Prostate Cancer Foundation Retreat, Carlsbad, CA

15. 11/17/2016 *Prostate Cancer Genetics: Leveraging Family Traits for Early Detection*. Fred Hutchinson Cancer Research Center Innovators Network. Seattle, WA
16. 12/23/2016 *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.
17. 03/18/2017 *Inherited Risk and Prostate Cancer Behavior*. Prostate Cancer Symposium, Institute for Prostate Cancer Research; Fred Hutchinson Cancer Research Center, Seattle, WA
18. 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
19. 05/24/2017 *Prostate Cancer Genetics*. UsTOO Greater Seattle Area Prostate Cancer Patient Support Group; Greenwood Community Center, Seattle, WA.
20. 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
21. 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
22. 11/06/2017 *Genetics and Genomics*. CCSG Prostate Program Cancer Retreat, Fred Hutchinson Cancer Research Center, Seattle, WA
23. 01/19/2018 *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.
24. 01/26/2018 *Expanding Clinical and Research Horizons in Prostate Cancer Genetics*. UW Medical Genetics Division Grand Rounds, Seattle, WA
25. 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
26. 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
27. 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
28. 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
29. 05/07/2018 *Prostate Cancer: Screening, Treatment and Genetics*. UW Internal Medicine Residents Report, University of Washington Medical Center, Seattle, WA
30. 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
31. 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
32. 07/17/2018 *Molecular Predictors of Prostate Cancer Progression and Mortality*. PNW SPORE Symposium, Fred Hutch Cancer Research Center, Seattle, WA

33. 08/09/2018 *Prostate Cancer Genetics and the GENTleMEN Study*. Overbaugh Lab 30th Year Symposium Retreat, Islandwood, Bainbridge Island, WA
34. 10/05/2018 *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.
35. 10/12/2018 *Prostate Cancer*. Transitions in Oncology Care: Pearls for the Primary Care Provider Conference, Talaris Conference Center, Seattle, WA.
36. 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
37. 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
38. 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
39. 09/06/2019 *Updates in Prostate Cancer Genetics*. Seattle Cancer Care Alliance Community Site Dinner Clinical Research Partnership Series; Seattle, WA
40. 01/09/2020 *From Cat Viruses to Men's Prostates: An Ongoing Research Journey*. UW Medical Scientist Training Program Monthly Research Meeting; Seattle, WA.
41. 01/24/2020 *Mutational Testing for Solid Tumors*. UW/Fred Hutch Hematology and Oncology Fellowship Solid Tumor Conference; Seattle, WA.
42. 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
43. 05/27/2020: *Prostate Cancer Genetics through a Medical Oncologist's Lens*. University of Washington, Radiation Oncology Grand Rounds, Seattle, WA. [invited Grand Rounds]
44. 07/15/2020: *Olaparib for Metastatic Castration Resistant Prostate Cancer*. Clinical Research Division Journal Watch; Fred Hutch Cancer Research Center, Seattle, WA
45. 07/22/2020: *Prostate Cancer Genetics*. Medscape CME Webinar; Seattle Cancer Care Alliance, Seattle WA
46. 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

12. Editorial Responsibilities:

Ad Hoc Reviewer for: Cancer, Clinical Cancer Research, Clinical Genitourinary Cancer, European Urology, Journal of Clinical Oncology, Journal of Clinical Oncology Precision Oncology, Journal of Oncology Practice, Oncotarget

13. 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 2017-2017-2018	Chair, Prostate Cancer Clinical Trials Consortium/PCF Genetics Working Group
October 2017	Co-Leader, Prostate Cancer Foundation DNA Repair Working Group
February 2018	Session Chair, DNA Repair, Prostate Cancer Foundation 24 th Scientific Retreat, Washington D.C.
June 2018	Prostate Cancer Foundation Delegation on Prostate Cancer Genetics, Tel Aviv, Israel
August 2019-May 2020-	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
	Guidelines Panel, National Comprehensive Cancer Network, (NCCN) Prostate Cancer
	Board of Directors, Us-TOO International Prostate Cancer Education and Support Network (private, non-profit 501(c)3)

14. Special Local Responsibilities:

2011	UW Hematology-Oncology Fellowship, fellow representative
2010-2011	UW Hematology-Oncology Fellows Orientation Handbook, first editor and author
2011-2012	UW Hematology-Oncology Solid Tumor Conference, fellow organizer
2014-2019	CAISIS/Genitourinary Cancer Clinical Research Database, faculty lead
2015-2016	SCCA Schwartz Center Rounds Planning Committee
2016-present	Fred Hutch/UW Cancer Consortium Data Safety Monitoring Committee
2018-2021	Fred Hutch/Clinical Research Division, Appointments and Promotions Committee
2019-present	Fred Hutch/Human Biology Division, Prostate Program Faculty Search Committee
2020-present	Associate Program Director, UW/Fred Hutch Medical Scientist Training Program

15. 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*

Supporting Agency: PCCTC, LLC (Medivation and Sanofi)

Performance Period: 07/14/16 – 11/30/21

Role: Site Primary Investigator

Level of Funding:

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.

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*

Supporting Agency: Janssen Research & Development, LLC

Performance Period: 12/28/16 – 12/31/21

Role: Site Primary Investigator

Level of Funding:

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.

Title: *Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men with Advanced Prostate Cancer (IRONMAN)*

Supporting Agency: Movember (via PCCTC, LLC)

Performance Period: 08/18/17 – 07/31/22

Role: PI

Level of Funding:

Project 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.

Title: PROSTATE CANCER CLINICAL TRIALS CONSORTIUM

Supporting Agency: US Department of Defense (DOD)

Performance Period: 09/30/2017 to 09/29/2021

Role: PI

Level of Funding:

Project Goals: The Department of Defense provides funding for infrastructure to support participation as a clinical site in the Prostate Cancer Clinical Trials Consortium

Title: *A phase 1b study of enzalutamide plus CC-115 in men with castration-resistant prostate cancer*

Supporting Agency: PCCTC, LLC (Celgene)

Performance Period: 02/01/17 to 12/31/21

Role: Site Primary Investigator

Level of Funding:

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: *Telehealth to reduce Prostate Cancer Burden in Rural Underserved Communities*

Supporting Agency: NIH/NCI

Performance Period: 07/01/18 – 12/31/20

Role: Supporting participant

Level of Funding:

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.

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*

Supporting Agency: Clovis Oncology, Inc

Performance Period: 07/26/2018 to 08/30/2021

Role: Primary Investigator

Level of Funding:

Project Goals: The major goal of this trial is to determine radiographic progression-free survival with 4 cycles of docetaxel with carboplatin followed by maintenance rucaparib in the treatment of patients with metastatic castration resistant prostate cancer with homologous recombination DNA repair deficiency.

Title: *Clinical qualification of DNA repair defects as biomarkers in metastatic prostate cancer using integrated genomics and tissue-based functional assays*

Supporting Agency: US Department of Defense (DOD)

Performance Period: 08/01/18 – 07/31/21

Role: Co-Investigator

Level of Funding: , 0.24 Calendar Months

Project Goals: The major goal is 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.

Title: *Targeting the Subtype of Metastatic Prostate Cancer Deficient in DNA Repair Capacity Instability Using Targeted Molecular Counting Methods*

Supporting Agency: US Department of Defense (DOD)

Performance Period: 08/01/18 – 07/31/21

Role: Co-Investigator

Level of Funding: , 0.60 Calendar Months

Project Goals: The major goal is to 1) Determine if germ-line and somatic aberrations in homologous recombination DNA re-pair pathways associate with responses to FDA-approved therapeutics in men with mCRPC. 2) Develop minimally-invasive biomarkers capable of distinguishing patients for

therapeutics targeting homologous recombination DNA repair pathways and ascertaining resistance mechanisms. 3) Identify rational drug combinations that exploit DNA repair vulnerabilities to eradicate prostate cancers with homologous recombination repair deficiency.

Title: *Pacific Northwest (PNW) Prostate Cancer Sponsored Program of Research Excellence (SPORE) Project 1: Molecular Predictors of Prostate Cancer Progression and Mortality*

Supporting Agency: NIH/NCI, Pacific Northwest SPORE

Performance Period: 9/01/18 – 8/31/23

Level of Funding: Direct Costs

Role: Co-Investigator

Project 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.*

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)*

Supporting Agency: Brotman Baty Institute

Performance Period: 02/01/2020 to 01/31/2021

Level of Funding:

Role:

Project Goals: The goal is to identify complex structural mutations in advanced prostate cancer families that have been missed by current sequencing approaches.

Title: *Cancer Clinical Investigator Team Leadership Award*

Supporting Agency: NCI, Cancer Consortium Grant

Performance Period: 03/04/2020 to 02/28/2022

Level of Funding: Direct Costs

Role: Primary Investigator

Project Goals: The major goal of this award is to develop access to clinical trials for patients using media and expand genetic care using new methods of delivery such as telehealth and molecular tumor boards, disseminating research opportunities to cancer center catchment and region. Investigator Initiated Study (Cheng)

Title: *PROMISE Registry: A Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness*

Supporting Agency: ACT/Brown

Performance Period: 06/19/2020 to 06/30/2022

Level of Funding: Direct Costs

Role: Co-Primary Investigator

Project 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.

Pending Research Support

Title: *Enhanced Genetic Awareness and Genetic Evaluation for Men Through Technology - The ENGAGEMENT Study*

Supporting Agency: DOD

Role: Co-Investigator

Title: *Technology-enhanced Acceleration of Germline Evaluation for Therapy – The TARGET study*

Supporting Agency: PCF

Role: Co-Investigator

Performance Period: 01/01/20 – 12/31/21

Level of Funding:

Project 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.

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
2013	PNW Prostate Cancer SPORE Career Enhancement Program: Evaluating cancer-associated circulating microRNAs as biomarkers of treatment response in metastatic prostate cancer
2015	Defining the role of cancer risk genes in early-onset, lethal prostate cancer, NIH/NCI (P50 CA097186); . Goal: to examine the role of germline cancer risk genes in early-onset, lethal prostate cancer and parlay the resulting data into future research.
2015-2017	A precision clinical trial targeting DNA repair defects, Institute for Prostate Cancer Research (IPCR); . Goal: determine if men with tumors that harbor DNA repair defects will exhibit enhanced sensitivity to platinum-based chemotherapy.
2015-2016	Identifying germline cancer risk genes in advanced prostate cancer. NIH/NCI (P50 CA097186); . Goal: to identify the underlying genetic cause in some hereditary prostate cancer families
2014-2017	CCSG: New Investigator Award; NIH/NCI (P30 CA015704); . Goal: to develop infrastructure to study the underlying genetic causes of early onset prostate cancer and familial prostate cancer.
2014-2018	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; . Goal: Determine overall survival in metastatic prostate cancer patients randomly assigned to androgen deprivation therapy (ADT) + TAK-700 vs ADT + bicalutamide.
2015-2018	Prostate Cancer Foundation Challenge Award: Exploiting DNA repair vulnerabilities as a precision oncology target in metastatic prostate cancer; . Goal: Test 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.
2015-2018	PCF Young Investigator Award: Identifying high-penetrance prostate cancer risk genes: leveraging families for next generation discovery and prevention; . Goal: Collect men with prostate cancer who are found via tumor testing to carry high-penetrance germline cancer risk mutations.

2015-2018	Phase I, open-label trial to evaluate the safety and immunogenicity of INO-5150 +/- INO-9012 in biochemically relapsed prostate cancer. Inovio Pharmaceuticals: . Goals: To test study drug INO-5150 (plasmid DNA vaccine) alone or in combination with INO-9012 (plasmid DNA vaccine for human interleukin 12) to determine safety and immunogenicity against prostate cancer cells. Role: Site PI
2014-2019	Genitourinary Cancer Clinical Research Database Support. Institute for Prostate Cancer Research: . Goals: to inventory, display, aggregate, and integrate comprehensive clinical information derived from patients with prostate cancer (and other GU malignancies). Pharmacogenetic dissection of protein synthesis control across the spectrum of PI3K pathway mutations in prostate cancer. Movember Foundation & Prostate Cancer Foundation: . Goals: To delineate the biology of various PI3K pathway mutations that occur in CRPC and develop strategies to effectively target tumors harboring these mutations. Role: Co-investigator
2016-2018	A phase I/II trial of concurrent chemohormonal therapy using enzalutamide (MDV-3100) and cabazitaxel in patients with metastatic castration resistant prostate cancer. PCCTC, LLC (Medivation and Sanofi): . 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. Role: Co-PI
2016-2019	Telehealth to Reduce Prostate Cancer Burden in Rural Underserved Communities. Cancer Center Support Grant: . Role: Co-Investigator

16. Bibliography:

Scopus Index (09/16/2020)
h-index: 17
Cumulative citations: 4,338

Google Scholar (09/16/2020)
h-index: 20
Cumulative citations: 5,802

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. Luring, 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., Pogossova-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.**, R. 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.*
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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]**
33. Schweizer, M.T., Haugk, K., McKiernan, J.S., Gulati, R., **Cheng, H.H.**, Maes, J.L., Dumpit, R.F., Nelson, P.S., Montgomery, B., McCune, J.S., Plymate, S.R., Yu, E.Y. A Phase I Study of Niclosamide in Combination with Enzalutamide in Men with Castration-Resistant Prostate Cancer. *PLOS ONE*, 2018 June 1. **[original work]**
34. **Cheng, H.H.***, Powers, J., Schaffer, K., Sartor, O., Practical Methods for Integrating Genetic Testing Into Clinical Practice for Advanced Prostate Cancer. *Am Soc Clin Oncol Educ Book*, 2018 May 23. (**HHC corresponding author*) **[review]**
35. Lim, D.M., Gulati, R., Aleshin-Guendel, S., Gawne, A., Wingate, J.T., **Cheng, H.H.**, Etzioni, R., Yu, E.Y., Undetectable Prostate-Specific Antigen After Short-Course Androgen Deprivation Therapy for Biochemically-Recurrent Prostate Cancer Patients Correlates with Time to Metastasis and Prostate Cancer-Specific Survival. *The Prostate*, 2018 Jul 10. **[original work]**
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38. Schweizer, M.T., Gulati, R., Beightol, M., Konnick, E.Q., **Cheng, H.H.**, de Sarkar, N., Yu, E.Y., Montgomery, R.B., Nelson, P.S., Pritchard, C.C. Clinical determinants for Successful Circulating Tumor DNA Analysis in Prostate Cancer. *The Prostate*, 2019 March 13. **[original work]**
39. Marshall, C.H., Sokolova, A.O., McNatty, A.L., **Cheng, H.H.**, Eisenberger, M.A., Bryce, A.H., Schweizer, M.T., Antonarakis, E.S. Differential response to olaparib therapy in men with metastatic castration-resistant prostate cancer harboring *BRCA1* or *BRCA2* versus *ATM* mutations. *European Urology*, 2019 Feb 21. **[original work]**
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prostatic ductal adenocarcinoma identifies a high prevalence of DNA repair gene mutations. *JCO Precis Oncol*, 2019 Apr 18. **[original work]**

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51. Diamantopoulos, L.N., Winters, B., Grivas, P., Ngo, S.D., Zeng, J., Hsieh, A., Gore, J.L., Liao, J., Yu, E.Y., Schade, G., Schweizer, M.T., Lee, J., Dighe, M., Lin, D.W., **Cheng, H.H.**, Tretiakova, M., True, L., Russell, K., Vakar-Lopez, F., Montgomery, B., Wright, J.L. Bladder Cancer Multidisciplinary Clinic (BCMC) model: impact on treatment recommendations (*in press, Bladder Cancer*) **[original work]**

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b) Book Chapters:

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2. Diamantopoulos, L.N., Khaki, A.R., Grivas, P., Gore, J.L., Schade, G., Hsieh, A., Lee, J.K., Yezefski, T., Yu, E.Y., Schweizer, M.T., **Cheng, H.H.**, Psutka, S.P., Lin, D.W., Tretiakova, M., Vakar-Lopez, F., Montgomery, B., Wright, J.L. Plasmacytoid urothelial carcinoma: a rare but aggressive bladder cancer variant with poor outcomes (*submitted*) [**original work**]

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2. **Cheng, H.H.**, Anderson, M.M., Overbaugh, J. *Determinants of Receptor Specificity for Feline Leukemia Virus Variants*. 2003 Cold Spring Harbor Meeting on Retroviruses, Cold Spring Harbor, NY. [Oral presentation]
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40. 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]
41. 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]
42. 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]
43. 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]
44. 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]
45. Winters, B., Ngo, S., Vakar-Lopez, F., Tretiakova, 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]
46. Diamantopoulos, L.N., Khaki, A.R., Vakar Lopez, F., Tretiakova, M., Gore, J.L., Schade, G.R., Psutka, S., Hsieh, A., Lee, J., Yezefski, T., Schweizer, M.T., **Cheng, H.H.**, Yu, E.Y., Grivas, P., Montgomery, B., Wright, J.L. *Patient (pt) characteristics, treatment patterns, outcomes and prognostic factors in plasmacytoid urothelial carcinoma (PUC)* American Society for Clinical Oncology, Annual Meeting, Chicago, IL (2019). [Abstract]
47. 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]
48. George, D., Mucci, L., 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., Omlin, A., Davis, I., Villanti, P., Vinson, J., Kantoff, P., *First 500 patients of IRONMAN: International Registry for Men with Advanced Prostate Cancer*. Prostate Cancer Foundation Annual Meeting, Carlsbad, CA (2019) [Abstract]
49. 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]

50. 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]
51. **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]
52. Graff, J.N., **Cheng, H.H.**, Vuky, J., Alumkal, J.J., Kreitner, D., Petreaca, D., Grivas, P., Schweizer, M.T., Higano, C.S., Yu, E.Y., Beer, T.M., *Phase II study of cabazitaxel (CAB) plus enzalutamide (ENZ) in metastatic castration resistant prostate cancer (mCRPC).* Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]
53. 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]
54. 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]
55. Diamantopoulos, L.N., Khaki, A.R., Gadzinski, A., Winters, B.R., Vakar-Lopez, F., Tretiakova, M., Gore, J.L., Schade, G., 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. *Micropapillary Urothelial Carcinoma: a Comparative Analysis of Oncologic Outcomes Compared to Conventional Urothelial Carcinoma.* Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]
56. Diamantopoulos, L.N., Sekar, R.R., Khaki, A.R., Winters, B.R., Vakar-Lopez, F., Tretiakova, M., Gore, J.L., Schade, G., 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. *Sarcomatoid Urothelial Cancer (SUC): An Aggressive Variant with A Unique Pattern of Recurrence.* Genitourinary Cancers Symposium, San Francisco, CA (2020). [Abstract]
57. 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]
58. 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 Association, Washington, DC (2020). [Abstract]
59. 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 Association, Washington, DC (2020). [Abstract]

60. 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]
61. 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]
62. 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]
63. 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]
64. 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]
65. 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]
66. 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]
67. 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]
68. 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]
69. 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]
70. 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]

71. 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 (2020). [Abstract]

17. National/International Invitational 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 *Men's Health—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. (*cancelled due to COVID19*) 06/20/2020 *Genetic Testing in Prostate Cancer*. Facing Our Risk of Cancer Empowered Annual Conference, Philadelphia, PA. [invited faculty]
24. (*rescheduled due to COVID19*) 10/14/2020 “*Prostate Cancer Genetics: Testing, Targeted Therapy and Early Detection*”. **Dana-Farber Genitourinary Oncology Seminar Series**, Boston, MA [invited faculty speaker]

CURRICULUM VITAE

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PERSONAL DATA

Place of birth: Bellevue, Washington
Citizenship: U.S.A.
Date of Birth: July 7, 1971

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-present

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-present
Medical Director Clinical Research Support Fred Hutchinson Cancer Consortium, Seattle, WA	2018-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
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

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	2004-present

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
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 Urology resident at University of Wisconsin	2011-2013
Daniel Lim – Current medical student at University of Washington	2017-present
Alex Carlson – Current medical student at University of Washington	2018-present
Olivia Do – Current medical student at University of Washington	2019-present
Lorin Ferris – Current medical student at University of Washington	2019-present
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

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 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 the National Comprehensive Cancer Network, Journal of Nuclear Medicine, Journal of Oncotargets and Therapy, Journal of Urology, 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, Prostate Cancer Charity, Prostate Cancer Foundation Challenge and Young Investigator Awards, PNW SPORE Pilot Projects, Solid Tumor Translational Research (STTR) Grant Program

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 Genitourinary Cancer (Prostate) Oral Abstract Session	2010
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 Genitourinary Cancer (Non-Prostate) Oral Abstract Session	2011
Advanced Prostate Cancer Chair (covering), SWOG Fall 2011 Group Meeting Genitourinary Committee	2011
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 Oncology and National Board of Medical Examiners	2017-2019
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 Prostate Cancer Task Force	2018-present
Imaging Committee Member, SWOG	2018-present
Member, Education Committee	2019-present
Association of American Cancer Institutes Member, Board of Governors, SWOG	2020-present

LOCAL RESPONSIBILITIES

4th Floor Solutions Committee, Seattle Cancer Care Alliance	2004–2006
Genitourinary Practice Committee University of Washington Department of Medicine	2004–2005
Recruitment and Community Outreach Core University of Washington Translational Grant Committee	2004–2005
Multicultural Affairs Advisory Board University of Washington Department of Medicine	2006–2007
Translational Research Task Force University of Washington Translational Grant Committee	2006–2008
Accreditation Council for Graduate Medical Education University of Washington Medicine Residency Program	2006–2017
Oncology and Hematology Fellowship Program Admissions Committee University of Washington / Fred Hutchinson Cancer Research Center	2006–present
Prostate Cancer Task Force Washington Comprehensive Cancer Control Partnership	2007–2008
Imaging Working Group Prostate Specialized Programs of Research Excellence (SPORE)	2007–2008
Quality Improvement/Safety Steering Committee Seattle Cancer Care Alliance	2007–2010
Medical Student Research Training Program Committee University of Washington School of Medicine	2008-2016
Medical Student Admissions Committee University of Washington School of Medicine	1995-1998 2009-2016
Institute for Prostate Cancer Research Committee University of Washington	2009-present
Grant Reviewer INBRE-WSU Spokane Institute for Translational Health Sciences	2010
Internal Medicine Residency Education Coordinator (Oncology) University of Washington	2010-2017
Core Faculty Designation, Internal Medicine Residency University of Washington	2010-present
Clinical Core Director Pacific Northwest Prostate Cancer SPORE	2012-present
Reviewer for the University of Washington American Cancer Society Summer Fellowship in Clinical Cancer Research	2013
New Faculty Search Committee Member University of Washington Pediatric Oncology and Seattle Children's Hospital	2013-2015
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 Liaison 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	

PEER REVIEW FUNDING

- Prostate Cancer Research Program Clinical Consortium Award.
W81XWH-16-PCRP-CCRSA (Higano)
Grant amount:
Source: Department of Defense
Role: Co-site principal investigator (5% effort)
Dates: 01/01/07 - 09/29/21 (3 successful competitive renewals)
- Pacific Northwest Prostate Cancer SPORE – Core D (Clinical)
P50 CA097186 (Nelson/Core D Yu and Gore)
Grant amount: (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)
- INTense Exercise foR surVivAL among men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL – MCRPC): A multicenter, randomized, controlled, phase III study
Grant amount:
Source: Movember GAP4
Role: Site principal investigator

Dates: 10/05/16 – 10/04/20

4. Cancer Consortium Support Grant
P30 CA015704 (Gilliland) / Clinical Research Support (Yu)
Grant amount:
Role: Medical Director, Clinical Research Support Office
Dates: 01/01/97 – 12/31/24
5. Lead Academic Participating Site (LAPS) Grant
UG1 CA233328 (Yu, Appelbaum)
Grant Amount:
Source: NIH/NCI
Role: Site co-Principal Investigator
Dates: 03/06/19 - 02/28/25

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:
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:
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:
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:
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 ¹⁸F-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:
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:
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:
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:
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:
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:
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:

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:

Source: Bezos family Immunotherapy Initiative
Role: Concept development and principal investigator
Dates: 07/01/15 – 06/30/18 (no cost extension)

PHARMACEUTICAL FUNDING: INVESTIGATOR INITIATED

1. Biologic tissue effect of sipuleucel-T on metastatic castration-resistant prostate cancer.

Grant amount:

Source: Dendreon
Role: Concept development and overall principal investigator
Dates: 01/27/15 – 04/14/22

2. A randomized phase II study of atezolizumab plus recombinant human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma.

Grant amount:

Source: Genentech, Inc. and NCI Cancer Immunotherapy Trials Network
Role: Concept development and overall national principal investigator
Dates: 06/28/19 – 09/30/22

3. 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:

Source: Bayer HealthCare Pharmaceuticals, Inc.
Role: Concept development and overall national principal investigator
Dates: 01/09/20 – 09/08/24

4. Fluciclovine (FACBC) PET/CT site-directed therapy of oligometastatic prostate cancer (FLU-BLAST-PC trial)

Grant amount:

Source: Blue Earth
Role: Concept development and overall principal investigator
Dates: 02/07/20 – 02/06/23

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:

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:

- 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:
 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:
 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:
 Source: OncoGeneX Technologies, 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:
 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:
 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:
 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:
Sources: Dendreon
Role: Site principal investigator for lead site
Dates: 09/01/14 – 08/31/18

PHARMACEUTICAL INITIATED FUNDING

1. 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:
Source: Merck Sharp &Dohme Corp.
Role: Site principal investigator
Dates: 11/16/16 – 11/15/21
2. Phase 1b/II trial of pembrolizumab (MK-3475) combination therapies in metastatic castration-resistant prostate cancer (KEYNOTE-365).
Grant amount:
Source: Merck Sharp &Dohme Corp.
Role: Concept and protocol co-developed with Merck and Overall Principal Investigator for international trial
Dates: 01/13/17 – 12/31/20
3. 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:
Source: Seattle Genetics, Inc.
Role: Steering committee member and Site principal investigator
Dates: 10/13/17 – 08/31/22
4. 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:
Source: Daiichi Sankyo
Role: Site principal investigator
Dates: 01/07/19 – 03/31/23
5. A phase 1, open-label, non-randomized, safety, tolerability, and pharmacokinetic study of TAS3681 in patients with metastatic castration-resistant prostate cancer.
Grant amount:
Source: Taiho
Role: Site principal investigator
Dates: 09/12/19 – 05/31/24

6. 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:
Source: Seattle Genetics, Inc.
Role: Site principal investigator
Dates: 12/10/19 – 04/30/25
7. A phase 1b/2 study of ibrutinib combination therapy in selected advanced gastrointestinal and genitourinary tumors.
Grant amount:
Source: Pharmacyclics, Inc.
Role: Site principal investigator
Dates: 01/06/20 – 09/25/24
8. 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:
Source: Merck Sharp & Dohme Corp.
Role: Site and overall international principal investigator
Dates: 01/17/20 – 05/31/24
9. DAROL: Darolutamide observational study in nonmetastatic castration-resistant prostate cancer patients.
Grant amount:
Source: Bayer AG
Role: Site and overall international principal investigator
Dates: 05/27/20 – 10/14/24
10. A multicenter, randomized, controlled phase 2 study: Efficacy and safety of ¹³¹I-1095 radiotherapy in combination with enzalutamide in metastatic castration-resistant prostate cancer patients who are ¹⁸F-DCFPyL prostate-specific membrane antigen-avid, chemotherapy-naïve, and progressed on abiraterone (ARROW).
Grant amount:
Source: Progenics Pharmaceuticals, Inc.
Role: Site and overall international principal investigator
Dates: 06/03/20 – 05/31/24

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:
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:
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:
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:
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:
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:
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:
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:
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:
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:
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:
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:
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:
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:
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:
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:

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:

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:

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:

Source: Merck Sharp & Dohme Corp.

Role: Site principal investigator

Dates: 03/22/16 – 03/21/18

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2. Kuo CJ, Farnebo F, Yu EY, Christofferson R, Swearingen RA, Carter R, von Recum HA, Yuan J, Kamihara J, Flynn E, D'Amato R, Folkman J, Mulligan RC. Comparative evaluation of the antitumor activity of antiangiogenic proteins delivered by gene transfer. *Proc Natl Acad Sci* 2001; 98(8):4605-4610. Epub March 27, 2001. PMID: 11274374. PMCID: 31881.
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4. Masutomi K, ^áYu EY, ^áKhurts S, Ben-Porath I, Currier JL, Metz GB, Brooks MW, Kaneko S, Murakami S, DeCaprio JA, Weinberg RA, Stewart SA, Hahn WC. Telomerase maintains telomere structure in normal human cells. *Cell* 2003; 114(2):241-253. ^á*These authors contributed equally to this work.* PMID: 12887925.

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6. Yu EY, Mankoff DM. Positron Emission Tomography (PET) Imaging as a Cancer Biomarker. *Expert Rev Mol Diagn* 2007; 7(5):659-672. PMID: 17892371.
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- *11. Yu EY, Gulati R, Telesca D, Jiang P, Tam S, Russell KJ, Nelson PS, Etzioni RD, Higano CS. Duration of first off treatment interval is prognostic for time to castration resistance and death in men with biochemical relapse of prostate cancer treated on a prospective trial of intermittent androgen deprivation. *J Clin Oncol* 2010; 28(16):2668-2673. Epub April 26, 2010. PMID: 20421544. PMCID: 2881848.
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cancer. *Urology* 2011; 77 (5):1166-1171. PMID: 21539969. PMCID: 3394099. NIHMSID: 340775.

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- *17. Yu EY, Kuo KF, Gulati R, Chen S, Gambol TE, Hall SP, Jiang PY, Pitzel P, Higano CS. Long-term dynamics of bone mineral density during intermittent androgen deprivation for men with non-metastatic, hormone-sensitive prostate cancer. *J Clin Oncol* 2012; 30(15):1864-1870. Epub April 9, 2012. PMID: 22493411. PMCID: 3383183.
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130. Smith MR, Sandhu SK, Kelly WK, Scher HI, Efsthathiou E, Lara P, Yu EY, George DJ, Chi KN, Summa J, Kothari N, Zhao X, Espina BM, Ricci DS, Simon JS, Tran N, Fizazi K, GALAHAD Investigators. Phase II study of niraparib in patients with metastatic castration-resistant prostate cancer and biallelic DNA-repair gene defects: Preliminary results of GALAHAD. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 202). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.
131. Massard C, Retz M, Hammerer P, Quevedo F, Fong PCC, Berry WR, Gurney H, Piulats JM, Joshua A, Linch MD, Kolinsky M, Romano E, Sridhar SS, Conter HJ, Augustin M, Wu, H, Schloss C, Poehlein CH, Yu EY. KEYNOTE-365 Cohort B: Pembrolizumab plus docetaxel and prednisone in abiraterone or enzalutamide-pretreated patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 170). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.

132. Fong PCC, Retz M, Drakaki A, Massard C, Berry WR, Romano E, Bono JS, Feyereabend S, Appleman LJ, Conter HJ, Sridhar SS, Shore ND, Linch MD, Joshua A, Gurney H, Wu, H, Schloss C, Poehlein CH, Yu EY. KEYNOTE-365 Cohort C: Pembrolizumab plus enzalutamide in abiraterone-pretreated patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 171). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.
133. Petrylak DP, Balar AV, O'Donnell PH, McGregor BA, Heath EI, Yu EY, Galsky MD, Hahn NM, Gartner EM, Pinelli J, Melhem-Bertrandt A, Rosenberg JE. EV-201: Results of enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer previously treated with platinum and immune checkpoint inhibitors. *J Clin Oncol* 37, 2019 (suppl; abstr LBA4505). Oral presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.
134. Yu EY, Massard C, Retz M, Tafreshi A, Carles J, Hammerer P, Fong PCC, Shore N, Joshua AM, Linch MD, Gurney H, Romano E, Augustin M, Piulats JM, Wu H, Schloss C, Poehlein CH, De Bono JS. Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castrate-resistant prostate cancer: Cohort A of the phase 1b/2 KEYNOTE-365 study. *J Clin Oncol* 37, 2019 (suppl; abstr 5027). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.
135. Nyame YA, Holt SK, Winters B, Psutka SP, Dash A, Schade GR, Lin DW, Diamantopoulos LN, Grivas P, Yu EY, Gore JL, Wright JL. Increasing use of neoadjuvant chemotherapy in muscle-invasive bladder cancer: Prognostic impact of non-standard of care regimens. *J Clin Oncol* 37, 2019 (suppl; abstr 4532). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.
136. Khaki AR, Diamantopoulos LN, Devitt ME, Drakaki A, Shreck E, Joshi M, Velho PI, Alonso L, Nelson AA, Liu S, Moses MW, Barata PC, Hoimes CJ, Galsky MD, Sonpavde G, Yu EY, Shankaran V, Lyman GH, Grivas P. Outcomes of patients with metastatic urothelial cancer and poor performance status receiving anti-PD(L)1 agents. *J Clin Oncol* 37, 2019 (suppl; abstr 4525). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.
137. Winters B, Diamantopoulos LN, Tretiakova MS, True LD, Lee JH, Zeng J, Liao J, Cheng HH, Schweizer MT, Hsieh AC, Yu EY, Schade GR, Gore JL, Lin DW, Dighe M, Vakar-Lopez F, Russell JR, Grivas P, Montgomery RB, Wright JL. Bladder Cancer Multidisciplinary Clinic model: Impact on imaging, pathology and treatment recommendations. *J Clin Oncol* 37, 2019 (suppl; abstr 4537). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.
138. Bandini M, Pederzoli F, Madison R, Briganti A, Plimack ER, Ross JS, Niegisch G, Yu EY, Bamias A, Agarwal N, Sridhar SS, Rosenberg JE, Bellmunt J, Galsky MD, Gallina A, Salonia A, Montorsi F, Ali SM, Chung J, Necchi A. Squamous cell variant histology in muscle-invasive bladder cancer: A comprehensive clinical, genomic, and therapeutic assessment from multiple datasets. *J Clin Oncol* 37, 2019 (suppl; abstr 4535). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.
139. Yu EY, Fling S, Salim B, Sweis RF, Chatta GS, Jain RK, Delacroix SE, Moon H, Lacroix A, Kaiser JC, Sharon E, Cheever MA, Pachynski R. A randomized phase II study of atezolizumab plus recombinant human IL-7 (CYT107) or atezolizumab alone in patients with locally advanced or metastatic urothelial carcinoma: A Cancer Immunotherapy Trials Network trial (CITN-14). *J*

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140. Fong PCC, Retz M, Drakaki A, Massard C, Berry WR, Romano E, Bono JS, Feyerabend S, Appleman LJ, Conter HJ, Sridhar SS, Shore ND, Linch MD, Joshua A, Gurney H, Wu, H, Schloss C, Poehlein CH, Yu EY. Pembrolizumab plus enzalutamide in abiraterone-pretreated patients with metastatic castration-resistant prostate cancer: Cohort C of the phase 1b/2 KEYNOTE-365 study. *J Clin Oncol* 37, 2019 (suppl; abstr 5010). **Poster Discussion Session at ASCO Annual Meeting, Chicago, IL, Jun. 2019.**
141. Graham L, Reder N, Gulati R, Grivas P, Wright JL, Yu EY, Hou W, Nega K, Yezefski T, Montgomery RB, Mostaghel EA, Ellis WJ, True LD, Lin DW, Nelson PS, Schweizer MT. Targeting backdoor androgen synthesis through AKR1C3 inhibition, A presurgical hormonal ablative trial in high risk localized prostate cancer. *J Clin Oncol* 37, 2019 (suppl; abstr 5081). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.
142. Massard C, Retz M, Hammerer P, Quevedo F, Fong PCC, Berry WR, Gurnery H, Piulats JM, Joshua A, Linch MD, Kolinsky M, Romano E, Sridhar SS, Conter HJ, Augustin M, Wu, H, Schloss C, Poehlein CH, Yu EY. Pembrolizumab plus docetaxel and prednisone in abiraterone or enzalutamide-pretreated patients with metastatic castration-resistant prostate cancer: Cohort B of the phase 1b/2 KEYNOTE-365 study. *J Clin Oncol* 37, 2019 (suppl; abstr 5029). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.
143. Grunewald CM, Henn A, Galsky MD, Plimack ER, Harshman LC, Yu EY, Crabb SJ, Pal SK, Alva AS, Powles T, De Giorgi U, Agarwal N, Bamias A, Ladoire S, Necchi A, Vaishampayan UN, Sternberg CN, Bellmunt J, Baniel J, Niegisch G. Impact of timing of adjuvant chemotherapy following radical cystectomy for bladder cancer on patient survival. *J Clin Oncol* 37, 2019 (suppl; abstr e16017). ASCO Annual Meeting, Chicago, IL, Jun. 2019.
144. Diamantopoulos LN, Khaki AR, Vakar-Lopez F, Tretiakova MS, Gore JL, Schade GR, Psutka SP, Hsieh AC, Lee JK, Yezefski T, Schweizer MT, Cheng HH, Yu EY, Grivas P, Montgomery RB, Wright JL. Patient characteristics, treatment patterns, outcomes and prognostic factors in plasmacytoid urothelial carcinoma. *J Clin Oncol* 37, 2019 (suppl; abstr e16007). ASCO Annual Meeting, Chicago, IL, Jun. 2019.
145. Yu EY, Lu X, Kim J, Antonarakis ES. KEYLYNK-010: Phase 3 study of pembrolizumab plus olaparib vs. enzalutamide or abiraterone in enzalutamide- or abiraterone-pretreated patients with metastatic castration-resistant prostate cancer who had progression on chemotherapy. *ESMO Congress Abstract 893TIP*, 2019 European Society of Medical Oncology Congress. Barcelona, Spain, Sept. 2019. Poster presentation at ESMO Congress, Barcelona, Spain, Sept. 2019.
146. Smith MR, Sandhu S, Kelly WK, Scher HI, Efstathiou E, Lara P, Yu EY, George DJ, Chi KN, Saad F, Summa J, Freedman JM, Mason GE, Zhu E, Ricci DS, Simon JS, Cheng S, Fizazi K. Pre-specified interim analysis of GALAHAD: A phase 2 study of niraparib in patients with metastatic castration-resistant prostate cancer and biallelic DNA-repair gene defects. *ESMO Congress Abstract LBA50*, 2019 European Society of Medical Oncology Congress. Barcelona, Spain, Sept. 2019. Poster presentation at ESMO Congress, Barcelona, Spain, Sept. 2019.

147. McGregor BA, O'Donnell PH, Balar A, Petrylak D, Rosenberg JE, Yu EY, Quinn DI, Shah S, Pinelli J, Hepp Z, Galsky MD. Quality of life of metastatic urothelial cancer patients treated with enfortumab vedotin following platinum-containing chemotherapy and anti-programmed death 1 or anti-programmed death-ligand 1 (PD-1/L1) therapy: Data from EV-201 cohort 1. *ESMO Congress Abstract* 921P, 2019 European Society of Medical Oncology Congress. Barcelona, Spain, Sept. 2019. Poster presentation at ESMO Congress, Barcelona, Spain, Sept. 2019.
148. Appleman LJ, Piulats J, Mar N, Arranz JA, Joshua A, Mayer TM, Shore N, Wu H, Schloss C, Yu EY. KEYNOTE 365 Cohort D: Phase 1b/2 study of pembrolizumab plus abiraterone acetate and prednisone in metastatic castration-resistant prostate cancer. *Journal for ImmunoTherapy of Cancer* Nov. 26 Suppl P382. Poster presentation at 2019 Society for Immunotherapy of Cancer at National Harbor, MD, Nov. 2019.
149. Yu EY, Park SH, Huang YH, Bennamoun M, Xu L, Kim J, Antonarakis EA. Pembrolizumab plus olaparib vs. enzalutamide or abiraterone in patients with metastatic castration-resistant prostate cancer who experienced progression on chemotherapy: Phase 3 KEYLYNK-010 study. *Journal for ImmunoTherapy of Cancer* Nov. 26 Suppl P390. Poster presentation at 2019 Society for Immunotherapy of Cancer at National Harbor, MD, Nov. 2019.
150. Graham L, Montgomery RB, Cheng HH, Yu EY, Alva AS, Schweizer MT. Mismatch repair deficiency in metastatic prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 194). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.
151. Carlson AS, Acevedo R, Lim DM, Gulati R, Yu EY, Schweizer MT. Impact of DNA damage repair mutations on treatment outcomes in men receiving conventional therapy for metastatic castration resistant prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 172). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.
152. Yu EY, Laidley D, Pouliot F, Probst S, Saad F, Sabbagh R, Sartor AO. A multicenter, randomized, controlled phase II study: Efficacy and safety of PSMA-targeted radioligand therapy ¹³¹I-1095 plus enzalutamide in ¹⁸F-DCFPyL PSMA scan avid, metastatic castration-resistant prostate cancer patients post-abiraterone progression (ARROW). *J Clin Oncol* 38, 2020 (suppl 6; abstr TPS260). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.
153. Graff JN, Cheng HH, Vuky J, Alumkal JJ, Kreitner D, Petreaca D, Grivas P, Schweizer MT, Higano CS, Chen Y, Yu EY, Beer TM. Phase II study of cabazitaxel plus enzalutamide in metastatic castration-resistant prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 86). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.
154. Miller NJ, Khaki AR, Diamantopoulos LN, Bilen MA, Santos VS, Morales-Barrera R, Devitt ME, Nelson AA, Shreck E, Assi H, Rodriguez-Vida A, Lythgoe M, Drakaki A, Joshi M, Velho PI, Moses MW, Galsky MD, Sonpavde G, Yu EY, Grivas P. Histologic subtype and response to immune checkpoint inhibitor therapy in advanced urothelial cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 495). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.
155. Sokolova A, Marshall CH, Lozano R, Grivas P, Higano CS, Lotan TL, Montgomery RB, Nelson P, Olmos D, Schweizer MT, Yezefski T, Yu EY, Paller CJ, Castro E, Antonarakis ES, Cheng HH.

Treatment response comparisons between *ATM* and *BRCA2* germline carriers for metastatic castration resistant prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 63). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

156. Smith MR, Fizazi K, Sandhu SK, Kelly WK, Efstathiou E, Lara P, Yu EY, George DJ, Chi KN, Saad F, Summa J, Freedman JM, Mason G, Espina BM, Zhu E, Ricci DS, Snyder LA, Simon JS, Cheng S, Scher HI. Niraparib in patients with metastatic castration-resistant prostate cancer and biallelic DNA-repair gene defects: Correlative measures of tumor response in phase II GALAHAD study. *J Clin Oncol* 38, 2020 (suppl 6; abstr 118). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.
157. Cheng HH, DeJong M, Yu EY, Gulati R, Rettig M, Higano CS, Nelson P, Pritchard CC, Montgomery RB. A pilot study of docetaxel and carboplatin for treatment of patients with metastatic castration resistant prostate cancer containing biallelic inactivation of genes in the *BRCA1/2* pathway. *J Clin Oncol* 38, 2020 (suppl 6; abstr 127). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.
158. Yu EY, Park SH, Huang YH, Bennamoun M, Xu L, Kim J, Antonarakis ES. Phase III study of pembrolizumab plus olaparib versus enzalutamide or abiraterone acetate in patients with metastatic castration-resistant prostate cancer who progressed on chemotherapy: KEYLYNK-010. *J Clin Oncol* 38, 2020 (suppl 6; abstr TPS256). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.
159. Wong RL, Duong MT, Tangen C, Agarwal N, Cheng HH, Vogelzang NJ, Hussain M, Thompson IM, Quinn DI, Yu EY. Survival outcomes and risk group validation from SWOG S0925, a randomized phase II study of androgen deprivation +/- cixutumumab, in new metastatic hormone-sensitive prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 106). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.
160. Diamantopoulos LN, Khaki AR, Gadzinski AJ, Winters B, Vakar-Lopez F, Tretiakova MS, Gore JL, Schade GR, Psutka SP, Hsieh AC, Lee JK, Yezefski T, Schweizer MT, Cheng HH, Yu EY, Lin DW, Montgomery RB, Grivas P, Wright JL. Micropapillary urothelial carcinoma: A comparative analysis of oncologic outcomes compared to conventional urothelial carcinoma. *J Clin Oncol* 38, 2020 (suppl 6; abstr 459). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.
161. Yu EY, Piulats JM, Gravis G, Laguerre B, Arija JAA, Oudard S, Fong PCC, Kolinsky MP, Augustin M, Feyerabend S, Kam AE, Gurney H, Tafreshi A, Retz M, Berry WR, Mar N, Wu H, Schloss C, Poehlein CH, De Bono JS. KEYNOTE-365 cohort A updated results: Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 100). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.
162. Berry WR, Fong PCC, Piulats JM, Appleman LJ, Conter HJ, Feyerabend S, Shore ND, Gravis G, Laguerre B, Gurney H, Retz M, Romano E, Mourey L, De Bono JS, Kam AE, Emmenegger U, Wu H, Schloss C, Poehlein CH, Yu EY. KEYNOTE-365 cohort C updated results: Pembrolizumab plus enzalutamide in abiraterone-pretreated patients with metastatic castrate-resistant prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 102). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.

163. Kolinsky MP, Gravis GG, Piulats JM, Sridhar SS, Romano E, Berry WR, Gurney H, Retz M, Appleman LJ, Boegemann M, De Bono JS, Joshua AM, Emmenegger U, Conter HJ, Laguerre B, Wu H, Schloss C, Poehlein CH, Yu EY. KEYNOTE-365 cohort B updated results: Pembrolizumab plus docetaxel and prednisone in abiraterone or enzalutamide-pretreated patients with metastatic castrate-resistant prostate cancer. *J Clin Oncol* 38, 2020 (suppl 6; abstr 103). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2020.
164. Yu EY, Fong P, Piulats JM, Appleman L, Feyerabend S, Shore N, Gravis G, Laguerre B, Retz M, Romano E, Mourey L, de Bono JS, Kam A, Emmenegger U, Wu H, Schloss C, Poehlein C, Berry W. Pembrolizumab plus enzalutamide in abiraterone-pretreated patients with metastatic castration-resistant prostate cancer: Updated results from KEYNOTE-365 cohort C. Abstract PD16-12, 2020. Oral (virtual) presentation at the 2020 Annual Meeting of the American Urological Association Education and Research, Inc., Washington, DC, May 2020.
165. Soria F, Black PC, Fairey AS, Cookson MS, Yu EY, Kassouf W, Dall'Era MA, Sridhar SS, McGrath JS, Wright JL, Thorpe AC, Morgan TM, Holzbeierlein JM, Bivalacqua TJ, North S, Barocas DA, Lotan Y, Grivas P, Stephenson AJ, Shah JB, Van Rhijn BW, Spiess PE, Sharait SF, Gontero P. Neoadjuvant chemotherapy plus radical cystectomy versus radical cystectomy alone in clinical T2 bladder cancer patients without hydronephrosis: Results from a large multicenter cohort study. Abstract PD60-05. Presentation at the 2020 Annual Meeting of the American Urological Association Education and Research, Inc., Washington, DC, May 2020.
166. Yu EY, Laidley D, Pouliot F, Probst S, Sabbagh R, Esposito G, Saad F, Sartor AO. A multicenter, randomized, controlled phase II study: Efficacy and safety of PSMA-targeted radioligand therapy ¹³¹I-1095 plus enzalutamide in ¹⁸F-DCFPyL PSMA scan avid, metastatic castration-resistant prostate cancer patients post-abiraterone progression (ARROW). *J Clin Oncol* 38: 2020 (suppl; abstr TPS5596). Poster presentation at 2020 ASCO Virtual Scientific Program, May 2020.
167. Yu EY, Pieczonka CM, Briganti A, Murphy DG, Thierry L, Luz M, Suzuki H, Thiery-Vuillemin A, Ortiz JA, Guan R, Armstrong AJ. DAROL: DARolutamide Observational study patients in nonmetastatic castration-resistant prostate cancer patients. *J Clin Oncol* 38: 2020 (suppl; abstr TPS5593). Poster presentation at 2020 ASCO Virtual Scientific Program, May 2020.
168. Kelly WK, Danila DC, Edenfield WJ, Aggarwal RR, Petrylak DP, Sartor AO, Sumey CJ, Dorff TB, Yu EY, Adra N, Waterhouse DM, Armstrong AJ, Horvath L, Pook DW, Appleman LJ, Lau A, Salvati M, Kouros-Mehr H. Phase I study of AMG 509, a STEAP1 X CD3 T cell-recruiting XmAb 2+1 immune therapy, in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol* 38: 2020 (suppl; abstr TPS5589). Poster presentation at 2020 ASCO Virtual Scientific Program, May 2020.
169. Sridhar SS, Kolinsky MP, Gravis G, Mourey L, Piulats Rodriguez JMM, Romano E, Berry WR, Gurney H, Retz M, Appleman LJ, Boegemann M, De Bono JS, Joshua AM, Emmenegger U, Conter HJ, Laguerre B, Wu H, Qiu P, Schloss C, Yu EY. Pembrolizumab plus docetaxel and prednisone in patients with abiraterone acetate or enzalutamide-pretreated metastatic castration-resistant prostate cancer: KEYNOTE-365 cohort B efficacy, safety, and biomarker results. *J Clin Oncol* 38: 2020 (suppl; abstr 5550). Poster presentation at 2020 ASCO Virtual Scientific Program, May 2020.

170. Yu EY, Piulats Rodriguez JMM, Gravis G, Laguerre B, Arija JAA, Oudard S, Fong PCC, Kolinsky MP, Augustin M, Todenhofer T, Kam AE, Gurney H, Tafreshi A, Retz M, Berry WR, Mar N, Wu H, Qiu P, Schloss C, De Bono JS. Pembrolizumab plus olaparib in patients with docetaxel-pretreated metastatic castration resistant prostate cancer: KEYNOTE-365 cohort A efficacy, safety, and biomarker results. *J Clin Oncol* 38: 2020 (suppl; abstr 5544). Poster presentation at 2020 ASCO Virtual Scientific Program, May 2020.
171. Conter HJ, Shore ND, Berry WR, Fong PCC, Piulats Rodriguez JMM, Appleman LJ, Todenhofer T, Gravis G, Laguerre B, Gurney H, Retz M, Romano E, Mourey L, De Bono JS, Kam AE, Emmenegger U, Wu H, Qiu P, Schloss C, Yu EY. Pembrolizumab plus enzalutamide in patients with abiraterone acetate-pretreated metastatic castration-resistant prostate cancer: KEYNOTE 365 cohort C efficacy, safety, and biomarker results. *J Clin Oncol* 38: 2020 (suppl; abstr 5545). Poster presentation at 2020 ASCO Virtual Scientific Program, May 2020.
172. Do OA, Ferris L, Holt SK, Ramos J, Harshman LC, Plimack ER, Crabb SJ, Pal SK, De Giorgi U, Ladoire S, Baniel J, Necchi A, Vaishampayan UN, Golshayan AR, Bamias A, Bellmunt J, Srinivas S, Dorff TB, Galsky MD, Yu EY. Treatment of metastatic recurrence of urothelial carcinoma after previous cisplatin-based chemotherapy: A retrospective comparison of different chemotherapy regimens. *J Clin Oncol* 38: 2020 (suppl; abstr e17005).
173. Ngo S, Diamantopoulos LN, Maldonado R, O'Malley RB, Laidlaw G, Fintelmann FJ, Holt SK, Gore JL, Schade GR, Lin DW, Grivas P, Montgomery RB, Hsieh AC, Cheng HH, Yezefski T, Schweizer MT, Yu EY, Wright JL, Psutka SP. Skeletal muscle index and adverse events during a bladder cancer treatment episode. *J Clin Oncol* 38: 2020 (suppl; abstr e17016).
174. Diamantopoulos LN, Sekar RR, Khaki AR, Miller N, Gadzinski AJ, Psutka SP, Gore JL, Schade GR, Lin DW, Tretiakova MS, Vakar-Lopez F, True LD, Hsieh AC, Cheng HH, Yu EY, Schweizer MT, Yezefski T, Montgomery RB, Grivas P, Wright JL. Perioperative blood transfusion and postoperative outcomes in patients undergoing radical cystectomy for bladder cancer. *J Clin Oncol* 38: 2020 (suppl; abstr e17012).
175. Sekar RR, Diamantopoulos LN, Khaki AR, Vakar-Lopez F, Tretiakova MS, Psutka SP, Holt SK, Gore JL, Schade GR, Lin DW, Hsieh AC, Lee JK, Yezefski T, Schweizer MT, Cheng HH, Yu EY, True LD, Montgomery RB, Grivas P, Wright JL. Sarcomatoid urothelial carcinoma: Oncologic outcomes from a tertiary center and SEER-Medicare data. *J Clin Oncol* 38: 2020 (suppl; abstr e17033).
176. Diamantopoulos LN, Ngo S, Maldonado R, O'Malley RB, Laidlaw G, Fintelmann FJ, Holt SK, Gore JL, Schade GR, Lin DW, Grivas P, Montgomery RB, Hsieh AC, Cheng HH, Yezefski T, Schweizer MT, Yu EY, Wright JL, Psutka SP. Associations between baseline body composition and cancer-specific mortality following neoadjuvant chemotherapy and radical cystectomy for bladder cancer. *J Clin Oncol* 38: 2020 (suppl; abstr e17015).
177. Gravis G, Kolinsky MP, Mourey L, Piulats JM, Sridhar SS, Romano E, Berry WR, Gurney H, Retz M, Appleman LJ, Boegemann M, De Bono JS, Joshua AM, Emmenegger U, Conter HJ, Laguerre B, Wu H, Schloss C, Poehlein C, Yu EY. KEYNOTE-365 cohort B updated results: Pembrolizumab plus docetaxel and prednisone in abiraterone or enzalutamide-pretreated patients with metastatic castration-resistant prostate cancer. *European Association of Urology*; Abstract 560, 2020. 21st International European Association of Urology Virtual Meeting, July 2020.

178. Piulats JM, Yu EY, Gravis G, Laguerre B, Arranz J, Oudard S, Fong PCC, Kolinsky MP, Augustin M, Feyerabend S, Kam AE, Gurney H, Tafreshi A, Retz M, Berry WR, Mar N, Wu H, Schloss C, Poehlein C, De Bono JS. Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castration resistant prostate cancer: KEYNOTE-365 cohort A updated results. *European Association of Urology*; Abstract 561, 2020. 21st International European Association of Urology Virtual Meeting, July 2020.
179. Feyerabend S, Berry WR, Fong PCC, Piulats JM, Appleman LJ, Conter H, Shore N, Gravis G, Laguerre B, Gurney H, Retz M, Romano E, Mourey L, De Bono JS, Kam AE, Emmenegger U, Wu H, Schloss C, Poehlein C, Yu EY. KEYNOTE 365 cohort C updated results: Pembrolizumab plus enzalutamide in abiraterone-pretreated patients with metastatic castration-resistant prostate cancer. *European Association of Urology*; Abstract 562, 2020. 21st International European Association of Urology Virtual Meeting, July 2020.
180. Marchioni M, Mir MC, Zargar H, Grivas P, Dall'era MAD, Spiess PES, Van Rhijn BW, Lotan Y, Bivalacqua TJ, Holzerbeierlein JM, Thorpe A, Yu EY, Shariat SF, Kassouf W, Barocas DA, Daneshmand S, Dinney CP, McGrath JS, Sridhar SS, Wright J, North S, Stephenson AJ, Xylinas E, Black P. Nomogram predicting bladder cancer specific mortality after neoadjuvant chemotherapy and radical cystectomy for muscle-invasive bladder cancer: Results of an international consortium. *European Association of Urology*; Abstract 1100, 2020. 21st International European Association of Urology Virtual Meeting, July 2020.
181. Soria F, Black PC, Fairey AS, Cookson MS, Yu EY, Kassouf W, Dall'era MA, Sridhar SS, McGrath JS, Wright JL, Thorpe AC, Morgan TM, Daneshmand S, Holzbeierlein JM, Bivalacqua TJ, North S, Barocas DA, Lotan Y, Grivas P, Stephenson AJ, Shah JB, Van Rhijn BW, Spiess PE, Shariat SF, Gontero P. *European Association of Urology*; Abstract PT406, 2020. 21st International European Association of Urology Virtual Meeting, July 2020.

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 ¹¹C-acetate and ¹⁸F-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 protocol 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 ¹³¹I 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.” Bellevue, 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 improvements.” 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.

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 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.” 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 ¹⁸F-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 Angeles, 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)/Society 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.
- Ottawa Dinner Round: “Integrating immune-oncology within the current treatment of advanced urothelial carcinoma.” Ottawa, 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 implications 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 ¹⁷⁷Lu-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.” 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.

Michael Schweizer, MD

1. Personal Data:
 - a. Place of birth: Bryn Mawr, PA
 - b. Citizenship: United States
 - c. Date of birth: 5/18/1981
2. Education:

2004 – 2008	<i>Temple University School of Medicine, Philadelphia, PA</i> Doctor of Medicine, May 2008
1999 – 2004	<i>University of Delaware, Newark, DE</i> Bachelor of Chemical Engineering, May 2004
3. Postgraduate Training:

2011 – 2014	Medical Oncology Fellowship, <i>The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD</i>
2008 – 2011	Internal Medicine Residency, <i>The University of Chicago, Chicago, IL</i>
4. Faculty Positions Held:

2014 – Present	Assistant Professor Internal Medicine, Division of Medical Oncology, <i>The University of Washington, Seattle, WA</i>
2014 – 2019	Assistant Professor, Clinical Research Division, <i>Fred Hutchinson Cancer Research Center, Seattle, WA</i>
2019 – Present	Associate Professor, Clinical Research Division, <i>Fred Hutchinson Cancer Research Center, Seattle, WA</i>
2020 – Present	Associate Professor Internal Medicine, Division of Medical Oncology, <i>The University of Washington, Seattle, WA</i>
5. Hospital Positions Held:

2014 – Present	Attending Physician, <i>University of Washington Medical Center, Seattle, WA</i>
2014 – Present	Attending Physician, <i>Seattle Cancer Care Alliance, Seattle, WA</i>
6. Honors:

2015	Department of Defense Physician Research Training Award
2015	Prostate Cancer Foundation Young Investigator Award
2014 – present	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
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9. Professional Organizations:

2012 – present	American Society of Clinical Oncology, Member ID: 166489
2012 – present	American Association for Cancer Research, Member ID: 274966
2014 – Present	Southwest Oncology Group
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 – present	Mentor to Laura Graham MD, Heme-Onc Fellow UW/FHCRC
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 – present	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
12. Special National Responsibilities:

2014 – 2018, 2020	Grant and Funding Organization Reviews: Department of Defense Prostate Cancer Research Program
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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, Genitourinary Oncology Advanced Disease Meeting

2017 – present Leader, Seattle Cancer Care Alliance, Prostate Cancer Clinical Pathway Team

14. Research Support

Ongoing Research Support:

W81XWH-16-1-0484 Schweizer (PI) 09/30/16 – 09/29/21
Pharmacologic Dose Testosterone to Treat Castration-Resistant Prostate Cancer: Mechanisms of Action and Drivers of Response

The major goal of this project is to determine germ-line and somatic features that are predictive of response to Supra-Physiological Testosterone (SPT) and evaluate the mechanisms of action underlying the observed clinical effects of SPT.

Role: PI

Industry Sponsored Trial Schweizer (PI) 10/14/16 – 06/30/21
Protocol WO29636: A Phase III, Open-Label, Multicenter, Randomized Study of Atezolizumab vs. Observation as Adjuvant Therapy in Patients with High-Risk Muscle-Invasive Urothelial Carcinoma after Surgical Resection

The major goal of this trial is to evaluate the efficacy and safety of adjuvant treatment with atezolizumab compared with observation in patients with muscle-invasive urothelial carcinoma who are at high risk for recurrence following resection.

Role: Site PI

Investigator Initiated Trial McNeel (PI) 01/30/17 – 01/29/21
A Phase I Study of a DNA Vaccine Encoding Androgen Receptor Ligand-Binding Domain (AR LBD), With or Without Granulocyte Macrophage Colony-Stimulating Factor Adjuvant, in Patients With Metastatic Prostate Cancer

The major goal of this study is to determine if a vaccine called pTVG-AR can enhance patients' immune response against prostate cancer.

Role: Site PI

Investigator Initiated Trial Schweizer (PI) 04/12/17 – 04/30/21
A Phase 2 Study of ARN-509 in Active Surveillance Patients

The major goal of this study is to determine if a 90-day course of ARN-509 will lead to a negative repeat prostate biopsy in active surveillance patients.

Role: PI

Industry Sponsored Trial Schweizer (PI) 07/27/18 – 04/30/23
A Phase Ib Safety and Tolerability Study of ZEN003694 in Combination with Enzalutamide or Abiraterone in Patients with Metastatic Castration-Resistant Prostate Cancer

The major goal of this study is to determine the safety, tolerability, and maximum tolerated dose of ZEN003694 in combination with enzalutamide in patients with mCRPC who have progressed during prior treatment with enzalutamide or apalutamide or with abiraterone.

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Role: Site PI

Investigator Initiated Trial Schweizer (PI) 08/01/18 – 03/31/23
Bipolar Androgen Therapy Plus Olaparib in Patient with Castration-Resistant Prostate Cancer

The major goal of this study is to determine whether treating prostate cancer patients with bipolar androgen therapy plus olaparib will result in high response rates, particularly in patients with DNA damage repair deficiencies.

Role: PI

Industry Sponsored Trial (Schweizer PI) 03/19/19 – 05/01/24
A Phase I, First-in-Human, Dose Escalation Study of JNJ-63898081, in Subjects with Advanced Stage Solid Tumors

The major goal of this study is to determine whether JNJ-63898081 will direct the body's immune cells to kill the malignant cells overexpressing prostate-specific membrane antigen (PSMA).

Role: Site PI

Investigator Initiated Trial (Schweizer PI) 07/25/19 – 06/30/24
Erdaftinib plus Abiraterone Acetate or Enzalutamide in Double Negative Prostate Cancer

The major goal of this study is to determine the objective tumor response rate in subjects with measurable lesions as defined by RECIST v1.1 criteria in mCRPC patients with a DNPC molecular phenotype receiving either enzalutamide or abiraterone acetate in combination with erdaftinib.

Role: PI

Industry Sponsored Trial (Schweizer PI) 01/09/20 – 01/31/25
A Phase 3 Randomized, Double-Blind Study of Nivolumab or Placebo in Combination with Docetaxel, in Men with Metastatic Castration-resistant Prostate Cancer (CheckMate 7DX: CHECKpoint pathway and nivolumAB clinical Trial Evaluation 7DX) (CA2097DX)

The current study aims to demonstrate that treatment with docetaxel in combination with nivolumab will be efficacious in participants with mCRPC. Additional objectives of the study include characterization of safety and tolerability, as well as pharmacokinetics, potential predictive biomarkers, and changes in patient reported outcomes for quality of life assessments.

Role: Site PI

Industry Sponsored Trial (Schweizer PI) 02/28/20 – 01/31/25
CART-PSMA-TGFβRDN-02: A Phase I Open-Label, Multi-Center Study of PSMA Targeted Genetically Modified Chimeric Antigen Receptor T Cells in Patients with Metastatic Castration Resistant Prostate Cancer

The major goal of this trial is to establish the safety of PSMA targeted CAR T-cell therapy in men with metastatic castration-resistant prostate cancer. This study also seeks to determine if there is preliminary evidence for clinical efficacy and explore potential biomarkers associated with response/resistance.

Role: Site PI

Industry Sponsored Trial (Schweizer PI) 03/23/20 – 02/28/25
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)

The major goal is to look at Pembrolizumab (MK-3475) Plus Enzalutamide Plus ADT Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer.

Role: Site PI

Investigator Initiated Trial (Schweizer PI) 05/15/20 – 02/28/25
Durvalumab (MEDI4736) and Olaparib (AZD2281) for treatment of biochemically recurrent prostate cancer in men predicted to have a high neoantigen load: a pilot study

The major goal of this study is to evaluate the efficacy of durvalumab plus olaparib in genomic subgroups of prostate cancer expected to be sensitive to immunotherapy.

Role: PI

Recently Completed Research:

W81XWH-14-2-0189 Denmeade (PI) 01/01/15 – 03/29/20
A Randomized Phase II Study Comparing Bipolar Androgen Therapy vs. Enzalutamide in Asymptomatic Men with Castration Resistant Metastatic Prostate Cancer: The TRANSFORMER Trial
The major goal of this study is to determine if treatment with supraphysiologic testosterone will improve radiographic progression free survival compared to enzalutamide in men with metastatic castrate-resistant prostate cancer post-treatment with abiraterone.
Role: Site PI

P30 CA015704 Gilliland (PI) 01/01/16 – 12/31/19
Cancer Center Support Grant: New Investigator Support
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 use next generation sequencing to determine the prevalence of genomic hypermutation within the general population of prostate cancer patients and determine if mismatch repair deficiency underlies this phenotype.
Role: Project PI

Industry Sponsored Research Lee (PI) 05/01/18 – 04/30/19
Therapeutic Targeting of Castration-Resistant Prostate Cancer with the CEACAM5 Antibody-drug Conjugate (ADC) IMMU-130 and the Trop2 ADC IMMU-132
The major goal of this study is to profile the expression of the tumor antigens CEACAM5 and Trop2 in metastatic prostate cancers and to test antibody drug conjugates targeting these antigens in preclinical models of androgen receptor-null prostate cancer.
Role: Co-Investigator

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6. **Schweizer, M.T.**, Cheng, H.H., Nelson, P.S. & Montgomery, R.B. Two Steps Forward and One Step Back for Precision in Prostate Cancer Treatment. *J Clin Oncol*, Jco2001755 (2020). [editorial]
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46. Maughan, B.L., Xhou, X.C., Suzman, D.L., Nadal, R., Bassi, S., **Schweizer, M.T.** & Antonarakis, E.S. Optimal sequencing of docetaxel and abiraterone in men with metastatic castration-resistant prostate cancer. *The Prostate* 75, 1814-1820 (2015). [original work]
47. ***Schweizer, M.T.**, Antonarakis, E.S., Wang, H., Ajiboye, A.S., Spitz, A., Cao, H., Luo, J., Haffner, M.C., Yegnasubramanian, S., Carducci, M.A., Eisenberger, M.A., Isaacs, J.T. & Denmeade, S.R. Effect of bipolar androgen therapy for asymptomatic men with castration-

- resistant prostate cancer: results from a pilot clinical study. *Science translational medicine* 7, 269ra262 (2015). [original work]
48. Nadal, R., Zhang, Z., Rahman, H., **Schweizer, M.T.**, Denmeade, S.R., Paller, C.J., Carducci, M.A., Eisenberger, M.A. & Antonarakis, E.S. Clinical activity of enzalutamide in Docetaxel-naive and Docetaxel-pretreated patients with metastatic castration-resistant prostate cancer. *The Prostate* 74, 1560-1568 (2014). [original work]
 49. Suzman, D.L., Lubner, B., **Schweizer, M.T.**, Nadal, R. & Antonarakis, E.S. Clinical activity of enzalutamide versus docetaxel in men with castration-resistant prostate cancer progressing after abiraterone. *The Prostate* 74, 1278-1285 (2014). [original work]
 50. Nadal, R., **Schweizer, M.**, Kryvenko, O.N., Epstein, J.I. & Eisenberger, M.A. Small cell carcinoma of the prostate. *Nature reviews. Urology* 11, 213-219 (2014). [review]
 51. **Schweizer, M.T.**, Zhou, X.C., Wang, H., Bassi, S., Carducci, M.A., Eisenberger, M.A. & Antonarakis, E.S. The influence of prior abiraterone treatment on the clinical activity of docetaxel in men with metastatic castration-resistant prostate cancer. *European urology* 66, 646-652 (2014). [original work]
 52. **Schweizer, M.T.** & Drake, C.G. Immunotherapy for prostate cancer: recent developments and future challenges. *Cancer metastasis reviews* 33, 641-655 (2014). [review]
 53. **Schweizer, M.T.** & Antonarakis, E.S. Chemotherapy and its evolving role in the management of advanced prostate cancer. *Asian journal of andrology* 16, 334-340 (2014). [review]
 54. **Schweizer, M.T.**, Lin, J., Blackford, A., Bardia, A., King, S., Armstrong, A.J., Rudek, M.A., Yegnasubramanian, S. & Carducci, M.A. Pharmacodynamic study of disulfiram in men with non-metastatic recurrent prostate cancer. *Prostate cancer and prostatic diseases* 16, 357-361 (2013). [original work]
 55. **Schweizer, M.T.**, Zhou, X.C., Wang, H., Yang, T., Shaikat, F., Partin, A.W., Eisenberger, M.A. & Antonarakis, E.S. Metastasis-free survival is associated with overall survival in men with PSA-recurrent prostate cancer treated with deferred androgen deprivation therapy. *Annals of oncology: official journal of the European Society for Medical Oncology / ESMO* 24, 2881-2886 (2013). [original work]
 56. **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]
 57. **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]
 58. **Schweizer, M.T.** & Antonarakis, E.S. Abiraterone acetate: a hat trick of clinical benefits. *The Lancet. Oncology* 13, 1173-1174 (2012). [review]
 59. **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]

60. **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. 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.
2. **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
3. **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.
4. **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.
5. **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.
6. **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.
7. **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.

8. **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.
 9. **Schweizer MT**, Zhou XC, Wang H, Yang T, Shaikat 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.
 10. **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:
- | | |
|------|---|
| 2019 | Speaker, 26 th Annual Prostate Cancer Foundation Scientific Retreat. <i>FGFR-inhibition in Double Negative Prostate Cancer: Rationale and Future Directions</i> , Carlsbad, CA. October 25, 2019 |
| 2019 | Speaker, 5 th Annual Men's Health Update. <i>Prostate Cancer: A Lifelong Disease</i> , Seattle, WA. August 23, 2019 |
| 2019 | Speaker, Gordon's Research Conference: Hormone-dependent Cancers. <i>Targeting Prostate Cancer Drug Resistance</i> , Newry, ME. August 7, 2019 |
| 2019 | Keynote Speaker, Brotman Baty Institute for Precision Medicine: Cell-free DNA Symposium, <i>Applications of cfDNA in Prostate Cancer</i> , Seattle, WA. April 17, 2019. |
| 2019 | Speaker, UWMC Chief of Medicine Conference, <i>Germ Cell Tumors/Testicular Cancer</i> , Seattle, WA. March 19, 2019 |
| 2019 | Speaker, Selected Topics in Hematology / Oncology Fellow's Lecture Series, <i>Bladder Cancer</i> , Seattle, WA. March 15, 2019 |
| 2019 | Speaker, Nuclear Medicine Topical Conference, <i>Prostate Cancer 101</i> , Seattle, WA. March 12, 2019. |
| 2019 | Speaker, Prostate Cancer SPORE Seminar, <i>Targeting Backdoor Androgen Synthesis vis AKRIC3 Inhibition</i> , Seattle, WA. February 28, 2019 |
| 2019 | Speaker, Skagit Valley Hospital, <i>Emerging Therapies in Cancer: New Treatments for Prostate Cancer</i> , Mt Vernon, WA. February 27, 2019 |
| 2019 | Speaker, VA Puget Sound Health Care System, <i>Oncologic Emergencies</i> , Seattle, WA. February 26, 2019. |
| 2018 | Speaker, Cancer Immunotherapy Trial Network Meeting, <i>CDK12 Mutation as a Biomarker for Response to Immune Checkpoint Blockade</i> , 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 Cancers*, 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.

CURRICULUM VITAE

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 Seattle Cancer Care Alliance
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 Seattle, WA 98109
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EDUCATION*Undergraduate*

Bryn Mawr College Bryn Mawr, Pennsylvania	1970-1971
Clark University Worcester, Massachusetts	1972-1975

Medical

University of Massachusetts Worcester, Massachusetts	1975-1979
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Post Graduate

Internal Medicine Residency Mayo Graduate School of Medicine Rochester, Minnesota	1979-1982
Hematology/Oncology Fellowship University of Washington Seattle, Washington	1982-1984
AACR/ASCO Clinical Trials Graduate Workshop Vail, Colorado	1998
ASCO Leadership Seminar Alexandria, Virginia	2011

FACULTY APPOINTMENTS

Acting Instructor, Department of Medicine School of Medicine, University of Washington	1984-1988
Acting Assistant Professor, Department of Medicine School of Medicine, University of Washington	1988-1989
Associate in Clinical Research Fred Hutchinson Cancer Research Center	1988-2008
Assistant Professor, Department of Medicine School of Medicine, University of Washington	1989-1997
Associate Professor, Department of Medicine School of Medicine, University of Washington	1997-2008
Adjunct Associate Professor, Department of Urology School of Medicine, University of Washington	1997-1999
Associate Professor, Department of Urology School of Medicine, University of Washington	1999-2008
Professor, Department of Medicine School of Medicine, University of Washington	2008-2020

Professor, Department of Urology School of Medicine, University of Washington	2008-2020
Member, Clinical Research Division Fred Hutchinson Cancer Research Center	2008-2020
Affiliate Member, Dept of Urologic Sciences University of British Columbia	2013-present
Medical Director, Prostate Cancer Supportive Care Program Vancouver Prostate Centre, Vancouver General Hospital	2013-present

TRAINEES (last 5 years)

Jennifer Bossio, PhD	2015-present
Lindsay Hedden, PhD	2015-present
Evandro Bezerra, MD	2017-2019
Sarah Weller, MSc	2017-2019

HONORS AND AWARDS

National Honor Society	1969
Phi Beta Kappa	1975
Lange Award, Outstanding Medical Student	1979
American Medical Writers Association	2005
America's Top Doctors List	2005 – present
Alpha Omega Alpha	2007
Fellow, American College of Physicians	2008
Prostate Cancer Challenge Award	2011
Forbes Distinguished Alumni Award, Bancroft School	2015
Top Cancer Doctors Award, Newsweek	2015
National Association of Professional Women, VIP Woman of the Year	2015-2016

BOARD CERTIFICATION

American Board of Internal Medicine	1982
Medical Oncology	1985

MEDICAL LICENSES

Minnesota	1979-1982
Washington	1982-present
California	2010-present

PROFESSIONAL ORGANIZATIONS

Washington State Medical Association	1985-present
American Society of Clinical Oncology	1985-present
Southwest Oncology Group	1985-present
American Association for Cancer Research	1992-2010
Puget Sound Oncology Consortium	1994-2015
American Society of Hematology	1994-present
Society of Women in Urology	1996-present
American Urological Association	1997-present
Washington State Medical Oncology Society	1999-present
The Society of Urologic Oncology	2002-present
Washington State Prostate Cancer Coalition	2002-present
European Society for Medical Oncology	2013-present

EDITORIAL BOARDS

American Cancer Society
Clinical Care for Prostatic Disease
Clinical Genitourinary Cancer
Clinical Prostate Cancer
Journal of Clinical Oncology

NATIONAL RESPONSIBILITIES

American Society of Clinical Oncology (ASCO)	
Scientific Program Committee	2003-2005
Scientific Program Committee, ASCO Prostate Cancer Symposium	2004-2005
American College of Radiology Appropriateness Criteria Panel Member	2005-2008
Ad Hoc ASCO Prostate Cancer Guideline Review Panel	2006
Candidate for ASCO Nominating Committee	2008
Cancer Education Committee – Genitourinary Cancer Track	2008-2011
Candidate for Nominating Committee	2014
Member, Continuing Education Committee	2015-present
Chair, Continuing Education Committee	2017-2018
American College of Radiology (ACR)	
Consultant, Expert Panel on Radiation Oncology-Prostate	2008-2009
American Urological Association (AUA)	
Treatment of Localized Prostate Cancer Consensus Committee	2001
External peer reviewer for Localized Prostate Cancer Treatment Guidelines	2016
American Association of Cancer Research (AACR)	
Scientific Program Committee, 2018 AACR Annual Meeting	2017-2018
Society of Urologic Oncology (SUO)	2003
Consensus Panel on Hormone Refractory Prostate Cancer	
Southwest Oncology Group (SWOG)	
Oncology Discipline Chair, Genitourinary Committee	1993-present
Endpoints Review Committee, Prostate Cancer Prevention Trial	1998-2004
Specialized Program of Research Excellence in Prostate Cancer (SPORE)	
Pacific Northwest PC SPORE Clinical Core Director	2002-2012
Co-chair, InterSPORE Clinical Trials Concept Review Committee	2002-2005
National Comprehensive Cancer Network (NCCN)	
Member, Prostate Cancer Guidelines Panel	2010-present
NCCN/VA CRPC Curriculum Development Committee	2015
Panel Member, Value Pathways Task Force	2018-
National Cancer Institute (NCI)	
Member, SxQOL Drug Development Task Force	2008-2015
Prostate Cancer Working Group (PCWG)	
PSA Working Group	2001-2004
PCWG 2	2004-2008
PCWG 3	2011-2016
Prostate Cancer Foundation (PCF)	
Standing Review Committee	2010-present
PCF-Canada ASAP 2012	2012

PCF-Australia/Movember MRTA-3 review panel member	2012
PCF-Canada/Movember Transformational Science Award reviewer	2017
Eastern Cooperative Oncology Group Reverse Site Visit	2003
American Joint Committee on Cancer Genitourinary Task Force	2005-2007
West Hawaii Cancer Symposium Co-Chair and Co-organizer	2000-present
Treatment and the Focal Lesion Paradigm Consensus Panel Member, International Task Force on Prostate Cancer	2005-2006
International Bisphosphonate Summit Meeting Chair and Organizer	2002
UpToDate in Oncology Peer Review Board	2005-2006
Chapter Editor, Supportive Care for Prostate Cancer Patients	2019-present

INDEPENDENT DATA SAFETY MONITORING BOARDS

Member, 2 Millenium phase 3 trials	2010-2014
Member, SOTIO phase 3 trial	2014-present
Member, Alliance Foundation Trials (AFT)	2016-present
Member, Movember GAP 4 (INTERVAL)	2016-present
Chair, Advantagene phase 3 trial	2016-present

SCIENTIFIC STEERING COMMITTEES

Cell Genesys GVAX Steering Committee, global PI for VITAL 1 phase 3	2008-2009
Cougar Biotech (Abiraterone Acetate) Steering Committee	2008-2010
AstraZeneca (ENTHUSE/zibotentan) Steering Committee, global PI for phase 3	2008-2012
Medivation (STRIVE) Steering Committee	2010-2015
Dendreon (PROCEED Registry) Steering Committee	2010-present
Teva (OGX-011 Custirsen) Steering Committee, global co-PI with Chi and de Bono	2011-2016
Bayer Xofigo (REASSURE Registry) Steering Committee	2011-present
Bayer RA 223 Phase 3 Steering Committee, global co-PI with Matthew Smith	2013-present
MorphoSys (MOR209) Steering Committee	2011-present
Ferring (PRONOUNCE) Steering Committee	2015-present
Pfizer Talazoparib phase 2 Steering Committee	2016-present
Clovis (TRITON) Steering Committee	2016-present
Bayer (Xofigo) Real World Evidence Steering Committee	2019-Present

SCIENTIFIC ADVISORY BOARDS since 2010

Amgen (XGEVA denosumab) Advisory Board	2008-2011
Medivation (PREVAIL) Advisory Board	2010-2014
Bristol-Myers Squibb (IDEA) Advisory Board	2011
Genentech Prostate/Bladder Advisory Board	2011
Orion (ODM-201) Advisory Board	2012
Novartis – Prostate Cancer Advisory Board	2012
Dendreon Sequencing Therapy Advisory Board	2012
Veridex Steering Committee	2012-2013
Dendreon Data Mining/PDAAC	2013
Johnson & Johnson Cellsearch Advisory Board	2013
AbbVie – Lupron Advisory Board	2013
Ferring – Firmagon Intermittent Therapy	2013

Bayer ERA223 Advisory Board	2013-present
BHR – Estragel Advisory Board	2014
Astellas (XTANDI) Advisory Board	2014-2016
Astellas Global Medical Affairs Advisory Board	2015
Churchill Prostate Cancer Advisory Board	2015
Emergent (STRIVE/TERRAIN) Advisory Board	2015-2016
Blue Earth Diagnostics Advisory Board	2015-present
Dendreon Advisory Board	2016
Endocyte Advisory Board	2016-present
Asana BioSciences Advisory Board	2016-present
Orion Advisory Board	2017-present
Hinova Advisory Board	2018-present
Bayer – Darolutamide Global Aramis Advisory Board	2018-present
Novartis – PMSA	2019
Janssen – Apalutamide Advisory Board	2019
Ferring – FIRMAGON Advisory Board	2019
Carrick Therapeutics Advisory Board	2019

LOCAL RESPONSIBILITIES

State of Washington

American Cancer Society, Northwest Chapter	1998-2002
Washington State Prostate Cancer Coalition Task Force	2002-present

University of Washington/Fred Hutchinson

Institute for Prostate Cancer Research Committee	1999-2014
Sponsored Programs/Human Subjects Faculty Advisory Committee	2004-2006
Research Trials Office Oversight Committee	2002-2006

University of Washington Search Committees:

Associate Director of Clinical Research Division	2002-2005
Phase I Clinical Trials Director of Medical Oncology	2006-2007
Renal/Melanoma Faculty	2007-2008
Lung and Head and Neck Faculty	2008-2010

Seattle Cancer Care Alliance

Joint Oncology Planning Committee, GU Patient-Care Subcommittee	1999-2001
Space Planning Committee	2008-2010
SCCA Strategic Planning Committee	2008-2009

COMMUNITY SERVICE

Eastside Prostate Cancer Support Group	1997-present
Bellevue Rotary Club	1997
American Cancer Society, Northwest Chapter, Prostate Cancer Task Force	1998-2006
Northwest Hospital Prostate Cancer Support Group	1998
Northwest Prostate Cancer Foundation	2000
Washington State Prostate Cancer Coalition	2002-present
Tacoma Prostate Cancer Support Group	2006
UsTOO in Seattle	2010-present

INVITED TALKS AND LECTURES SINCE 2012

UNIVERSITY/LOCAL

1. Fred Hutchinson Cancer Research Center's 2nd Symposium on Cancer Survivorship for Clinicians: Monitoring and Managing the Side Effects of Androgen Deprivation Therapy for Prostate Cancer. Seattle, WA. February 2012.

2. "New approaches to androgen deprivation therapy", Virginia Mason GU Tumor Board, Virginia Mason Medical Center. Seattle, October 2012.
3. 12th Annual Pacific Northwest Prostate Cancer Conference, Seattle, WA. October 2012.
4. "Immunotherapy for Prostate Cancer", IPCR Symposium, Fred Hutchinson Cancer Research Center, Seattle, March 2013.
5. "Beyond hormonal therapy", PNW Prostate Cancer SPORE Retreat, Seattle, July 2013.
6. 13th Annual Pacific Northwest Prostate Cancer Conference, Seattle, September 2013.
7. PNW Prostate Cancer SPORE Retreat, Seattle, July 2014.
8. 14th Annual Pacific Northwest Prostate Cancer Conference, Seattle, September 2014.
9. "New Treatments on the Horizon" 15th Annual Pacific Northwest Prostate Cancer Conference, Seattle, September 2015.
10. "Androgen deprivation therapy and cardiovascular risk: What's the real story?" Fred Hutchinson Cancer Research Center, Grand Rounds, Seattle, April, 2016.
11. "Hormone therapy and cardiovascular risk: What do we know?" 16th Annual Pacific Northwest Prostate Cancer Conference, Seattle, September, 2016.
12. 15th Annual Pacific Northwest Prostate Cancer Conference, Seattle, September 2015.
13. 16th Annual Pacific Northwest Prostate Cancer Conference, Seattle, September 2016
14. 17th Annual Pacific

NATIONAL/INTERNATIONAL

1. ASCO GU Satellite Symposium. "Sequencing of New and Emerging Agents in mCRPC." San Francisco, CA. February 2012.
2. Fresenius Kabi AG, FORCE Meeting: The Evolving Treatment Paradigm for Castration Resistant Prostate Cancer. "Advances in supportive care for cancer management." Ho Chi Minh City, Vietnam. February 2012.
3. Fresenius Kabi AG, FORCE Meeting: Monitoring and Managing the Side Effects of Androgen Deprivation Therapy for Prostate Cancer. "Management of PSA Recurrent." Ho Chi Minh City, Vietnam. February 2012.
4. Clinical Care Options Satellite Symposium. "Metastatic prostate cancer case: Skeletal related events". ASCO Annual Meeting. Chicago, IL. June 2012.
5. Chinese Society of Clinical Oncology. "Optimal hormonal therapy for metastatic prostate Cancer" and "Current standard of practice after ASCO 2012: the evolving treatment paradigm prostate cancer". Best of ASCO China, Nanjing, China. July 2012.
6. Best of ASCO Satellite Symposium: Pathways to Progress in Castration-Resistant Prostate Cancer and Renal Cell Carcinoma: Practical Guidance for Clinicians. "Androgens still matter in castration resistant prostate cancer: targeting androgen signaling beyond castration resistance." San Diego, CA. August 2012.
7. 15th Annual West Hawaii Cancer Symposium. "Health Care Reform and Clinical Trials." Kailua-Kona, HI. September 2012.
8. MD Anderson Cancer Center Comprehensive Board Review Course. "Prostate Cancer 2012" Houston, TX. September 2012.
9. "Novel immunotherapeutic approaches in metastatic castration resistant prostate cancer". GU ASCO Satellite Symposium: Castration-Resistant Prostate Cancer, Important Questions, Encouraging Answers. Orlando, FL. February 2013.
10. "Leveraging the immune system in prostate cancer". GU ASCO Satellite Symposium: Research to Practice Symposium: A Live Investigator Think Tank. Orlando, FL. February 2013.
11. Gold Journal (*Urology*) Roundtable Resource Center. "Immunotherapy in clinical practice." Chicago, IL. February 2013. Urology on line <http://education.goldjournal.net/path.php?1396:0:Media:title:bxvcs>

12. "Latrogenic side effects of androgen deprivation therapy: a practical clinical approach" and "Systemic management of CRPC, Panel discussion". Issues and Controversies in Prostate Care 2013: Review of prostate cancer clinical trials. Whistler, BC. March 2013.
13. ASCO Satellite Symposium: The Team Quiz Challenge: Bone Modifying Agents in the Treatment of Cancer. Program Director. "Metabolic and skeletal complication of andrograph deprivation therapy." Chicago, IL. June 2013.
14. ASCO Satellite Symposium: Modern management of metastatic castration-resistant prostate cancer in 2013 and beyond: navigating the successes, hurdles, and practicalities. "Immunotherapy for Advanced Prostate Cancer: Current status and future potential." Chicago, IL. June 2013.
15. ASCO Education Session, Androgen Deprivation Therapy for Prostate Cancer. "Metabolic and skeletal complications of androgen deprivation therapy." Chicago, IL. June 2013.
16. "Intermittent androgen deprivation: Recommendations." NCCN Prostate Cancer Panel meeting. Philadelphia, PA. June 2013.
17. "Prostate cancer 2013: a case based review", 23rd Annual Mayo Clinic Hematology Oncology Reviews, Amelia Island, FL. August 2013.
18. "New Treatment Options for Metastatic Prostate Cancer", 16th Annual West Hawaii Cancer Symposium, Kailua-Kona, HI. September 2013.
19. "Holistic Approach to PCa Therapy: A Multidisciplinary Opportunity." Chair, AbbVie Advisory Board. Vancouver, BC. September 2013.
20. "Overall survival benefit with Radium-223: Pre and post docetaxel." and "Novel immunotherapeutic approaches in Prostate Cancer." 1st International State-of-the-Art Uro-Oncology Conference on Prostate and Kidney Cancers, EUOG, Amsterdam, Netherlands. September 2013.
21. "Identifying common molecular features of ERG positive tumors in primary and castration-resistant prostate cancer", Annual Prostate Cancer Foundation Retreat, National Harbor MD. October 2013.
22. "Real-world experience with Sipuleucel-T in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) ≥80 years-old: data from PROCEED", Western AUA Conference, Monterey CA. November 2013.
23. "Use of intermittent androgen deprivation therapy based on mathematical modeling of PSA and other parameters", Mathematical Modeling Workshop, Institute of Industrial Science, University of Tokyo Japan. December 2013.
24. "Non-hormone Therapy for Metastatic Castration-Resistant Prostate Cancer: Chemotherapy, Bone-Targeted Treatments and Others", Scripps 34th Annual Conference of Clinical Hematology & Oncology, San Diego CA. February 2014.
25. "Advancing the Standard of Cancer Care: New Developments in the Treatment of Hormone Refractory Prostate Cancer", NCCN Annual Meeting, Fort Lauderdale, Florida. March 2014.
26. "Radium-223 for the treatment of metastatic castration resistant prostate cancer." ERA-223 Investigator Meeting. San Diego, CA. April 2014.
27. "On the Shoulders of Giants – Prostate Cancer Therapy: How Did We Get Here and Where Are We Going" Topic: Immunotherapy for Prostate Cancer, ASCO Annual Meeting, Chicago. May 2014.
28. "New developments in the treatment of metastatic castration resistant prostate cancer." And "The evolving role of chemotherapy for metastatic castration resistant prostate cancer." Mexican Urologic Oncology Society Annual Meeting. Acapulco, Mexico. July 2014.
29. MD Anderson Cancer Center Comprehensive Board Review Course. "Prostate Cancer 2014" Houston, TX. September 2014.
30. "Effect of prior abiraterone or enzalutamide on sipuleucel-T manufacture in PROCEED Registry patients." Western Section AUA Meeting. Maui, HI. October 2014.
31. Movember Foundation Revolutionary Team 3 Award Grant Review. Panel member. Sydney Australia. November 2014.

32. "Prostate Cancer, a glance at the near future." 1st International Geriatric Oncology Meeting. Rome, Italy. December 2014.
33. "Advanced Prostate Cancer: using Sip-T first in mCRPC", Dendreon National Sales Meeting, Santa Barbara, CA. January 2015.
34. ASCO CME Committee meeting. Alexandria, VA. February 2015.
35. "Novel Therapies: Radiopharmaceuticals for Castration-Resistant Prostate Cancer", New York GU, 8th Annual Interdisciplinary Congress, New York, NY. March 2015.
36. Panelist for the OncLive TV Peer Exchange Channel. Expert Panel Discussion: "Management of mCRPC; A Practical Review of Guideline Updates and Case Study Perspectives" (video). New Orleans, LA. May, 2015
37. "STRIVE, A Multicenter Phase 2 Study of Enzalutamide versus Bicalutamide in Men with Nonmetastatic or Metastatic Castration-Resistant Prostate Cancer." AUA Annual Meeting, Plenary Session. New Orleans, LA. May 2015.
38. ASCO Post Interviewer. ASCO Annual Meeting, Chicago, IL. June 2015
39. "Advances in hormonal therapy for prostate cancer over the last five years." Regional Summit on Practical and Emerging Trends in Genitourinary Malignancies, San Francisco, CA. June 2015.
40. "Implementation of the Prostate Cancer Supportive Care Program, A Comprehensive Approach for Men with Prostate Cancer and Their Partners." Multinational Association of Supportive Care in Cancer Annual Meeting. Copenhagen, Denmark. June 2015.
41. "Radium 223 Benefit in Castration Resistant Prostate Cancer", 33rd National Congress in Oncology, Mexican Society of Oncology. Cancun, Mexico. October 2015.
42. "Changing landscape in early castration-resistant prostate cancer." Astellas Advisory Board Meeting. Budapest, Hungary. November 2015.
43. FDA "Type A" Meeting (Churchill Pharma). Silver Spring, MD. November 2015.
44. "Androgen Deprivation Therapy: What's the real story about cardiovascular risk?", Provincial Tumour Group Meeting. Vancouver, Canada. November 2015.
45. Movember Prostate Cancer Outcomes: Global Initiative to Compare and Reduce Variation. Delegate. Culver City, CA. December 2015.
46. "Analysis of the PROCEED registry by baseline prostate-specific antigen (PSA) quartiles: Preliminary analysis of real-world sipuleucel-T (sip-T) use." Poster presentation. ASCO-GU Symposium. San Francisco, CA. January 2016.
47. Session 7: Testicular Cancer. Session Monitor. ASCU-GU Symposium. San Francisco, CA. January 2016.
48. "Successful implementation of a disease-specific survivorship program for men with prostate cancer (PC) and their partners." Poster presentation. 2016 Cancer Survivorship Symposium: Advancing Care and Research. San Francisco, CA. January 2016.
49. "Utilization of sexual health and pelvic floor physiotherapy services in Vancouver's Prostate Cancer Supportive Care (PCSC) Program. 2016 Cancer Survivorship Symposium: Advancing Care and Research. San Francisco, CA. January 2016.
50. "Management of metastatic prostate cancer." Mayo Clinic: Clinical and Multidisciplinary Hematology and Oncology 2016 13th Annual Review. Scottsdale, AZ. January 2016.
51. ASCO CME Subcommittee Meeting. Alexandria, VA. February 2016.
52. "Integrating immunotherapy in the management of metastatic castration resistant prostate cancer." And "Challenging Case Debates." New York GU, 9th Annual Interdisciplinary Congress, New York, NY. March 2016.
53. "Prostate Cancer: A Discussion of the Latest Developments to Change Care in the Oncology Clinic." Program Director: Optimizing the Treatment of Advanced Prostate Cancer: Expert Review of the Latest Data and Guideline Recommendations. CCO/ NCCN Satellite Symposium at ASCO. Chicago, IL. June 2016.
54. "Utilization of sexual health and pelvic floor physiotherapy services in Vancouver's Prostate Cancer Support Care Program." Poster presentation. ASCO Annual Meeting. Chicago, IL. June 2016.

55. Prostate Cancer Co-chair. 2nd RIMOG New and Emerging Therapeutic Options in Geriatric Oncology Meeting. Florence, Italy. July 2016.
56. "Arv-7 Story and clinical implications." 17th Asia-Pacific Prostate Cancer Conference. Melbourne, Australia. August/September, 2016.
57. "ADT and Cardiovascular Risk." 17th Asia-Pacific Prostate Cancer Conference. Melbourne, Australia. August/September, 2016.
58. "Successful Implementation of a Prostate Cancer Survivorship Program." 17th Asia-Pacific Prostate Cancer Conference. Melbourne, Australia. August/September, 2016.
59. "Pain and the Prostate Cancer Patient." 17th Asia-Pacific Prostate Cancer Conference. Melbourne, Australia. August/September, 2016.
60. MD Anderson Cancer Center Comprehensive Board Review Course. "Prostate Cancer 2016" Houston, TX. September 2016.
61. Module 2: "Sequence and Selection of Secondary Hormonal Therapy, Immunotherapy and Cytotoxic Therapy for Patients with mCRPC", Research to Practice Satellite Symposium - Cases from the Community: Clinical Investigators Provide their Perspectives on Emerging Research and Actual Patients with Advanced Prostate Cancer. Orlando, FL. February, 2017.
62. "The changing landscape of metastatic castration-resistant prostate cancer." Genentech Grand Rounds. San Francisco, CA. February 2017.
63. "Update of On-going phase 3 trials in metastatic hormone sensitive prostate cancer." 2nd Advanced Prostate Cancer Consensus Conference (APCCC). St. Gallen, Switzerland. March, 2017.
64. "Isotope therapy and PARP inhibitors for advanced prostate cancer." and "Case debates: best practices." New York GU, 10th Annual Interdisciplinary Congress, New York, NY. March 2017.
65. "Best practices for the management of metastatic castration-resistant prostate cancer across the disease continuum." Practicing Clinicians Exchange (PCE) Symposium. Anaheim, CA. March 2017.
66. "Personalized sequencing in castration-resistant prostate cancer." PER Medical Crossfire Symposia. Chicago, IL. June 2017.
67. "The changing treatment landscape for metastatic castration-resistant prostate cancer" and "Considerations for sequencing of therapy for metastatic castration resistant prostate cancer." Japanese Society of Medical Oncology. Kobe, Japan. June 2017.
68. "The changing landscape of metastatic prostate cancer over the last 20 years." West Hawaii Cancer Symposium. Kona, HI. September 2017.
69. MD Anderson Cancer Center Comprehensive Board Review Course. "Prostate Cancer" Houston, TX. September 2017.
70. "Updates in Prostate Cancer: New Cancer Drugs." Seventh Annual Prostate Cancer Advocacy Symposium: A National Summit. Detroit, MI. September 2017.
71. "Treatment decisions in a new therapeutic landscape in men with mCRPC." Thai Society of Clinical Oncology Symposium. Bangkok, Thailand. November 2017.
72. "Focus on Safety Issues of Newer Hormonal Therapies." prIME Oncology CME-certified Symposium: Hormonal Therapy in Prostate Cancer: Improving Clinical Outcomes in Metastatic and Non-Metastatic Disease. San Francisco, CA. February 2018.
73. "Early Use of Systemic Therapy: Abiraterone Versus Docetaxel for Hormone-Sensitive Prostate Cancer." New York GU: 11th Annual Interdisciplinary Prostate Cancer Congress and Other Genitourinary Malignancies. New York, NY. March 2018.
74. "Prostate Cancer Disparities: Focus on African American Men." American Association for Cancer Research (AACR) Annual Meeting 2018. Chicago, IL. April 2018.
75. "Role of Data Monitoring Committees in Complicated Trials." Society for Clinical Trials (SCT) Annual Meeting. Portland, OR. May, 2018.

76. "Balancing Toxicities, and Therapeutics Perspective." 2018 ASCO Annual Meeting Session: Metastatic Prostate Cancer Tumor Board: Optimizing Patient Selection and Treatment. Chicago, IL. June 2018.
77. "Off Protocol Treatment of Oligometastatic Hormone Sensitive or CRPC Disease with SRRT." Asia-Pacific Prostate Cancer Conference (APCC). Brisbane, Australia. August 2018.
78. "Implementation of an Electronic Patient Reported Outcome System in the Prostate Clinic at the Vancouver Prostate Centre." Asia-Pacific Prostate Cancer Conference (APCC). Brisbane, Australia. August 2018.
79. "Hormone Sensitive Metastatic Disease: Treatment Options." Asia-Pacific Prostate Cancer Conference (APCC). Brisbane, Australia. August 2018.
80. "New Options in MO CRPC – Who (if anybody) needs treatment." Asia-Pacific Prostate Cancer Conference (APCC). Brisbane, Australia. August 2018.
81. "Current Data & Takeaways: Radium-223's Role as a Life-Prolonging Agent." ESMO 2018 Industry Satellite Symposium. Munich, Germany. October 2018.
82. "To Screen or Not to Screen – That is the Question." The University of Massachusetts Medical School Grand Rounds. Worcester, MA. October 2018.
83. "Biologic Rationale for Next-Generation AR Inhibitors." Global Summit on Genitourinary Malignancies. Banff, Canada. November 2018.
84. "A Walk in the PARP: Therapeutic Strategies Targeting DNA Repair Defects in Prostate Cancer." ASCO GU 2019 Clinical Care Options Satellite Symposium, Program Director. San Francisco, CA. February, 2019.
85. "DNA Repair in Prostate Cancer (PARP Inhibitors)." New York GU: 12th Annual Interdisciplinary Prostate Cancer Congress and Other Genitourinary Malignancies. New York, NY. March 2019
86. "Prostate Cancer Diagnosis and Treatment: What's new in 2019?" American College of Physicians (ACP) Internal Medicine Meeting. Philadelphia, PA. April 2019.
87. "The Changing Landscape of Castration Resistant Prostate Cancer." Industry Global Web Seminar, Keynote Speaker, Seattle, WA / Tokyo, Japan. May, 2019.
88. "Next Generation Advanced, mCRPC and nmCRPC." 20th Future Directions in Urology Symposium: Directions for the Next Generation of Treatments. Session discussant. Colorado Springs, CO. August 2019.
89. "Node-Positive Prostate Cancer (N1 but M0)." Advanced Prostate Cancer Consensus Conference (APCCC). Session 2 Co-Chair. Basel Switzerland. August 2019.
90. "Management of Castration-Resistant Prostate Cancer – Treatment of nmCRPC debate." Advanced Prostate Cancer Consensus Conference (APCCC). Session 6. Basel Switzerland. August 2019.
91. "New Perspectives in Non-metastatic CRPC." 3rd Annual Global Summit on Genitourinary Malignancies. Banff, Canada. October 2019

PEER-REVIEWED PUBLICATIONS

1. Tallman MS, McGuffin RW, Higano CS, Starkebaum G, Collins SJ, Johnston H, Singer JW, Perry DJ, Kunath A. Bone marrow transplantation in a patient with myelodysplasia associated with diffuse eosinophilic fascitis. *Am J Hematol*. 1987 24(1):93-99.
2. Abdel-Nabi HH, Schwartz AN, Higano CS, Wechter DG, Unger MW. Colorectal carcinoma: Detection with indium-111 anticarcinoembryonic-antigen monoclonal antibody ZCE-025. *Radiology*. 1987 164(3):617-621.
3. Livingston RB, Griffin BR, Higano CS, Laramore GE, Rivkin SE, Goldberg RS, Schulman SF. Combined treatment with chemotherapy and neutron irradiation for limited non-small cell lung cancer: A Southwest Oncology Group Study. *J Clin Oncol*. 1987 5(11):1716-1724.
4. Mortimer JE, Higano CS. Continuous infusion 5-fluorouracil and folinic acid in disseminated colorectal cancer. *Cancer Invest*. 1988 6(2):129-132.

5. Tallman MS, Nemunaitis JJ, McGuire TR, Yee GC, Hughes TE, Almgren JD, Appelbaum FR, Higano CS, McGuffin RW, Singer JW, Thomas ED. Comparison of two intravenous cyclosporine infusion schedules in marrow transplant recipients. *Transplantation*. 1988 45(4):810-813.
6. McGuire TR, Tallman MS, Yee GC, Nemunaitis JJ, Higano CS, McGuffin RW, Singer JW. Influence of infusion duration on the efficacy and toxicity of intravenous cyclosporine in bone marrow transplant patients. *Transplant Proc*. 1988 20(3 Suppl 3):501-504.
7. Russell KJ, Boileau MA, Ireton RC, Higano CS, Collins C, Koh WJ, Griffin BR, Chapman WH, Griffin TW. Transitional cell carcinoma of the urinary bladder: histologic clearance with combined 5-FU chemotherapy and radiation therapy. Preliminary results of a bladder-preservation study. *Radiology*. 1988 167(3):845-848.
8. Griffin BR, Livingston RB, Stewart GR, Higano CS, Russell KJ, Griffin TW, Laramore GE. Prophylactic cranial irradiation for limited non-small cell lung cancer. *Cancer*. 1988 62(1):36-39.
9. Collins C, Higano CS, Livingston RB, Griffin BR, Keppen MD, Miller TP. Cyclophosphamide, vincristine, cisplatin, VP-16 and radiation therapy in extensive small-cell lung cancer. A Southwest Oncology Group study. *Cancer Chemother Pharmacol*. 1989 24(2):128-132.
10. Higano CS, Livingston RB. Oral dipyridamole and methotrexate in human solid tumors: a toxicity trial. *Cancer Chemother Pharmacol*. 1989 23(4):259-262.
11. Jacobson AF, Cerqueira MD, Breitz HB, Whitley MA, Higano CS. Pleuroperitoneal communication associated with malignant ascites. A potential cause for new pleural effusion suggestive of pulmonary embolism. *Clin Nucl Med*. 1990 May; 15(5):317-320.
12. Bianco JA, Higano CS, Singer JW, Appelbaum FR, McDonald GB. The somatostatin analog octreotide in the management of the secretory diarrhea of the acute intestinal graft-versus-host disease in a patient after bone marrow transplantation. *Transplantation*. 1990 49(6):1194-1195.
13. Higano CS, Brixey M, Bryant EM, Durnam DM, Doney K, Sullivan KM, Singer JW. Durable complete remission of acute nonlymphocytic leukemia associated with discontinuation of immunosuppression following relapse after allogeneic bone marrow transplantation: A case report of a graft-versus-leukemia effect. *Transplantation*. 1990 50(1):175-177.
14. Bianco JA, Pepe MS, Higano CS, Appelbaum FR, McDonald GB, Singer JW. Prevalence of clinically relevant bacteremia following upper gastrointestinal endoscopy in bone marrow transplant recipients. *Am J Med*. 1990 89(2):134-136.
15. Russell KJ, Boileau MA, Higano CS, Collins C, Russell AH, Koh WJ, Cole SB, Chapman WH, Griffin TW. Combined 5-fluorouracil and irradiation for transitional cell carcinoma of the urinary bladder. *Int J Radiat Oncol Biol Phys*. 1990 19(3):693-699.
16. Abdel-Nabi HH, Schwartz AN, Wechter DG, Higano CS, Ortman-Nabi JA, Unger MW. Scintigraphic detection of gastric and pancreatic carcinomas with In-111 ZCE 025 monoclonal antibody. *World J Surg*. 1991 15(1):122-127.
17. Nemunaitis J, Buckner CD, Appelbaum FR, Higano CS, Mori M, Bianco J, Epstein C, Lipani J, Hansen J, Storb R, et al. Phase I/II trial of recombinant human granulocyte-macrophage colony-stimulating factor following allogeneic bone marrow transplantation. *Blood*. 1991 77(9):2065-2071.
18. Higano CS, Crowley J, Livingston RB, Goodwin JW, Barlogie B, Stuckey WJ. A weekly cisplatin-based induction regimen for extensive non-small cell lung cancer. A Southwest Oncology Group study. *Cancer*. 1991 67(10):2439-2442.
19. Nemunaitis J, Meyers JD, Buckner CD, Shannon-Dorcy K, Mori M, Shulman H, Bianco JA, Higano CS, Groves E, Storb R, Hansen J, Appelbaum FR, Singer JW. Phase I trial of recombinant human macrophage colony-stimulating factor in patients with invasive fungal infections. *Blood*. 1991 78(4):907-913.
20. Higano CS, Goodman P, Craig JB, Kish JA, Rivkin SE, Wolf M, Crawford ED. Phase II evaluation of amonafide in renal cell carcinoma. A Southwest Oncology Group study. *Invest New Drugs*. 1991 9(4):361-363.
21. Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991 324:1685-1690.
22. Case DC Jr, Gerber MC, Gams RA, Crawford J, Votaw ML, Higano CS, Pruitt BT, Gould J. Phase II study of intravenous idarubicin in unfavorable non-Hodgkin's lymphoma. *Cancer Res*. 1992 52(14):3871-3874.

23. Hommeyer SC, Teefey SA, Jacobson AF, Higano CS, Bianco JA, Colacurcio CJ, McDonald GB. Venooclusive disease of the liver: prospective study of US evaluation. *Radiology*. 1992 184(3):683-686.
24. Higano CS, Raskind WH, Singer JW. Use of alpha interferon for treatment of relapse of chronic myelogenous leukemia in chronic phase after allogeneic bone marrow transplantation. *Blood*. 1992 80(6):1437-1442.
25. Higano CS, Raskind WH, Singer JW. Use of interferon alfa-2a to treat hematologic relapse of chronic myelogenous leukemia after bone marrow transplantation. *Acta Haematol*. 1993;89 Suppl 1:8-14.
26. Wolf GT, Fisher SG, Department of Veterans Affairs Laryngeal Cancer Study Group. Effectiveness of salvage neck dissection for advanced regional metastases when induction chemotherapy and radiation are used for organ preservation. *Laryngoscope*. 1992 102:934-939.
27. Case DC Jr, Gerber MC, Gams RA, Crawford J, Votaw ML, Higano CS, Pruitt BT, Gould J. Phase II study of intravenous idarubicin in unfavorable non-Hodgkin's lymphoma. *Leuk Lymphoma*. 1993 10 Suppl:73-79.
28. Jacobson AF, Teefey SA, Lee SP, Hollister MS, Higano CS, Bianco JA. Frequent occurrence of new hepatobiliary abnormalities after bone marrow transplantation: results of a prospective study using scintigraphy and sonography. *Am J Gastroenterol*. 1993 88(7):1044-1049.
29. Jacobson AF, Teefey SA, Higano CS, Bianco JA. Increased lung uptake of 99Tcm-sulfur colloid as an early indicator of the development of hepatic veno-occlusive disease in bone marrow transplant patients. *Nucl Med Commun*. 1993 14(8):706-711.
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33. Higano CS, Ellis WJ, Russell K, Lange PH. Intermittent androgen suppression with leuprolide and flutamide for prostate cancer: a pilot study. *Urology*. 1996 48(5):800-804.
34. Higano CS, Crowley JJ, Veith RV, Livingston RB. A phase II trial of intravenous vinorelbine in previously untreated patients with extensive small cell lung cancer, a Southwest Oncology Group study. *Invest New Drugs*. 1997 15(2):153-156.
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39. Deck AJ, True LD and Higano CS. Tricuspid valve metastasis from testicular carcinoma: a case report and review of the literature. *Urology*. 2000 56(2):330.
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versus AA alone as first-line therapy for castration-resistant prostate cancer (CRPC) with bone metastases (BM) in an international multicenter database. *J Clin Oncol* 38, 2020 (suppl 6; abstr 30). Poster presentation. ASCO 2020 Genitourinary Cancers Symposium, San Francisco, CA. February 2020.

339. De Bono JS, Mehra N, Higano CS, Saad F, Buttiglieri C, Mata M, Chen HC, Healy CG, Paccagnella ML, Czibere A, Fizazi K. TALAPRO-1: A phase II study of talazoparib (TALA) in men with DNA damage repair mutations (DDRmut) and metastatic castration-resistant prostate cancer (mCRPC)—First interim analysis (IA). *J Clin Oncol* 38, 2020 (suppl 6; abstr 119). Poster presentation. ASCO 2020 Genitourinary Cancers Symposium, San Francisco, CA. February 2020.
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HIGANO SUPPORT

GRANTS - Current

W81XH-16-PCRP-CCRSA (Higano)

09/30/2017 – 09/29/2021

DOD Prostate Cancer Research Program

USA Med Research Acq Activity I Dana Herndon I 820 Chandler St
Fort Detrick, MD 21702-5014

Prostate Cancer Clinical Trials Consortium – Member Site

The Department of Defense provides funding for infrastructure to participate as a clinical site in the Prostate Cancer Clinical Trials Consortium.

Role: Clinical Site PI

CLINICAL TRIAL CONTRACTS - Current

Protocol # D4620C00001 (Higano)

10/01/2013 - 04/30/2021

AstraZeneca AB

1800 Concord Pike | Wilmington, DE 19850

A Phase I, Open-label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumor Activity of Ascending Doses of AZD8186 in Patients with Advanced Castrate-resistant Prostate Cancer (CRPC), Squamous Non-Small Cell Lung Cancer (sqNSCLC), Triple Negative Breast Cancer (TNBC) and Patients with Known PTEN-deficient Advanced Solid Malignancies, with Expansion to Assess the Pharmacodynamic Activity of AZD8186 within Prospectively-validated PTEN-deficient Tumors

The primary goal is to investigate the safety and tolerability of AZD8186 when given orally to patients with advanced castrate-resistant prostate cancer (CRPC), squamous non-small cell lung cancer (NSCLC) and triple negative breast cancer (TNBC) and known PTEN-deficient advanced solid malignancies.

Role: Site PI

Protocol # 15396 (Higano)

09/17/2014 - 09/16/2020

Bayer Health Care

Montville, NJ

A phase III randomized, double-blind, placebo-controlled trial of Radium-223 dichloride in combination with abiraterone acetate and prednisone/ prednisone in the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve subjects with bone predominant metastatic castration-resistant prostate cancer (CRPC)

The primary goal is to compare, in subjects with asymptomatic or mildly symptomatic chemotherapy-naïve bone predominant metastatic castration-resistant prostate cancer, the clinical benefit of radium-223 dichloride versus placebo in combination with abiraterone and prednisone/prednisolone.

Role: Global PI/Site PI

Protocol # 16913 (Higano)

03/16/2016 - 02/29/2024

Bayer Health Care

Kelly Peters | Katnar Health, LLC | 11960 Westline Industrial Dr, Ste 180 | St. Louis, MO 63149

REASSURE – Radium-223 alpha Emitter Agent in Safety Study in mCRPC population for long-term evaluation

The primary goal is to assess the incidence of second primary malignancies among patients with metastatic Castration

Resistant Prostate Cancer (mCRPC) receiving Radium-223 in routine clinical practice.

Role: Site PI

Protocol # B7791001 (Higano)

04/18/2016 - 04/30/2021

Pfizer

Megan Shannon | 235 East 42nd Street | New York, NY 10017

A Phase 1 Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Escalating Doses of a Vaccine-based Immunotherapy Regimen (VBIR) for Prostate Cancer (PF-06753512)

The primary goal is to assess safety and tolerability of increasing dose levels of the prostate cancer vaccine-based immunotherapy regimen (PrCa VBIR) components.

Role: Site PI

Protocol # B030013 (Higano)

03/16/2017-03/15/2022

Hoffman LaRoche

Prasanna Bhende | Covance | 206 Carnegie Center | Princeton, NJ 08540

A Phase IB, Open-Label Study of the Safety and Tolerability of Atezolizumab in Combination with Radium-223 Dichloride in Patients with Castrate-Resistant Prostate Cancer Who Have Progressed Following Treatment with an Androgen Pathway Inhibitor

The primary goals are to assess the safety and tolerability of atezolizumab when given in combination with radium-223 dichloride in patients with mCRPC and to identify a recommended treatment schedule.

Protocol # 9785-CL-0123 (Higano)

03/20/2017 – 05/31/2022

Astellas Pharma Global Development, Inc

Courtney Paul (INC Research) | 4800 Falls of Neuse Rd, Suite 600 | Raleigh, NC 27609

A Phase 2 Open-label Extension Study for Subjects With Prostate Cancer Who Previously Participated in an Enzalutamide Clinical Study

The primary goal of the study is to provide access to continued treatment for subjects who are currently participating in an enzalutamide clinical study, sponsored by Astellas or Medivation, for their prostate cancer and who are continuing to derive clinical benefit based on the assessment of the investigator.

Protocol # CO-338-063 (Higano)

08/21/2018-04/30/2023

Clovis Oncology, Inc

Anthony Golsorkhi, MD | Clovis Oncology | San Francisco, CA

TRITON3: A Multicenter, Randomized, Open-label Phase 3 Study of Rucaparib versus Physician's Choice of Therapy for Patients with Metastatic Castration-resistant Prostate Cancer Associated with Homologous Recombination Deficiency

The primary goal of the study is to assess the efficacy of rucaparib versus physician's choice of treatment based on radiographic progression free survival (rPFS0 in mCRPC patients with HRD who progressed on prior AR-directed therapy and have not yet received chemotherapy in the castration-resistant setting.

Protocol # 000108 (Higano)

11/21/2018-07/31/2023

Ferring Pharmaceuticals

Ashley Underhill (IQVIA) | 4820 Emperor Blvd, Q Plaza Room 895E | Durham, NC 27703

A Multi-Center, Randomized, Assessor-Blind, Controlled Trial Comparing the Occurrence of Major Adverse Cardiovascular Events (MACEs) in Patients with Prostate Cancer and Cardiovascular Disease Receiving Degarelix (GnRH Receptor Antagonist) or Leuprolide (GnRH Receptor Agonist)

The primary goal of the study is to assess the effect of a GnRH receptor antagonist on the risk of occurrence of MACEs as compared to GnRH receptor agonist in patients with prostate cancer and cardiovascular disease.

Protocol # eFT508-0009 (Higano)

01/11/2019-12/31/2023

eFFECTOR Therapeutics

Angela White (Medpace) | 5375 Medpace Way | Cincinnati, OH 45240

A Phase 2 Non-randomized Open-label Study Examining the Effect of eFT508 in Patients with Advanced Castrate-resistant Prostate Cancer (CRPC)

The primary goal of the study is to assess the anti-tumor response of eFT508 in advanced CRPC.

Protocol # 18-150 (Higano)

04/24/2019-09/30/2020

Memorial Sloan Kettering Cancer Center/Bayer Pharmaceuticals

Melanie Chen (MSKCC) | 1275 York Ave | New York, NY 10065

Phase III Trial of Docetaxel vs. Docetaxel and Radium-223 for Metastatic Castration-Resistant Prostate Cancer (mCRPC)

The primary goal of the study is to compare overall survival for subjects treated with docetaxel versus subjects treated with docetaxel plus radium-223.

CLINICAL TRIAL CONTRACTS - Pending

Protocol # HC1119-CS-03 (Higano)

Hinova Pharmaceuticals (USA) Inc.

April Gadow (PPD) | 3900 Paramount Parkway | Morrisville, NC 27650

PROCADE: A Multinational, Phase 3, Randomized, Double-Blind, Non-Inferiority, Efficacy and Safety Study of Oral HC-1119 versus Enzalutamide in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

The primary goal of the study is to determine the efficacy of HC-1119 as compared to enzalutamide as assessed by overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) until Week 24.

Protocol # BAY 88-8223/16996 (Higano)

Bayer AG

Sondra Giovannelli (Covance) | 206 Carnegie Center | Princeton, NJ 08540

PROCADE: A Multinational, Phase 3, Randomized, Double-Blind, Non-Inferiority, Efficacy and Safety Study of Oral HC-1119 versus Enzalutamide in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

The primary goal of the study is to determine the efficacy of HC-1119 as compared to enzalutamide as assessed by overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) until Week 24.

Protocol # ARV-110-mCRPC-101 (Higano)

Arvinas, Inc

Spencer Hubbard (IQVIA) | 395 Winchester Ave | New Haven, CT 06511

A phase 1, open-label, dose escalation clinical trial to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of ARV-110 in patients with metastatic castration-resistant prostate cancer who have progressed on at least two prior systemic therapies

The primary goal of the study is to evaluate the safety and tolerability of ARV-110 in successive cohorts of patients with prostate cancer in order to estimate the maximum tolerated dose or maximum administered dose and select the recommended Phase 2 dose/schedule.

Protocol # BAY 1841788/20609 (Higano)

Bayer HealthCare Pharmaceuticals

Teri Bozowski (Theradex) | 100 Bayer Boulevard | Whippany, NJ 07981

A randomized, open-label, multicenter, Phase 2b study to evaluate physical function, including balance and daily activity, in participants with castration-resistant prostate cancer treated with darolutamide or enzalutamide

The primary goal of the study is to compare the effects of treatment with darolutamide vs. enzalutamide on **physical function** as assessed by the Timed Up and Go (TUG) test in participants with castration-resistant prostate cancer

GRANTS - Prior

Early Phase Clinical Research Support (Higano)

01/01/2019-12/31/2019

Seattle Translational Tumor Research (NCI P30 CA015704-41)

Heidi Tham | 1100 Fairview Ave N | Seattle, WA 98109

Mechanisms of Metabolic and Hormone Action on Plaque Formation in Brain and Carotid Vessels in Men Undergoing Androgen Deprivation Therapy

The primary goal is to measure the impact of androgen deprivation on metabolic, brain and cardiovascular endpoints.

Role: PI

PCF Challenge Award (Febbo/Higano)

09/01/2011 – 07/31/2019

Prostate Cancer Foundation

Howard R Soule, PhD | 1250 Fourth St | Santa Monica, CA 90401

A Pilot Study of the Effects of Cabozantinib (XL184) on Bone Turnover and the Microenvironment in Men with Non-Metastatic and Metastatic Castration-Resistant Prostate Cancer

The primary goal is to assess the impact of cabozantinib on markers of bone turnover and microenvironment in men with no evidence of bone metastases.

Role: Co-PI

D2017-1893 Movember Discovery Grant (Brotto)

01/01/2017 – 06/30/2019

Prostate Cancer Canada

Stuart Edmonds | 2 Lombard St 3rd Flr | Toronto, ON M5C 1M1

Innovations in the treatment of sexual dysfunction and couple intimacy after prostate cancer: A randomized trial of mindfulness versus cognitive behavioural therapy.

Role: Co-PI

W81XWH-09-1-0144 (Higano)

12/25/2014 - 09/29/2017

DOD Prostate Cancer Research Program

Activity

Dana Herndon | 820 Chandler St | Fort Detrick, MD 21702-5014

Prostate Cancer Clinical Trials Consortium – Member Site

The Department of Defense provides funding for infrastructure to participate as a clinical site in the Prostate Cancer Clinical Trials Consortium. Role: Clinical Site PI

W81XWH-BAA-11-1 (Basch)

11/06/2013 - 2/28/2017

UNC-Chapel Hill (DoD flow through)

Mark Kramer | 450 West Drive, CB 7295 | Chapel Hill, NC 27599

DOD Prostate Cancer Research Program: Observational Longitudinal Study of Pain in Men with Metastatic Castrate-Resistant Prostate Cancer

The primary goal is to estimate the proportion of pain palliation responders and the proportion experiencing pain progression

as measured by items from the Brief Pain Inventory (BPI) among patients with metastatic castrate-resistant prostate cancer starting systemic therapy.

Role: Site PI

W81XWH-09-1-0144 (Higano)

04/01/2009-12/31/2014

DOD Prostate Cancer Research Program

USA Med Research Acq Activity | Dana Herndon | 820 Chandler St

Fort Detrick, MD 21702-5014

Prostate Cancer Clinical Trials Consortium – Member Site

The Department of Defense provides funding for infrastructure to participate as a clinical site in the Prostate Cancer Clinical Trials Consortium. Role: Clinical Site PI

U19 AT-006028-03 (Standish)

09/29/2010-08/31/2013

Bastyr/UW Oncomycology Research Center

Bastyr University | Marie Kirkman | 14500 Juanita Dr NE, Room 459 | Seattle, WA 98028-4966

Project 2 (Higano/Wenner):

Enhancing innate immunity by combining PSK with docetaxel in prostate cancer

The primary goal of this phase 1 study is to establish the MTD of PSK alone and in combination with docetaxel and to study the immune effects of each alone and in combination.

Role: Project 2 Co-PI

R01 CA 120933 (Cherrier)

08/07/2007-5/31/2013

NIH/NCI

Assessment of Cognitive and Mood Effects from ADT in Men with Prostate Cancer

The primary goal of this project is to assess the affects of androgen deprivation therapy on mood, information processing, and quality of life

Role: Co-Investigator

P50 CA 097186-06 (Nelson)

09/14/2007-8/31/2012

Fred Hutchinson Cancer Research Center (NIH/NCI flow through)

Jill Lauson | 1100 Fairview Ave N | Seattle, WA 98109

Pacific Northwest Prostate Cancer SPORE

Clinical Core D (Higano)

The major goals of this project are to design and execute clinical trials relevant to SPORE projects, to support and enhance the CAISIS clinical data repository, and to support and engage the SPORE Advocacy Committee in SPORE activities in the Pacific Northwest.

Role: Director Clinical Core D

P50 CA 097186 (Lange)

09/01/02-08/31/07

NIH/NCI

Pacific Northwest Prostate Cancer Specialized Program of Research Excellence (SPORE)

The main goal of this project is to understand the molecular biology of prostate cancer through all stages of its progression.

Focus will be on analyzing gene and protein expression in the entire spectrum of prostate tumors, from those clinically localized and slow-growing to those advance and highly aggressive. The major goals of Core E are to establish a unified database to serve as a clinical data repository, design and execute clinical trials relevant to SPORE projects, and to support and engage the SPORE Advocacy Committee in SPORE activities in the Pacific Northwest.

Role: Co-investigator and Director Clinical Core E (Higano)

CLINICAL TRIAL CONTRACTS - Prior

Protocol # 401 (Higano)

12/18/2014 - 12/31/2019

Emergent BioSolutions

Seattle, WA

A Phase 1 Study of ES414 in Patients with Metastatic Castration-Resistant Prostate Cancer

The primary goal is to identify the maximum tolerated dose and determine clinical activity of ES414 in patients with mCRPC that have not received prior chemotherapy.

Role: Site PI

Protocol # ARN-509-002 (Higano)

02/15/2013 - 12/31/2019

Aragon Pharmaceuticals, Inc

Rich Heyman | 12780 El Camino Real #301 | San Diego, CA 92130

The Role of Highly Selective Androgen Receptor (AR) Targeted Therapy in Men with Biochemically Relapsed Hormone Sensitive Prostate Cancer

The primary goals are to compare the mean change in QOL as measured by total FACT-P score after 12 months of therapy with ARN-509 monotherapy compared with LHRHa monotherapy in men with BCR, and; to compare the mean change in QOL as measured by total FACT-P score after 12 months of therapy of ARN-509 + LHRHa vs. LHRHa monotherapy in men with BCR.

Role: Site PI

Protocol # ARN-509-003 (Higano)

01/12/2014 - 12/31/2019

Aragon Pharmaceuticals, Inc

Rich Heyman | 12780 El Camino Real #301 | San Diego, CA 92130

A Multicenter Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men with Non-Metastatic (M0) Castration-Resistant Prostate Cancer

The primary goal is to demonstrate superiority in the metastasis-free survival (MFS) of men with high risk NM-CRPC treated with ARN-509 versus placebo.

Role: Site PI

Protocol # 16544 (Higano)

12/03/2014 - 03/01/2019

Bayer Health Care

Montville, NJ

A Randomized Open-Label Phase IIa Study Evaluating the Efficacy and Safety of Radium-223 Dichloride in Combination with Abiraterone Acetate or Enzalutamide in Subjects with Castration Resistant Prostate Cancer (CRPC) who have Bone Metastases

The primary goal is to describe radiological progression free survival (rPFS) in subjects treated with radium-223 dichloride 50 kBq/kg administered every 4 weeks; radium-223 dichloride 50 kBq/kg administered every 4 weeks together with abiraterone acetate 1000 mg orally daily plus prednisone orally twice daily (bid); or radium-223 dichloride 50 kBq/kg administered every 4 weeks together with enzalutamide 160 mg orally daily.

Role: Site PI

Protocol # MDV3100-09 (Higano)

11/06/2012 - 10/31/2018

Medivation, Inc

Lynn Bui, MD | 525 Market St, 36th fl | San Francisco, CA 94105

STRIVE: A Multicenter Phase 2, Randomized, Double-Blind, Efficacy and Safety Study of Enzalutamide vs. Bicalutamide in Men with Prostate Cancer Who Have Failed Primary Androgen Deprivation Therapy

The primary goal is to determine the benefit of enzalutamide (formerly MDV3100) as compared to bicalutamide as assessed by progression-free survival (PFS).

Role: Site PI

Protocol # MDV3100-03 (Higano)

02/15/2011 – 09/30/2018

Medivation, Inc.

Alicia Tyson | 201 Spear St, 3rd fl | San Francisco, CA 94105

PREVAIL: A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naïve Patients with Progressive Metastatic Prostate Cancer who have Failed Androgen Deprivation Therapy.

The primary goals are to determine the benefit of MDV3100 as compared to placebo as assessed by overall survival, and to determine the benefit of MDV3100 as compared to placebo as assessed by radiographic progression-free survival (rPFS).

Role: Site PI

Protocol # S-3100-1-01 (Higano)

06/27/2007-05/31/2018

Medivation, Inc.

Herb Waddell | 55 Hawthorne Street | San Francisco, CA 94105

A Phase I Open-Label Dose-Escalation Safety and Pharmacokinetic Study of MDV3100 in Patients with Castration-Resistant Prostate Cancer

The primary goal is to determine the safety and tolerability profile of MDV3100, including the dose-limiting toxicities (DLTs), and the maximum tolerated dose (MTD; if possible) when administered orally to subjects with castration-resistant prostate cancer.

Role: Site PI

Protocol # P10-3 (Higano)

04/25/2012 - 07/31/2017

Dendreon Corporation

Mark Frohlich, MD/Chief Medical Officer | 1301 2nd Ave, Ste 3200 | Seattle, WA 98101

A Registry of Sipuleucel-T Therapy in Men with Advanced Prostate Cancer

The primary goal is to further quantify the risk of cerebrovascular events (CVEs) following sipuleucel-T therapy for all subjects.

Role: Site PI, Member Steering Committee

Protocol # DST4964g (Higano)

06/01/2012 - 03/31/2017

Genentech, Inc

Daniel Maslyar | 1 DNA Way | South San Francisco, CA 94080

A Phase I, Open-Label Study of the Safety and Pharmacokinetics of Escalating Doses of DSTP3086S in Patients with Metastatic Castration-Resistant Prostate Cancer.

The primary goals are to evaluate the safety and tolerability of every-3-week administration and of weekly administration of DSTP3086S to patients with CRPC, and; to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of every-3-week administration and of weekly administration of DSTP3086S to patients with CRPC, and; to identify the recommended Phase II dose of every-3-week administration and of weekly administration of DSTP3086S (at or below the MTD) in patients with CRPC.

Role: Site PI

Protocol # BC1-10 (Higano)

07/30/2012 - 09/30/2016

Algeta ASA

Kari Lyseng | Kjelsaveien 172 A | NO 0411 Oslo | NORWAY

A Phase I/IIa Study of Safety and Efficacy of Alpharadin with Docetaxel in Patients with Bone Metastases from Castration-Resistant Prostate Cancer

The primary goals are to establish a recommended dose of Alpharadin to be used with docetaxel, and; to investigate safety and explore efficacy of the recommended dose of Alpharadin used with the standard treatment regimen of docetaxel in patients with bone metastases from castration resistant prostate cancer, and; to evaluate the feasibility of patient self-reporting of pain intensity and analgesic use via an interactive voice response (IVR) system.

Role: Site PI, member phase 1 working group

Protocol # P07-2 (Higano)

09/10/2010 - 05/31/2016

Dendreon Corporation

Jovine Umail | 1301 Second Ave, Ste 3200 | Seattle, WA 98101

A Randomized, Multicenter, Single Blind Study in Men with Metastatic Androgen Independent Prostate Cancer to Evaluate Sipuleucel-T Manufactured with Different Concentrations of PA2024 Antigen

The primary goal is to compare the cumulative CD54 upregulation ratio between each of the cohorts.

Role: Site PI

Protocol # ARN-509-001 (Higano)

11/01/2011 - 01/28/2016

Aragon Pharmaceuticals, Inc

Rich Heyman | 12780 El Camino Real #301 | San Diego, CA 92130

An Open-Label, Phase 1/2 Safety, Pharmacokinetic, and Proof-of-Concept Study of ARN-509 in Patients with Progressive Metastatic Castration-Resistant Prostate Cancer

The primary goal of Phase 1 is to assess the safety of ARN-509 in patients with progressive advanced castration-resistant prostate cancer (CRPC), and determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of ARN-509 that leads to a dose limiting toxicity (DLT) in a maximum of 30% of patients.

The primary goal of Phase 2 is to determine PSA response at 12 weeks according to PCWG2 criteria.

Role: Site PI

Protocol # XRP6258-CABAZL06056 (Higano)

12/23/2013 - 01/29/2016

Sanofi US Services Inc

Debra Dawson | 55 Corporate Drive | Bridgewater, NJ 08807

Phase II Trial to Evaluate Benefit of Early Switch from First-Line Docetaxel/Prednisone to Cabazitaxel/Prednisone and the Opposite Sequence, Exploring Molecular Markers and Mechanisms of Taxane Resistance in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Who Have Not Received Prior Chemotherapy

The primary goal is to explore the benefit of an early switch from docetaxel/prednisone to cabazitaxel/ prednisone in men with mCRPC who do not achieve $\geq 30\%$ prostate-specific antigen (PSA) decline from baseline by cycle 4 with the initial docetaxel treatment (in comparison with historical control of patients who were treated with docetaxel and did not switch).

Role: Site PI

Protocol # P11-4 (Higano)

09/06/2012 - 04/14/2015

Dendreon Corporation

Mark Frohlich, MD/Chief Medical Officer | 1301 2nd Ave, Ste 3200 | Seattle, WA 98101

Immune Monitoring Protocol in Men with Prostate Cancer Enrolled in a Clinical Trial of Sipuleucel-T

The primary goal is to evaluate the immune response induced by sipuleucel-T.

Role: Site PI

Protocol # C14009 (Higano)

08/18/2010 - 03/31/2015

Millennium Pharmaceuticals, Inc.

Laurie LoBue | 40 Landsdowne Street | Cambridge, MA 02139

A Randomized Phase 2 Study of Docetaxel/Prednisone with or without MLN8237, a Novel Aurora A Kinase Inhibitor, in Patients with Castration-Resistant Prostate Cancer Preceded by a Phase 1 Dose-Escalation

The primary goals are to assess the safety and tolerability of MLN8237 administered in patients with solid tumors, including patients with CRPC who are eligible to receive treatment with docetaxel and to determine the recommended dose and schedule of the combination regimen of MLN8237 and docetaxel applicable to future development in phase 2 studies.

Role: Site PI

Protocol # OGX-011-11 (Higano)

08/04/2011 - 12/31/2014

Teva Pharmaceutical Industries

Shawn T Conahan, PhD | 425 Privet Road | PO Box 1005 | Horsham, PA 19044-8005

A Randomized Phase 3 Study Comparing Standard First-Line Docetaxel/Prednisone to Docetaxel/Prednisone in Combination with Custirsen (OGX-011) in Men with Metastatic Castrate Resistant Prostate Cancer

The primary goal is to ascertain whether the survival time distribution for patients randomized to the investigational arm is consistent with longer survival as compared to patients randomized to the control arm.

Role: International Co-PI

Protocol # OGX-11-11 CTC (Higano)

01/19/2012 - 11/3/2014

Teva Pharmaceutical Industries, Ltd

Finance Manager – R&D Division | Industrial Zone, Kiryat Nordau | Netanya | ISRAEL

Enumeration of Circulating Tumour Cells in Patients Enrolled in Protocol OGX-011-11

The primary goals are to enumerate CTCs at baseline and cycle 2 and 4 in CRPC patients enrolled to Study Protocol OGX-011-11, and; to demonstrate that the addition of OGX-011 increases the frequency and magnitude of CTC count falls, and; to confirm that CTC count falls associate with overall survival benefit meeting criteria for surrogacy.

Role: Site PI

Protocol #XL 184-203 (Higano)

05/06/2011 - 05/06/2014

Exelixis, Inc.

Pamela A Simonton | 170 Harbor Way | PO Box 511 | South San Francisco, CA 94083-0511

A Randomized Discontinuation Study of XL 184 Subjects with Advanced Solid Tumors

The primary goal is to evaluate the efficacy of cabozantinib (XL184) in subjects with advanced solid tumors

Role: Site PI

Protocol # OGX-011-11SP (Higano)

04/16/2012 - 04/15/2013

Teva Pharmaceutical Industries, Ltd

Shawn T Conahan, PhD | 425 Privet Road | PO Box 1005 | Horsha, PA 19044-8005

Pharmacokinetic and Cardiac Monitoring Study Supplement to Protocol OGX-011-11: A Randomized Phase 3 Study Comparing Standard First-Line Docetaxel/Prednisone to Docetaxel/Prednisone in Combination with Custirsen (OGX-011) in Men with Metastatic Castrate Resistant Prostate Cancer

The primary goals are to determine if custirsen alone or if co-administered with docetaxel alters ECG intervals and morphology with special emphasis on changes in the QTcF interval duration, and; to explore if co-administration of docetaxel and custirsen alters the pharmacokinetics of custirsen, and; to explore if co-administration of docetaxel and custirsen alters the pharmacokinetics of docetaxel, and; to explore the urinary metabolites of custirsen.

Role: Site PI

Protocol # OGX-011-10 (Higano)

11/01/2010 - 04/04/2013

OncoGenexTechnologies

Scott Cormack | 400-1001 West Broadway | Vancouver, BC V6H 4B1 | CANADA

A Randomized, Placebo-Controlled, Double-Blind, Phase 3 Study Evaluating the Clinical Benefit of Adding Custirsen to Docetaxel Retreatment/Prednisone as an Option for Second-Line Therapy in Men with Castrate Resistant Prostate Cancer.

The primary goal is to ascertain whether the investigational arm has a greater proportion of patients with durable pain palliation as compared to the control arm.

Role: Site PI

Protocol # CC 055511 (Higano)

06/18/2008 - 12/31/2012

University of California San Francisco

Alice Chin | 1600 Divisadero St, Box 1770 | San Francisco, CA 94115

A Randomized Phase II Study of Intermittent Chemotherapy or Intermittent Chemotherapy with Maintenance GM-CSF in Patients with Previously Untreated Metastatic Hormone Refractory Prostate Cancer

The primary goal is to determine time to disease progression while receiving chemotherapy (i.e. time to chemotherapy resistance) for both arms (intermittent docetaxel/prednisone with or without maintenance GM-CSF).

Role: Site PI

Protocol # CURC/CUOG AVIAS-0601 (Higano)

04/05/2007 - 11/30/2012

Canadian Urology Research Consortium

Patty Djan | Sunnybrook and Women's College Health Sciences Centre | 2075 Bayview Avenue, Ste A3 04 | Toronto, ON M4N 3M5 | CANADA

Multicentre, Double-Blind Study Comparing 0.5mg Dutasteride vs Placebo Daily in Men Receiving Intermittent Androgen Ablation Therapy for Prostate Cancer

The primary goal is to assess the effect of therapy with repeat oral once daily dosing of dutasteride 0.5mg on the length of the off-treatment interval in men receiving intermittent androgen ablation therapy for localized prostate cancer.

Role: Site PI

Protocol # CRPC2 (Higano)

12/16/09 - 8/30/2012

Medivation, Inc.

Contract Administration | 201 Spear St, 3rd fl | San Francisco, CA 94105

A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in

Patients with Progressive Castration-Resistant Prostate Cancer Previously Treated with Docetaxel-Based Chemotherapy

The primary goal is to determine the benefit of MDV3100 as compared to placebo as assessed by overall survival.

Role: Site PI

Protocol # IMCL CP13-0603 (Higano)

07/19/2007 - 06/30/2012

ImClone Systems, Inc.

John Blanchette | 33 ImClone Dr | Branchburg, NJ 08876

Phase II Single Arm, Open-Label Study of IMC-A12 in Asymptomatic, Chemotherapy-Naïve Patients with Metastatic Androgen-Independent Prostate Cancer.

The primary goals are to determine the composite time to disease progression for chemotherapy-naïve patients with asymptomatic, metastatic androgen-independent prostate cancer (AIPC) treated with IMC-A12 every other week, and; to determine the safety and pharmacokinetic profile of IMC-A12 administered at a dose of 20 mg/kg every 3 weeks in chemotherapy-naïve patients with asymptomatic, metastatic AIPC.

Role: Site PI

Protocol #IMCL CP18-0601A (Higano)

12/04/2008 - 06/17/2012

ImClone Systems, Inc.

Clinical Affairs Department | 33 ImClone Dr | Branchburg, NJ 08876

A Phase 2, Multicenter, Randomized Study of IMC-A12 or IMC-1121B plus Mitoxantrone and Prednisone in Metastatic Androgen-Independent Prostate Cancer Following Disease Progression on Docetaxel-Based Chemotherapy

The primary goal is to determine a composite progression-free survival (PFS) associated with the treatment regimen in each arm of the study.

Role: Site PI

Protocol # CMCS110A2101 (Higano)

01/15/2009 - 01/15/2012

Novartis

Wanda Ruiz, PhD | 59 Route 10 | East Hanover, NJ 07936-1080

A Phase I/II Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of MCS110 in Patients with Prostate Cancer and Bone Metastases

The primary goal of the dose escalation phase is to determine the maximum-tolerated dose (MTD) or optimal biological dose (OBD) and to characterize dose limiting toxicity (DLT) of escalating doses of MCS110 administered as an IV infusion every

2 weeks on a 28-day cycle in patients with asymptomatic castrate-resistant prostate cancer with bone metastases who have not received any bisphosphonates in the 12 months prior to enrollment.

The primary goal of the dose expansion phase is to assess the effect of MCS110 administered as an IV infusion every 2 weeks on a 28-day cycle on bone resorption marker uNTx in patients with asymptomatic castrate-resistant prostate cancer with bone metastases who have not received any bisphosphonates in the 12 months prior to enrollment.

Role: Site PI

Protocol # IMCL CP13-0501 (Higano)

08/19/2005 - 12/31/2011

ImClone Systems, Inc

Tom Perone | 33 ImClone Dr | Branchburg, NJ 08876

A Phase 1 Study of Weekly Anti-Insulin-Like Growth Factor-1 Receptor (IGF-IR) Monoclonal Antibody IMC-A12 in Patients with Advanced Solid Tumors

The primary goal is to establish the safety profile and maximum tolerated dose (MTD) of the anti-IGF-IR monoclonal antibody IMC-A12 administered weekly in patients with advanced solid tumors who no longer respond to standard therapy or for whom no standard therapy is available.

Role: Site PI

Protocol # AURA-6202-007 (Higano)

02/01/2008 - 12/31/2011

Nerviano Medical Sciences

Elma Ravizza | Viale Pasteur 10 | 20014 Nerviano (MI) | ITALY

A Phase II Study of PHA-739358 in Patients with Metastatic Hormone Refractory Prostate Cancer

The primary goal is to assess the antitumor activity of PHA-739358 administered as IV infusion according to two different dose schedules in metastatic HRPc patients progressing on standard, docetaxel-based, 1st-line chemotherapy for HRPc based on PSA response rate and to select the best dose schedule for further investigation.

Role: Site PI

Protocol # AMG 102-20070611 (Higano)

11/01/2008 - 10/31/2011

Amgen, Inc

Maria Earle | One Amgen Center Drive, MS 28-1-A | Thousand Oaks, CA 91320

A Phase 1b/2 Study to Assess the Safety and Efficacy of AMG 102 in Combination with Mitoxantrone and Prednisone in Subjects with Previously Treated Castrate Resistant Prostate Cancer

The primary goal is to identify safe dose levels of AMG 102, up to 15 mg/kg Q3W, to combine with mitoxantrone and prednisone (MP).

Role: Site PI

Protocol # MDX010-21 (Higano)

02/01/2006 - 02/01/2011

Medarex, Inc

Project Manager | 519 Route 173 West | Bloomsbury, NJ 08804

A Phase I/II, Open-Label, Dose-Escalation Study of MDX-010 Administered Every 3 Weeks for 4 Doses in Patients with Metastatic Hormone-Refractory Prostate Cancer

The primary goal is to determine the safety profile of escalating doses of MDX-010 (hereafter referred to as ipilimumab) with and without a single dose of focal radiotherapy administered every 3 weeks up to 4 times to patients with metastatic hormone-refractory prostate cancer (HRPC).

Role: Site PI

Protocol # D9902 (Higano)

10/01/2003 - 09/30/2010

Dendreon

Mark Frohlich, MD/Chief Medical Officer | 1301 2nd Ave, Ste 3200 | Seattle, WA 98101

A Randomized, Double Blind, Placebo Controlled Phase 3 Trial of Immunotherapy with Autologous Antigen Presenting Cells Loaded With PA2024 (Provenge®, APC8015) in Asymptomatic Subjects With Gleason Sum ≤ 7, Metastatic, Androgen Independent Prostatic Adenocarcinomas

The primary goal is to assess the safety and efficacy of sipuleucel-T in prolonging survival of men with metastatic androgen independent prostate cancer.

Role: Site PI

Protocol # G-0029 (Higano)

08/15/2005 - 08/31/2010

Cell Genesys

Karen Peterson | 500 Forbes Blvd | South San Francisco, CA 94080

A Phase III Randomized, Open-Label Study of CG1940 and CG8711 Versus Docetaxel and Prednisone in Patients with Metastatic Hormone-Refractory Prostate Cancer who are Chemotherapy-Naïve

The primary goal is to compare the duration of survival between the two treatment arms.

Role: Site PI

Protocol # APL-B-011-02 (Higano)

03/01/2006 - 02/28/2010

PharmaMar

Clementina Martinez | Avda. De los Reyes, 1 | Pol. Ind. La Mina-Norte | 28770-Colmenar Viejo | Madrid, Spain

A Phase II, Multicenter, Open-Label, Clinical and Pharmacokinetic Study of Aplidin® as a 3-hour IV Infusion Every 2 Weeks, in Relapsing or Refractory Patients with Androgen-Independent Prostate Adenocarcinoma

The primary goal is to assess the anti-tumor activity of Aplidin® given intravenously over 3-hours every 2 weeks, in patients with castrate metastatic adenocarcinoma of the prostate that have relapsed or progressed after two previous lines of systemic therapy, considering biological agents or chemotherapy as systemic therapy and taking into account that patients must have received prior docetaxel-based chemotherapy.

Role: Site PI