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PRINCIPAL INVESTIGATOR: Celestia Higano, MD

CONTRACTING ORGANIZATION: University of Washington

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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 30Sep2018-30Sep2019.

Major Progress: In the last year, UWash was the lead/co-lead site on 10 trials, opened 3 new trials, committed to 2 trials (all in various stages of opening), and completed accrual on 6 trials.

Results: UWash accrued 36 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.

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

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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 36 patients to PCCTC trials, 20 to therapeutic and 16 patients to non-therapeutic trials. See Appendix 1 for details.
      ii. 6 of 36 patients (17%) accrued during this reporting period were members of disproportionately affected populations.
      iii. Site did not submit any LOIs during the current report period.
      iv. Site participated in 15 PCCTC trials: 5 trials initiated by other PCCTC sites, 7 initiated by UWash and another site, and 3 initiated by UWash.
      v. Site met requirements of timely submission of quality data.
      vi. PI (Higano) is a member of the Scientific Oversight Committee, and Chairperson of the Publications Committee. Sub-Investigator (Cheng) is the Chairperson of the Germline Genetics Working Group.
      vii. PCCTC meetings at GU ASCO, ASCO, and PCF were attended by Dr. Higano +/- Drs. Yu, Cheng, and Schweizer.
      viii. Coordinator participates in monthly site conference calls. PI and/or co-I and sub-investigators participate in all monthly PI conference calls.
      ix. PI attended the EAB meeting held on 13Feb2019 in San Francisco, CA.
      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 nominated Dr. Cheng to chair the PCCTC Germline Genetics Working Group. She led the development and is the senior author on a PCCTC position paper on this topic (see bibliography). Dr. Cheng's participation in the PCCTC helped accelerate her reputation as a recognized expert in germline mutations in prostate cancer. As a result, she was invited to co-author a paper with Drs. Mohler and Higano entitled "Current recommendations for prostate cancer genetic testing: NCCN prostate guideline." Thus PCCTC participation has fostered both collaboration and academic growth for 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 two annual meetings directed at men with prostate cancer:

On May 11, 2019, the Institute for Prostate Cancer Research (IPCR) at UWash held the 8th annual meeting for the public on prostate cancer. The IPCR was co-founded by the PI 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.

On September 14, 2019, we held the 19th annual meeting of the Pacific NW Prostate Cancer Symposium. This is a joint effort, initially between OHSU and UWash, that now includes University of British Columbia. This meeting was attended by 425 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.

The PI was the former Director of the Clinical Core of the PC SPORE grant and established a 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.

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 Colombia (Vancouver).

Our website has been recently renovated to provide more user-friendly access to the latest information on prostate cancer research for patients.

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.

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 genomics in prostate cancer. Our group has driven changes in NCCN guidelines for 2019 and published in the area as well.

   b. **What was the impact on other disciplines?**
   - Provide guidance on the importance of an accurate family history.
   - Educate oncologists about germline versus somatic testing.
   - Address the 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.

   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 input from members of the PCCTC, including the PI, who are on the Prostate Panel of the NCCN. 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**
   Nothing to Report.

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

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

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

De Bono JS, Higano C, Saad F, Miller K, Casey M, Czibere A, Healy C, Fizazi K. TALAPRO-1: An open-label, response rate phase II study of talazoparib (TALA) in men with DNA damage repair defects (DDR) and metastatic castrationresistant prostate cancer (mCRPC) who previously received taxane-based chemotherapy (CT) and progressed on > 1 novel hormonal therapy (NHT). *Ann of Oncol* (2018) 29 (suppl 8). Poster presentation. ESMO Congress 2018, Munich Germany. October 2018.

De Bono JS, Hansen A, Choudhury AD, Cook N, Heath EI, Higano C, Linch M, Martin-Liberal J, Rathkopf DE, Wisinski KB, Barry S, de Bruin E, Brugger W, Colebrook S, Klinowska T, Moschetta M, Mortiner PGS, Siu LL, Shapiro G. AZD8186, a potent and selective inhibitor of PI3Kb/d, as monotherapy and in combination with abiraterone acetate plus prednisone (AAP), in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC). *Ann of Oncol* (2018) 29 (suppl 8). Poster presentation. ESMO congress 2018, Munich Germany. October 2018.

Yu EY, Massard C, Retz M, Tafreshi A, Galceran JC, Hammerer P, Fong PCC, Shore N, Joshua A, Linch MD, Gurney H, Romano E, Augustin M, Piulats JM, Wu H, Schloss C, Poehlein CH, De Bono JS. KEYNOTE-365 Cohort A: Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castrate-resistant prostate cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 145). Oral presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019

Smith MR, Sandhu SK, Kelly WK, Scher HI, Efstathiou 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

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. 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

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. 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

Yu, E. KEYNOTE-365 Cohort A: Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castration-resistant prostate cancer. *eCancerTV*. February 18, 2019. https://ecancer.org/video/7697/keynote-365-cohort-a--pembrolizumab-plus-olaparib-in-docetaxel-pretreated-patients-with-mcrpc.php

Yu, E. Results from KEYNOTE-365 in metastatic castration resistant prostate cancer. *OBRoncology*. February 22, 2019. https://www.youtube.com/watch?v=jJm_DQrHwIc

Yu, E. Results from KEYNOTE 365 in metastatic castration-resistant prostate cancer. *OncologyTube*. March 20, 2019. https://www.oncologytube.com/video/results-from-keynote-365-in-mcrpc

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

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

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

Pinder DM, Tombal BF, Armstrong AJ, Barrus JK, Beer TM, Evans CP, Heidenreich A, Higano CS, Kamba T, Lin P, Nikolayeva N, Sugg J, Steinberg JL, Tapin ME. Adverse Events of Special Interest Assessed by Review of Safety Data in Enzalutamide Castration-Resistant Prostate Cancer (CRPC) Trials. Presentation. 2019 SUNA urologic Conference, Lake Buena Vista, FL. September 2019.

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

b. **Journal publications (UWash author)**

VanderWeele DJ, Antonarakis ES, Carducci MA, Dreicer R, Fizazi K, Gillessen S, Higano CS, Morgans AK, Petrylak DP, Sweeney CJ, Hussain M. Metastatic Hormone-Sensitive Prostate Cancer: Clinical Decision Making in a Rapidly Evolving Landscape of Life-Prolonging Therapy. J Clin Oncol. 2019 Sep 10:JCO1901595.

Labrecque MP, Coleman IM, Brown LG, True LD, Kollath L, Lakely B, Nguyen HM, Yang YC, da Costa RMG, Kaipainen A, Coleman R, Higano CS, Yu EY, Cheng HH, Mostaghel EA, Montgomery B, Schweizer MT, Hsieh AC, Lin DW, Corey E, Nelson PS, Morrissey C. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. J Clin Invest. 2019 Jul 30;130:4492-4505.

Paller CJ, Antonarakis ES, Beer TM, Borno HT, Carlo MI, George DJ, Graff JN, Gupta S, Heath EI, Higano CS, McKay RR, Morgans AK, Patnaik A, Petrylak DP, Rettig MB, Ryan CJ, Taplin ME, Whang YE, Vinson J, Cheng HH, Giri VN; Germline Genetic Testing in Advanced Prostate Cancer; Practices and Barriers: Survey Results from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. PCCTC Germline Genetics Working Group. Clin Genitourin Cancer. 2019 Aug;17(4):275-282.e1.

Cheng HH, Sokolova AO, Schaeffer EM, Small EJ, Higano CS. Germline and Somatic Mutations in Prostate Cancer for the Clinician. J Natl Compr Canc Netw. 2019 May 1;17(5):515-521. Review.

Morris MJ, Loriot Y, Sweeney CJ, Fizazi K, Ryan CJ, Shevrin DH, Antonarakis ES, Pandit-Taskar N, Deandreis D, Jacene HA, Vesselle H, Petrenciuc O, Lu C, Carrasquillo JA, Higano CS. Radium-223 in combination with docetaxel in patients with castration-resistant prostate cancer and bone metastases: a phase 1 dose escalation/randomised phase 2a trial. Eur J Cancer. 2019 Jun;114:107-116.

Beltran H, Hruszkewycz A, Scher HI, Hildesheim J, Isaacs J, Yu EY, Kelly K, Lin D, Dicker A, Arnold J, Hecht T, Wicha M, Sears R, Rowley D, White R, Gulley JL, Lee J, Diaz Meco M, Small EJ, Shen M, Knudsen K, Goodrich DW, Lotan T, Zoubeidi A, Sawyers CL, Rudin CM, Loda M, Thompson T, Rubin MA, Tawab-Amiri A, Dahut W, Nelson PS. The Role of Lineage Plasticity in Prostate Cancer Therapy Resistance. Clin Cancer Res. 2019 Jul 30.

Schweizer MT, Antonarakis ES, Bismar TA, Guedes LB, Cheng HH, Tretiakova MS, Vakar-Lopez F, Klemfuss N, Konnick EQ, Mostaghel EA, Hsieh AC, Nelson PS, Yu EY, Montgomery RB, True LD, Epstein JI, Lotan TL, Pritchard CC. Genomic Characterization of Prostatic Ductal Adenocarcinoma Identifies a High Prevalence of DNA Repair Gene Mutations. JCO Precis Oncol. 2019;3. Epub 2019 Apr 18.

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 sites are publicly accessible presentations of our educational conferences for patients described above in section 3.d.
Pacific Northwest Prostate Cancer Conference
www.uwprostatecancer.org
Institute for Prostate Cancer Research
https://www.fredhutch.org/en/labs/clinical/ipcr/institute-prostate-cancer-research-symposium/past-symposiums/2018-ipcr-presentations.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:	Celestia Higano, MD
Project Role:	Principal Investigator
Person months worked:	3
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:	Martha Lee
Project Role:	Administrative Support
Person months worked:	1
Contribution to project:	Provides administrative support for consortium related activities for the PI and research team.

Name:	Erin Michelson
Project Role:	Clinical Research Coordinator
Person months worked:	1
Contribution to project:	Tracked trial accruals, LOI submissions, and provided monthly updates to PCCTC. Oversaw research team in management of protocol adherence and timeliness and quality of data collection. Served as point person for PCCTC activities. Participated in bi-weekly PCCTC conference calls.

Name:	Michelle Haug
Project Role:	Interim Clinical Research Coordinator
Person months worked:	2
Contribution to project:	Tracks trial accruals, LOI submissions, and provides monthly updates to PCCTC. Ensures research team adherence to protocols and timeliness and quality of data collection. Serves as point person for PCCTC activities and participates in bi-weekly PCCTC conference calls.

Name:	Kelly Crowder
Project Role:	Assistant Clinical Research Coordinator
Person months worked:	1
Contribution to project:	Participated in bi-weekly PCCTC conference calls. Worked with CRC to ensure research team adherence to protocols. Supported data and regulatory coordinators, ensuring data collection was accurate and timely, and that all regulatory procedures met local IRB requirements.

Name:	Sarah Finkelstein
Project Role:	Budget/Contract Manager
Person months worked:	2
Contribution to project:	Manages consortium budgets and contract, provides monthly reports to PI and CRC, 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:	Tina Dinh
Project Role:	Budget Startup Specialist
Person months worked:	2
Contribution to project:	Developed site budgets for PCCTC studies, and negotiated 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 Higano (PI), Yu (co-PI), Cheng (sub-I), and Schweizer (sub-I)

APPENDIX 1

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

01Oct2018-30Sep2019

PCCTC# (UW#)	Trial Title	UWash accrual Current / (Total)	Status	Lead Site(s)	Protocol Specific Biomarkers
c13-131 (UW13024)	A Phase 1 Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of Ascending Doses of AZD8186 in Patients with mCRPC and Patients with Known PTEN- deficient Tumors	0 / (17)	Closed 11/2018	UWash	Biopsy, PK, PD
c15-148 (CC9279)	A Phase 1/2 Trial of Concurrent Chemo-hormonal Therapy Using Enzalutamide (MDV-3100) and Cabazitaxel in Patients with mCRPC	3 / (29)	Closed 06/2019	UWash OHSU	WB-CTCs, Enum CTCs, PKs, NGS on tumor tissues.
c15-156 (CC9342)	A Randomized Phase 2 Study Comparing Bipolar Androgen Therapy vs Enzalutamide in Asymptomatic Men with CRPC: TRANSFORMER	0 / (28)	Closed 09/2018	JHU	Biopsy, CTC
c15-157 (UW14052)	A Phase 1 Study of ES414 in Patients with Metastatic Castration-Resistant Prostate Cancer	0 / (5)	Closed 11/2018	UWash UCSF	Biopsy, PK, CTC
c15-160 (CC9767)	A Phase 1b Study of Enzalutamide plus CC-115 in Men with CRPC	1 / (1)	Open	MSKCC	CTC, ctDNA, IMPACT, Explant Culturing, Organoids, IHC, Targeted
c15-166 (UW18003)	A Phase 1 Safety and Tolerability Study of ZEN003694 in Combination with Enzalutamide in Patients with mCRPC	5 / (5)	Closed 02/2019	UCSF	N/A
c16-169 (UW15030)	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-0675351)	2 / (10)	Open	UWash DU MSK	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 Metastatic Castration-Resistant Prostate Cancer (mCRPC)	0 / (0)	Open	MSK UWash	CTCs, ctDNA, AR-V7, aBSI
c16-181 (UW16081)	Phase Ib/II Trial of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (mCRPC) (KEYNOTE-365)	6 / (18)	Open	UWash	PKs, NGS on tumor tissue and blood, mRNA expression, PD-1/PD-L1.
c17-189 (UW16062)	A Phase 2 Efficacy and Safety Study of Niraparib in Men with Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies	0 / (1)	Open	UWash OSHU	PK, PD, Biomarkers: DNA Repair Mutations (NGS on tumor tissue).

PCCTC# (UW#)	Trial Title	UWash accrual Current / (Total)	Status	Lead Site(s)	Protocol Specific Biomarkers
c17-198 (UW17076)	A Multi-Center… Trial Comparing the Occurrence of Major Adverse Cardiovascular Events in Patients with Prostate Cancer and Cardiovascular Disease Receiving Degarelix (GnRH Rerceptor Antagonist) or Leuprolide (GnRH Receptor Agonist) PRONOUNCE	0 / (0)	Open	MSKCC UWash	N/A
c18-211 (UW17031)	*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)*	*N/A*	*Start-up*	*UWash*	*PK, CTC, ctDNA, Biomarkers, DNA repair mutations*
c18-213	*A Phase Ib/II Combination Trial of the PI3K-β Selective Inhibitor GSK2636771 with Pembrolizumab for PTEN-deficient Metastatic Castration-Resistant Prostate Cancer and Metastatic Endometrial Cancer Patients*	*N/A*	*Start-up/ On hold*	*UChicago*	
c19-231 (UW18051)	eFT508: A Phase 2 Non-randomized Open-label Study Examining the Effect of eFT508 in Patients with Advanced Castrate-resistant Prostate Cancer (CRPC)	3 / (3)	Closed 03/2019	DFCI UWash	PK, CTC, P-eIF4E status
	Total therapeutic accruals:	20 / (117)			
c16-170 (CC9853)	Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men with Advanced Prostate Cancer (IRONMAN)	16 / (42)	Open	Duke MSKCC DFCI	ctDNA, germline DNA, RNA, exosomes
	Total non-therapeutic accruals	16 / (42)			

Appendix 2

Copies of original journal articles

Metastatic Hormone-Sensitive Prostate Cancer: Clinical Decision Making in a Rapidly Evolving Landscape of Life-Prolonging Therapy

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Background

The majority of men who die as a result of metastatic prostate cancer developed castration-resistant disease that progressed from an earlier hormone-sensitive state. In 2004, the first life-prolonging therapy, docetaxel (DOC), was approved by the US Food and Drug Administration for metastatic castration-resistant prostate cancer (mCRPC). Since 2010, five additional agents were approved for mCRPC on the basis of prolonging median overall survival (OS) by up to 5 months: sipuleucel-T, cabazitaxel, abiraterone plus prednisone (AAP), enzalutamide (ENZA), and radium-223.[1-7] Recent practice-changing trials have demonstrated that rationally intensifying treatment of metastatic hormone-sensitive prostate cancer (mHSPC), by advancing effective therapy for mCRPC to the hormone-sensitive state, has a bigger impact on OS. This treatment includes DOC (CHAARTED [Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer] trial supported by STAMPEDE [Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy] Arm C and GETUG-15), AAP (LATITUDE [Abiraterone Acetate Plus Prednisone in Patients With Newly Diagnosed High-Risk Metastatic Castration-Sensitive Prostate Cancer] with additional support from STAMPEDE Arm G), ENZA (ENZAMET [Enzalutamide in First-Line Androgen-Deprivation Therapy for Metastatic Prostate Cancer], with support from ARCHES [Enzalutamide Plus Androgen-Deprivation Therapy for Metastatic Hormone-Sensitive Prostate Cancer]), and apalutamide (APA; TITAN [Apalutamide Plus Androgen-Deprivation Therapy (ADT) Versus ADT in Patients With Metastatic Hormone-Sensitive Prostate Cancer] trial).[8-14] The hazard ratios (HRs) for these agents in mHSPC are similar to those in mCRPC. Because OS is longer for mHSPC, however, these therapies have a larger absolute effect in this setting, with an unprecedented increase in median OS by more than 1 year. This supports the basic principle in oncology that advancement of effective therapies to earlier stages of disease leads to better therapeutic impact, with four agents now demonstrating improved survival in this setting.

Although encouraging, these trials leave us with several unanswered questions: How do we best personalize therapy on the basis of clinical subgroups? What is the role of focal therapy in the setting of effective systemic therapy? How should we incorporate molecular characteristics into management?

Clinical Subgroups

Selection of which agent to use for mHSPC is guided in part by disease burden, which is based on conventional imaging (computed tomography and bone scan). For more than 30 years, it has been recognized that prognosis in mHSPC is informed by the extent of disease burden.[15] The definitions of low volume/risk versus high volume/risk have varied, driven by metastases location[15-17] and/or number[18] of bone metastases. The CHAARTED trial was positive overall and supported androgen-deprivation therapy (ADT) plus DOC for patients with mHSPC.[9] A priori stratification was based in part on disease volume, with high volume defined as either visceral metastases or four or more bone lesions with one or more lesions beyond the axial skeleton per conventional imaging. The improvement in OS from DOC was primarily driven by benefit in patients with high-volume disease (HR, 0.63); there was no significant impact on OS in patients with low-volume disease[19] (HR, 1.04; Table 1). A similar result was seen in the post hoc analysis of GETUG-15.[20] CHAARTED was not powered for this subgroup analysis, however, and the subgroup was small. Post hoc analysis of STAMPEDE Arm C, expected to be reported later this year, will provide additional evidence.

In contrast, the benefit of the androgen receptor pathway inhibitors (ARPIs) AAP, ENZA, and APA seem to apply to all patients with mHSPC, regardless of disease burden. LATITUDE evaluated AAP in patients with high-risk disease (defined by Gleason score

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TABLE 1. Phase III Trials for Metastatic Hormone-Sensitive Prostate Cancer

Trial	Clinical Trials Information	Comparator Arm	Control Arm	No. of Trial Participants	PFS, HR or EP	OS, HR or EP	First Author or Status
Reported trials							
High volume/high risk							
Docetaxel							
CHAARTED	NCT00309985	ADT + DOC	ADT	513	0.58 (time to CRPC)	0.63	Kyriakopoulos[19]
GETUG-15	NCT00104715	ADT + DOC	ADT	183	NA	0.78	Gravis[20]
STAMPEDE Arm C	NCT00268476	ADT + DOC	ADT	724	NA	TBD	James[10]
ARPI							
LATITUDE	NCT01715285	ADT + AAP	ADT	955	NA	0.62	Fizazi[21]
STAMPEDE Arm G	NCT00268476	ADT + AAP	ADT	473	0.31 (FFS)	0.54	Hoyle[22]
ENZAMET	NCT02446405	ADT + ENZA (± DOC)	ADT + NSAA (± DOC)	588	0.45	0.80	Davis[13]
ARCHES	NCT02677896	ADT + ENZA (prior DOC allowed)	ADT (prior DOC allowed)	727	0.44 (rPFS)	TBD	Armstrong[23]
TITAN	NCT02489318	ADT + APA (prior DOC allowed)	ADT (prior DOC allowed)	660	0.53	0.68	Chi[14]
RT							
STAMPEDE Arm H	NCT00268476	RT to prostate	ADT (+ DOC possible)	1,120	NA	1.07	Parker[25]
HORRAD	ISRCTN06890529	RT to prostate	ADT	272	NA	1.06	Boevé[26]
Low volume/low risk							
Docetaxel							
CHAARTED	NCT00309985	ADT + DOC	ADT	277	0.70 (Time to CRPC)	1.04	Kyriakopoulos[19]
GETUG-15	NCT00104715	ADT + DOC	ADT	202	NA	0.9	Gravis[20]
STAMPEDE Arm C	NCT00268476	ADT + DOC	ADT	362	NA	TBD	James[10]
ARPI							
LATITUDE	NCT01715285	ADT + AAP	ADT	243	NA	0.72	Fizazi[21]
STAMPEDE Arm G	NCT00268476	ADT + AAP	ADT	428	0.24 (FFS)	0.66	Hoyle[22]
ENZAMET	NCT02446405	ADT + ENZA (± DOC)	ADT + NSAA (± DOC)	537	0.30	0.43	Davis[13]
ARCHES	NCT02677896	ADT + ENZA (prior DOC allowed)	ADT (prior DOC allowed)	423	0.24 (rPFS)	TBD	Armstrong[23]
TITAN	NCT02489318	ADT + APA (prior DOC allowed)	ADT (prior DOC allowed)	392	0.36	0.67	Chi[14]

(continued on following page)

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TABLE 1. Phase III Trials for Metastatic Hormone-Sensitive Prostate Cancer (continued)

Trial	Clinical Trials Information	Comparator Arm	Control Arm	No. of Trial Participants	PFS, HR or EP	OS, HR or EP	First Author or Status
RT							
STAMPEDE Arm H	NCT00268476	RT to prostate	ADT (+ DOC possible)	819	NA	0.68 (OS)	Parker[25]
HORRAD	ISRCTN06890529	RT to prostate	ADT	160	NA	0.68 (OS)	Boevé[26]
Not-reported trials							
ARPI							
STAMPEDE Arm J	NCT00268476	ADT + AAP + ENZA (DOC)	ADT (DOC)	1,800		Primary EP	Completed accrual 2016
PEACE-1	NCT01957436	ADT + DOC + AAP (± RT)	ADT + DOC (± RT)	1,173	Coprimary EP	Coprimary EP	Completed accrual 2018
ARASENS	NCT02799602	ADT + DOC + darolutamide	ADT + DOC	1,303		Primary EP	Complete approximately 2022
SWOG-1216	NCT01809691	ADT + orterenel	ADT + bicalutamide	1,313		Primary EP	Complete approximately 2022
RT							
PEACE-1	NCT01957436	ADT + DOC ± AAP + RT	ADT + DOC ± AAP	1,173	Coprimary EP	Coprimary EP	Completed accrual 2018
PLATON	NCT03784755	SST + ablative therapy for all sites	SST + ablative therapy for prostate	410	Primary EP		Complete approximately 2025
SWOG-1802	NCT03678025	SST + definitive treatment of prostate	SST	1,273		Primary EP	Complete approximately 2028

Abbreviations: AAP, abiraterone acetate plus prednisone; ADT, androgen-deprivation therapy; APA, apalutamide; ARASENS, ODM-201 in Addition to Standard Androgen-Deprivation Therapy and Docetaxel in Metastatic Castration-Sensitive Prostate Cancer; ARCHES, Enzalutamide Plus ADT for Metastatic Hormone-Sensitive Prostate Cancer; CHAARTED, Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; ARPI, androgen receptor pathway inhibitor; CRPC, castration-resistant prostate cancer; DOC, docetaxel; ENZA, enzalutamide; ENZAMET, Enzalutamide in First-Line Androgen-Deprivation Therapy for Metastatic Prostate Cancer; EP, end point; FFS, failure-free survival; HORRAD, Hormonal Therapy Versus Hormonal Therapy Plus Local External Radiation Therapy in Patients With Primary Diagnosed Metastasized Prostate Cancer; HR, hazard ratio; LATITUDE, Abiraterone Acetate Plus Prednisone in Patients With Newly Diagnosed High-Risk Metastatic Castration-Sensitive Prostate Cancer; NA, not available; NSAA, nonsteroidal anti-androgen; OS, overall survival; PFS, progression-free survival; PLATON, Local Ablative Therapy for Hormone-Sensitive Oligometastatic Prostate Cancer; rPFS, radiographic progression-free survival; RT, radiotherapy; SST, standard systemic therapy; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; TBD, to be determined; TITAN, Apalutamide Plus Androgen-Deprivation Therapy (ADT) Versus ADT in Patients With Metastatic Hormone-Sensitive Prostate Cancer.

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together with sites and number of metastases on conventional imaging) and showed survival improvement for these men.[11,21] Post hoc subgroup analysis of LATITUDE by disease volume (CHAARTED definition) confirmed benefit across subgroups, although the *P* value for benefit in low-volume disease was not significant. STAMPEDE Arm G included patients with metastatic high- or low-risk/volume disease (52%) and patients with high-risk nonmetastatic disease (48%) and was positive for OS in the whole population (HR, 0.63).[12] Post hoc analysis of patients with metastatic disease demonstrated improved OS in both high- and low-risk groups (LATITUDE definition; high-risk HR, 0.54; low-risk HR, 0.66). Similar results were seen in high- and low-volume disease (per CHAARTED definition).[22] ENZAMET (HR, 0.67) and TITAN (HR, 0.68) were both positive in the overall patient population, with benefit seen in high- and low-volume disease for ENZA and APA, respectively (ENZA HRs, 0.80 and 0.43; APA HRs, 0.68 and 0.67). Thus, the totality of the data indicates that patients with lower disease burden also benefit from earlier AAP. Of note, in ENZAMET and TITAN, there seemed to be less benefit of an ARPI for patients who also received DOC, which likely had a greater effect on the HR for those with high-volume disease than with low-volume disease. These studies generally excluded patients with histologies other than adenocarcinoma; poor performance status; recent cardiac events; or, for the trials involving anti-androgens, prior seizure, and the balancing of risks and benefits is critical in considering therapy intensification in these patients.

Although subgroup evaluation of volume/risk is informative, more is needed to personalize therapy better. Patients with metastases only in the lung, for example, are considered high volume/risk as a result of having visceral metastases, yet they may actually have prolonged responses to ADT alone.[24] The evolution of imaging technologies is a major confounding factor in the context of both those with M1 disease by conventional imaging and those with M0 disease by conventional imaging but M1 disease on next-generation imaging (eg, fluciclovine positron emission tomography or prostate-specific membrane antigen–targeted imaging). Trials to date have not incorporated next-generation imaging, and as such, how to factor in newer imaging for management decisions is not clear. Future trials should seek to refine subgroup definitions by incorporating newer imaging techniques and prospectively evaluating subgroup-specific therapy.

Focal Therapy

The role of local therapy to the prostate has been a subject of interest for decades but with no definitive data. The radiotherapy (RT) arm of STAMPEDE (Arm H) evaluated the impact of prostate RT in patients with mHSPC. After Arm H was fully accrued, the investigators annotated patients' volume of disease, having hypothesized that RT would be more beneficial in patients with low-volume mHSPC, and before analysis, specified these subgroups and powered Arm H accordingly. Improvement in failure-free survival with the addition of prostate RT was found for all patients (HR, 0.76). There was no OS benefit in the overall population (HR, 0.92), but patients with low-volume disease had an improved OS (HR, 0.68).[25] A similar effect was observed in the HORRAD (Hormonal Therapy Versus Hormonal Therapy Plus Local External Radiation Therapy in Patients With Primary Diagnosed Metastasized Prostate Cancer) trial for those with fewer than five metastases (HR, 0.68) and is summarized in a meta-analysis.[26,27] In both trials, ADT alone was the treatment for the majority of patients; in STAMPEDE, 16% of patients received additional DOC.

The role of radiation to oligometastatic disease has been an area of significant interest as well. Many patients with low-volume disease have oligometastatic disease by conventional imaging, and the question is whether they will benefit from RT to all sites of disease.[28] To date, trials that have evaluated metastasis-directed therapy have focused on delaying the initiation of ADT rather than on improvement in OS. This was true in STOMP (Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence), which targeted up to three metastases seen on next-generation imaging (choline positron emission tomography-computed tomography), and in ORIOLE (Observation Versus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer), an ongoing trial that targets up to three metastases seen on conventional imaging.[28,29] No definitive data support the survival benefit of this strategy, although several ongoing trials are evaluating the role of focal therapy in various settings. PEACE-1 is evaluating the role of local RT and/or AAP addition to ADT and DOC regardless of disease volume/risk, both for OS and for effect on local symptoms. The PLATON (Local Ablative Therapy for Hormone-Sensitive Oligometastatic Prostate Cancer) trial is comparing ablative therapy to the prostate versus to all sites of oligometastatic disease. Of note, patients in this trial are allowed to discontinue systemic therapy, which for the first time allows evaluation for cure with a combination systemic therapy and focal therapy approach. SWOG-1802 is testing the role of definitive therapy to the prostate, regardless of disease volume. The innovative design of SWOG-1802 offers definitive therapy only to those who are still responding to systemic therapy after 22 to 28 weeks, which thus spares those with primary refractory disease. It addresses whether the benefit of local prostate cancer control can be extended to more patients and whether treating the primary is relevant in an era of more-effective systemic therapy (akin to CARMENA [Clinical Trial to Assess the Importance of Nephrectomy], which replaces interferon with more-effective tyrosine kinase inhibitors).[30] In addition to improvements in survival, SWOG-1802 and PEACE-1 are evaluating treatment effects on quality of life.

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Molecular Characteristics

One way to improve upon risk stratification using disease-volume/risk subgroups is to incorporate molecular characteristics. In mCRPC, defects in the tumor suppressor genes *PTEN*, *RB1*, and *TP53* are associated with aggressive-variant prostate cancer, and patients with these alterations may benefit from platinum-based therapy.[31,32] Data suggest that loss of these genes also may inform risk in mHSPC because patients with intact tumor suppressor genes do well on ADT alone.[33] Similarly, decisions about the addition of local therapy to the prostate would be better personalized if they incorporated molecular characteristics of the disease. For example, the gene expression assay Decipher (Decipher Biosciences, San Diego, CA) predicts benefit from adjuvant or salvage RT.[34] Its performance in the metastatic setting is unknown.

To date, treatment of mHSPC is not biomarker targeted. The exception is the tissue agnostic indication in the United States for pembrolizumab for microsatellite instability-high or mismatch repair–deficient solid tumors. Numerous reports have cataloged the genomic landscape of localized prostate cancer or mCRPC.[35-40] Those that examined mHSPC have suggested that the same genetic alterations are present in this disease state, with frequencies intermediate between localized disease and CRPC.[33,41,42] These include loss of function of *PTEN* and DNA repair genes. (The major exception is androgen receptor alterations that arise only in mCRPC.) Early-phase trials have demonstrated in mCRPC the ability to target deficiency in DNA repair with poly (ADP-ribose) polymerase inhibitors or carboplatin and *PTEN* loss with phosphatidylinositol 3-kinase or AKT inhibitors.[32,41-47] When moved to mHSPC (in patients with the appropriate genomic profile), these therapies may improve outcomes more dramatically.

Current Practice in Response to Available Data

Many physicians understandably are concerned about making major changes to their practice on the basis of subgroup analyses of the trials described herein, some of which are post hoc. It comes down to a desire for conclusive data versus a willingness to tolerate some imperfection and to make the best decision possible on the basis of the data available. The trials that generate these results took many years to conduct and the willing participation of thousands of patients internationally. The generation of conclusive data about the proper setting to use DOC, an ARPI, and/or RT to the prostate would require many more years and many more patients, a large cost for validating a result that already has high confidence.

We take a pragmatic approach to interpreting these newly available results and conclude that they are sufficient to change practice but do not preclude further studies to confirm their value moving forward. As part of our pragmatic approach, we propose that pending conclusive data in patients with low-volume oligometastatic mHSPC on conventional imaging, it is reasonable to consider intensified therapy with ADT + ARPI, radiation to the prostate, and potentially radiation to metastatic sites, with an acknowledgment that fewer data exist for the latter approach. Moreover, if the patient achieves an undetectable prostate-specific antigen with durable control (eg, more than 2 to 3 years), it is reasonable to halt systemic therapy, especially if adverse events that are metabolic and quality-of-life impairing emerge, and observe until biochemical progression. Not all these strategies are supported by level 1 evidence at this time and should be undertaken on the basis of informed shared decisions that balance risks/benefits, comorbidities, emerging data, and patient preferences. In the meantime, the trials that test these hypotheses should continue, and patients preferentially should be offered the opportunity to participate in these trials. Individual patient data registries or meta-analyses, which depend on a global willingness for data sharing, will provide greater granularity on outcomes by subgroup in the real world. These are planned or ongoing.

In conclusion, since 2015, there has been significant improvement in survival for patients with mHSPC, with an unprecedented "return on investment" from DOC and ARPIs. Refinement of clinical subgroups and incorporation of molecular characteristics will help to personalize therapy by identifying for whom and how to intensify therapy. Yet, we remain far from eradicating metastatic disease. Continued discovery and evaluation of novel therapeutic vulnerabilities and a better understanding of mechanisms of resistance are critical to transforming care. These efforts to expand the patient populations that experience an exceptional response to systemic therapy will convert metastatic prostate cancer from deadly to chronic on our way to potential cure.

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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Metastatic Hormone-Sensitive Prostate Cancer: Clinical Decision Making in a Rapidly Evolving Landscape of Life-Prolonging Therapy

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Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer

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Metastatic castration-resistant prostate cancer (mCRPC) is a heterogeneous disease with diverse drivers of disease progression and mechanisms of therapeutic resistance. We conducted deep phenotypic characterization of CRPC metastases and patient-derived xenograft (PDX) lines using whole-genome RNA sequencing, gene set enrichment analysis, and immunohistochemistry. Our analyses revealed 5 mCRPC phenotypes based on the expression of well-characterized androgen receptor (AR) or neuroendocrine (NE) genes: AR-high tumors (ARPC), AR-low tumors (ARLPC), amphicrine tumors composed of cells coexpressing AR and NE genes (AMPC), double-negative tumors (i.e., AR^{-}/NE^{-}; DNPC), and tumors with small cell or NE gene expression without AR activity (SCNPC). RE1 silencing transcription factor (REST) activity, which suppresses NE gene expression, was lost in AMPC and SCNPC PDX models. However, knockdown of REST in cell lines revealed that attenuated REST activity drives the AMPC phenotype but is not sufficient for SCNPC conversion. We also identified a subtype of DNPC tumors with squamous differentiation and generated an encompassing 26-gene transcriptional signature that distinguished the 5 mCRPC phenotypes. Together, our data highlight the central role of AR and REST in classifying treatment-resistant mCRPC phenotypes. These molecular classifications could potentially guide future therapeutic studies and clinical trial design.

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Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer

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Metastatic castration-resistant prostate cancer (mCRPC) is a heterogeneous disease with diverse drivers of disease progression and mechanisms of therapeutic resistance. We conducted deep phenotypic characterization of CRPC metastases and patient-derived xenograft (PDX) lines using whole-genome RNA sequencing, gene set enrichment analysis, and immunohistochemistry. Our analyses revealed 5 mCRPC phenotypes based on the expression of well-characterized androgen receptor (AR) or neuroendocrine (NE) genes: AR-high tumors (ARPC), AR-low tumors (ARLPC), amphicrine tumors composed of cells coexpressing AR and NE genes (AMPC), double-negative tumors (i.e., AR^-/NE^-; DNPC), and tumors with small cell or NE gene expression without AR activity (SCNPC). RE1 silencing transcription factor (REST) activity, which suppresses NE gene expression, was lost in AMPC and SCNPC PDX models. However, knockdown of REST in cell lines revealed that attenuated REST activity drives the AMPC phenotype but is not sufficient for SCNPC conversion. We also identified a subtype of DNPC tumors with squamous differentiation and generated an encompassing 26-gene transcriptional signature that distinguished the 5 mCRPC phenotypes. Together, our data highlight the central role of AR and REST in classifying treatment-resistant mCRPC phenotypes. These molecular classifications could potentially guide future therapeutic studies and clinical trial design.

Introduction

The androgen receptor (AR) regulates cellular programs that promote the survival and proliferation of prostate cancer (PC) cells. Consequently, first-line treatment for metastatic PC centers on inhibiting AR activity through androgen deprivation therapy (ADT), resulting in the suppression of AR target genes and clinical remissions that generally last several years (1). However, ADT is not curative. PC recurs as castration-resistant prostate cancer (CRPC), typically with reactivated AR signaling. Second-generation AR pathway inhibitors (ARIs), such as enzalutamide (ENZ) and abiraterone (ABI), were designed to further repress AR signaling and are primarily used to treat CRPC. Although these agents extend survival, durable complete responses are rare and these therapies also eventually fail (2, 3).

Typically, the vast majority of metastatic CRPC (mCRPC) tumors progress with rising prostate-specific antigen (PSA/KLK3) levels despite standard of care treatment. Moreover, most mCRPC tumors are adenocarcinomas, which have robust AR program activity (4). Though rigorous epidemiological data are lacking, recent studies report that a substantial number of mCRPC tumors progressing on ARIs have lost AR signaling (5). Paralleling increased use of ARIs has been an increase in the proportion of treatment-resistant CRPC metastases that have AR-null phenotypes, i.e. tumors with diffuse small cell or neuroendocrine (NE) characteristics (SCNPC) or the recently described double-negative (DNPC) phenotype that lacks both NE and AR activity (5). A contemporary study evaluating the histology and molecular characteristics of 202 men with mCRPC found that 17% of the evaluable tumors were classified as SCNPC and this phenotype was associated with short-

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ened survival (6). Notably, a subset of tumors exhibited discordance between the pathological assessment of SCNPC and gene expression programs. Other tumors exhibited mixed phenotypes of NE features concurrent with AR activity, raising questions of intratumoral heterogeneity due to mixtures of cell types (6).

In addition to histology, the classification of cancers into subtypes with distinct functional features has been supplemented with transcript profiles. For example, transcript signatures subdivide breast cancers into groups that exhibit distinct outcomes (7). This subclassification, based on gene expression levels, has also been applied to localized PC and shown to associate with treatment outcomes (8, 9). In this study, we sought to characterize the phenotypic diversity of treatment-refractory mCRPC using both histological assessments and gene expression profiling. In addition to SCNPC and DNPC, we identified adenocarcinomas that had high AR activity (ARPC), measurable but low AR activity (ARLPC), and amphicrine tumors comprised of cells exhibiting both AR and NE activity (AMPC). Notably, a subset of DNPC tumors exhibited squamous differentiation. We determined that the relationships of 2 major factors regulating cell differentiation states, AR and RE1 silencing transcription factor (REST), associated with these mCRPC subtypes. We generated a 26-gene transcriptional signature that could be clinically useful for classifying mCRPC phenotypes and prioritizing treatment.

Results

Treatment-refractory mCRPC exhibits diverse phenotypes. To assess the diversity of phenotypes present following resistance to therapeutics used to treat metastatic PC, we evaluated 98 tumors obtained at rapid autopsy from 55 men between 2003 and 2017. Patient demographics and clinical data are summarized in Supplemental Table 2; supplemental material available online with this article; https://doi.org/10.1172/JCI128212DS1. All patients received ADT. The median duration of treatment was 4.2 years (range, 0.3–15.1 years). Patients also received a variety of other drugs including docetaxel (n = 44; 80%), abiraterone (n = 8; 15%), enzalutamide (n = 4; 7%) or both abiraterone and enzalutamide (n = 17; 31%). Bone, lymph nodes, and liver were the most frequent sites of metastasis.

To provide an initial evaluation of phenotypic diversity, we used histological assessments and immunohistochemical (IHC) analysis of proteins associated with AR-active adenocarcinomas (AR and PSA) and NE differentiation (chromogranin A, CHGA; synaptophysin, SYP). We observed 5 distinct mCRPC phenotypes: adenocarcinomas with near-uniform expression of AR and PSA, and lack of CHGA and SYP expression, classified as ARPC; adenocarcinomas with weak or heterogeneous expression of AR and PSA, and negative for CHGA and SYP, classified as AR-low PC (ARLPC); tumors composed of cells that coexpress AR, PSA, CHGA, and SYP, classified as amphicrine PC (AMPC); tumors with small cell or neuroendocrine histology with CHGA and SYP expression and lack of AR and PSA expression, classified as small cell or neuroendocrine PC (SCNPC); and tumors lacking detectable expression of AR, PSA, CHGA, and SYP, classified as double-negative PC (DNPC; Figure 1A).

Transcriptome profiles associate with mCRPC phenotypes. Morphologic and IHC analyses are the gold standard for pathologic diagnosis. However, the assessment of transcriptional programs has found utility in subclassifying breast tissue and cancers that exhibit similar histological characteristics (10, 11). We sought to develop a clearer understanding of the mCRPC disease continuum through transcriptome profiling by whole-genome RNA sequencing (RNA-Seq) of 98 mCRPC tumors. Patient metastases were first analyzed and segregated according to expression levels of a gene signature reflecting AR activity (AR panel; Figure 1B). The AR-regulated genes selected for the AR signature are well characterized in the literature and include *KLK3*, *NKX3-1*, *SLC45A3*, and *TARP* (12–14). Tumors were also analyzed and segregated depending on expression levels of NE-associated genes. We previously demonstrated that NE-associated genes can be separated into REST-repressed genes such as *SYP*, *CHGA*, *SNAP25*, and *SRRM4* (NEURO I panel; ref. 15), and transcription factors that regulate NE differentiation, such as *SOX2*, *POU3F2/BRN2*, *NKX2-1*, and *LMO3* (NEURO II panel; refs. 15–17). Applying the AR, NEURO I, and NEURO II gene expression sets to the mCRPC tumors clearly defined the 5 mCRPC subtypes (Figure 1B). ARPC tumors expressed AR-regulated genes but also showed heterogeneity with low expression of some NE genes. ARLPCs had attenuated AR expression with concomitant low expression of some AR-regulated genes. AMPCs expressed AR-associated genes and REST-repressed neuronal factors (NEURO I), but lacked expression of the NE-associated transcription factors (NEURO II). DNPC tumors were generally devoid of AR, NEURO I, and NEURO II panel genes. SCNPC tumors lacked AR expression and signaling but expressed both the NEURO I and NEURO II genes. Analysis of 62 corresponding tumor sites through IHC revealed that phenotypic determinations based on AR, PSA, CHGA, and SYP staining mirrored the phenotypic determinations made through RNA-Seq analysis (Supplemental Figure 1). Moreover, our rapid autopsy cohort included 34 patients, each with 2–3 metastatic sites characterized through RNA-Seq. This provided an opportunity to query the intertumoral phenotypic heterogeneity within patients. Of the 34 patients with 2–3 analyzed metastases, 5 patients (14.7%) displayed phenotypic differences between sites. However, this may underestimate the extent of heterogeneity, as 2–3 metastases generally represent a fraction of the total tumor burden. In addition, there can be intratumoral phenotypic heterogeneity that is not readily assessed through bulk RNA sequencing (Supplemental Figure 2).

To validate the results of the patient specimen analysis using an orthogonal system, we conducted RNA-Seq and IHC analyses on 18 CRPC LuCaP patient-derived xenograft (PDX) lines. The 5 distinct phenotypes were identified by IHC and accurately segregated according to the AR, NEURO I, and NEURO II gene expression profiles (Supplemental Figure 3, A and B).

To discover novel gene expression profiles for each of the mCRPC phenotypes, we cross-compared the patient metastases RNA-Seq data from the defined phenotypic cohorts (i.e., ARLPC, AMPC, DNPC, and SCNPC) relative to ARPC. This analysis generated a comprehensive list of unique and shared upregulated differentially expressed genes (vs. ARPC, up >3-fold and $P < 0.05$; Figure 1C and Supplemental Table 3). In addition, this analysis demonstrated that DNPC and SCNPC are markedly different from the other mCRPC phenotypes (806 and 1669 unique upregulated genes respectively; Figure 1C). Notably, the AR-null phenotypes (DNPC and SCNPC) share an additional 590 upregulated

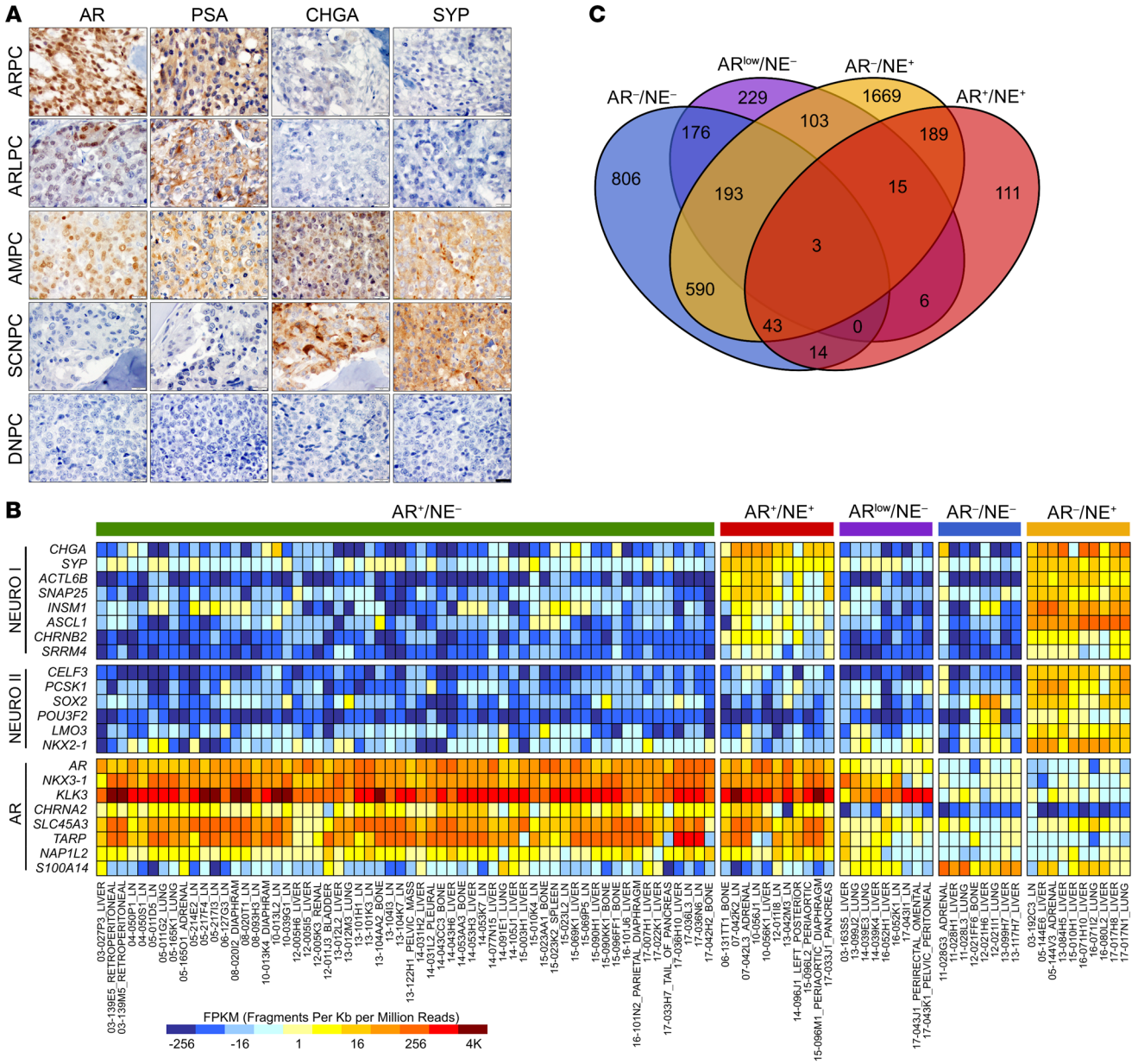


Figure 1. Molecular profiling of mCRPC reveals a heterogeneous disease. (**A**) IHC of 5 mCRPC sites from patients using antibodies to AR, PSA, CHGA, and SYP. Scale bars: 20 μM. (**B**) RNA-Seq heatmap of mCRPC specimens acquired through rapid autopsy from 2003–2017 (n = 98). REST-repressed NE genes are listed in the NEURO I panel (top), NE transcription factors are listed in the NEURO II panel (middle), and AR-associated genes are listed in the AR panel (bottom). Results are expressed as $\log_2$ fragments per kilobase of transcript per million mapped reads (FPKM) and colored according to scale. (**C**) Venn diagram showing the number of unique and shared upregulated genes between phenotypes relative to ARPC (up >3-fold; $P < 0.05$). ARPC (AR-high prostate cancer; AR^+/NE^-), ARLPC (AR-low prostate cancer; AR^{low}/NE^-), AMPC (amphicrine prostate cancer; AR^+/NE^+), DNPC (double-negative prostate cancer; AR^-/NE^-), and SCNPC (small cell or neuroendocrine prostate cancer; AR^-/NE^+).

genes relative to the AR-expressing phenotypes (Figure 1C). Furthermore, ARLPC, and AMPC share gene expression profiles similar to ARPC (Figure 1C).

Gene Set Enrichment Analysis (GSEA) determined that the 806 upregulated genes unique to DNPC were enriched in Gene Ontology biological process terms for response to external biotic stimulus ($P = 4.5 \times 10^{-18}$), immune system process ($P = 3.5 \times 10^{-15}$), and cornification ($P = 5.5 \times 10^{-9}$). As expected, the 1669 upregulated genes unique to SCNPC were enriched for core neuronal activities such as nervous system process ($P = 7.5 \times 10^{-12}$) and regulation of nervous system process ($P = 4.7 \times 10^{-10}$). Interestingly, the top processes for the 829 upregulated genes in common between SCNPC and DNPC included locomotory behavior ($P = 5.0 \times 10^{-07}$) and cell adhesion ($P = 2.1 \times 10^{-07}$), suggesting changes in metastatic potential common to AR-null phenotypes. The 229 upregulated genes unique to the ARLPC phenotype were enriched for processes in response to external biotic stimulus ($P = 3.3 \times 10^{-07}$) and regulation of inflammatory response ($P = 8.4 \times 10^{-06}$), while the 193 upregulated genes in common between ARLPC, DNPC, and SCNPC phenotypes were significantly enriched in acute inflammatory

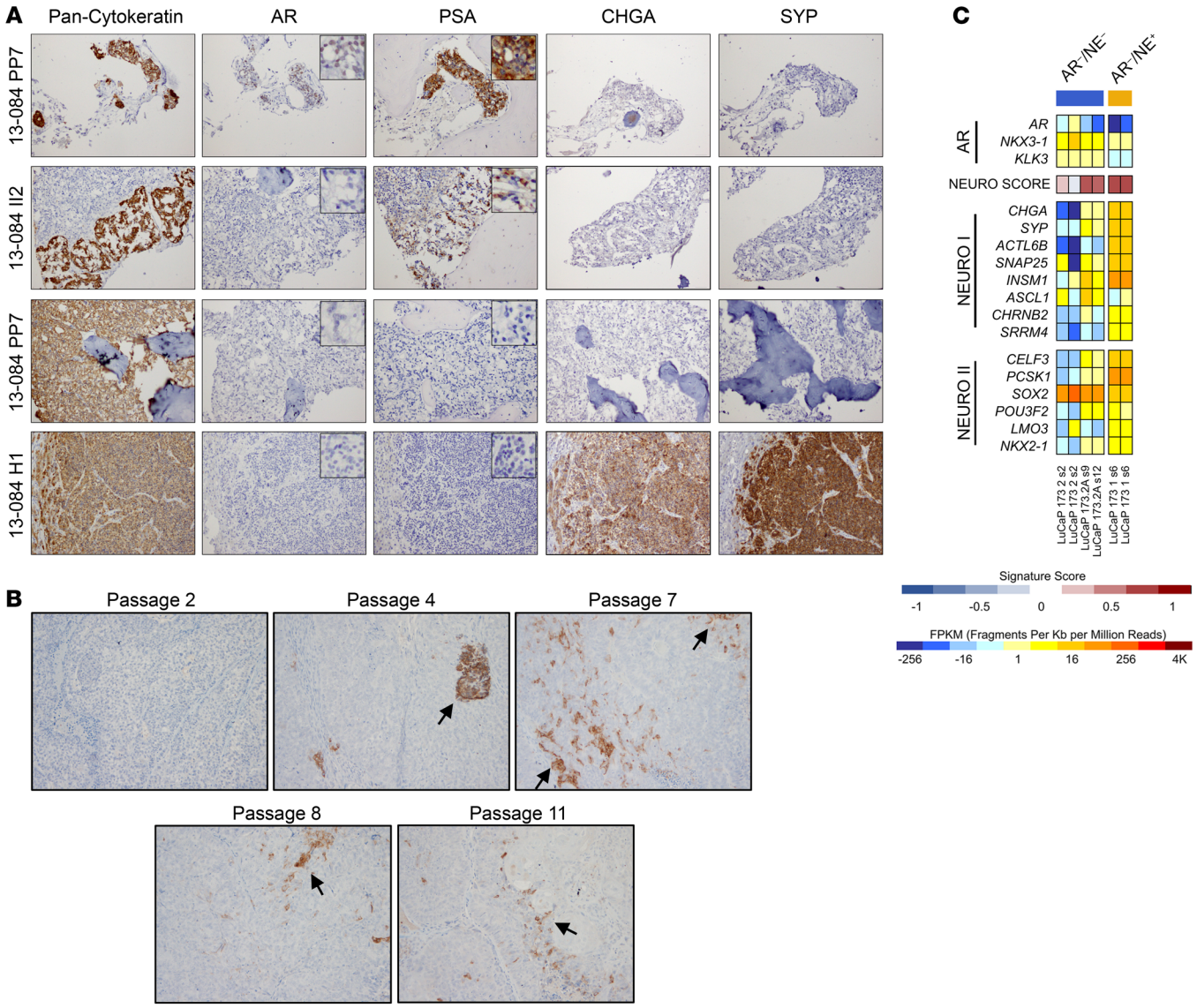


Figure 2. Disease progression is a continuum in mCRPC specimens. (**A**) IHC of different mCRPC sites from patient 13-084. Site PP7 (bone; ARPC), II2 (bone; ARLPC), PP7 (bone; DNPC), and H1 (liver, SCNPC). Primary antibodies were directed toward pan-cytokeratin, AR, PSA, CHGA, and SYP. Insets for AR and PSA staining are images of the same section using the ×400 objective lens. Original magnification 40×. (**B**) IHC of LuCaP 173.2 tumor sections from passages 2, 4, 7, 8, and 11 using a SYP antibody. Black arrows point to clusters of cells with SYP positivity. Magnification 100×. (**C**) RNA-Seq heatmap and NEURO score of LuCaP 173.1 and serial passages from LuCaP 173.2. Results are expressed as $\log_2$ FPKM or as enrichment scores and are colored according to scale.

response ($P = 4.0 \times 10^{-11}$) and defense response ($P = 1.3 \times 10^{-06}$). Finally, GSEA determined that the 111 upregulated genes unique to AMPC were not involved in any significant processes. However, the 250 common upregulated genes between AMPC and SCNPC were involved in ancillary neuronal processes such as neurotransmitter transport ($P = 4.4 \times 10^{-10}$) and synaptic vesicle localization ($P = 6.5 \times 10^{-09}$). Importantly, analysis of the 250 significantly upregulated genes shared between SCNPC and AMPC using the MSigDB C3-Transcription Factor Target database showed that REST was the top transcription factor pathway altered in the gene set ($P = 4.2 \times 10^{-35}$; Supplemental Table 4). Taken together, these data support the use of AR, NEURO I, and NEURO II genes to segregate mCRPC phenotypes and identify biologically relevant pathways that emphasize the heterogeneity of mCRPC.

mCRPC phenotypes represent a disease continuum. The relationships between different mCRPC phenotypes have not been clearly established though prior studies suggest that SCNPC is often derived from an AR-positive precursor, or share a common progenitor (18, 19). Thus, we investigated these relationships by studying the phenotypic progression of an individual with mCRPC and a complicated treatment history. At diagnosis in 2012, patient 13-084 had a PSA of 159 ng/mL and a prostate biopsy revealed an adenocarcinoma with a Gleason score of 4 + 5 = 9 and IHC demonstrating focal NE differentiation. He was treated with leuprolide and bicalutamide but ensuing CT and bone scans revealed numerous metastases in liver, lung, and bone. Platinum-based chemotherapy was initiated due to the possible presence of SCNPC with cycles of carboplatin/irinotecan (5 cycles) or cisplatin/irinotecan

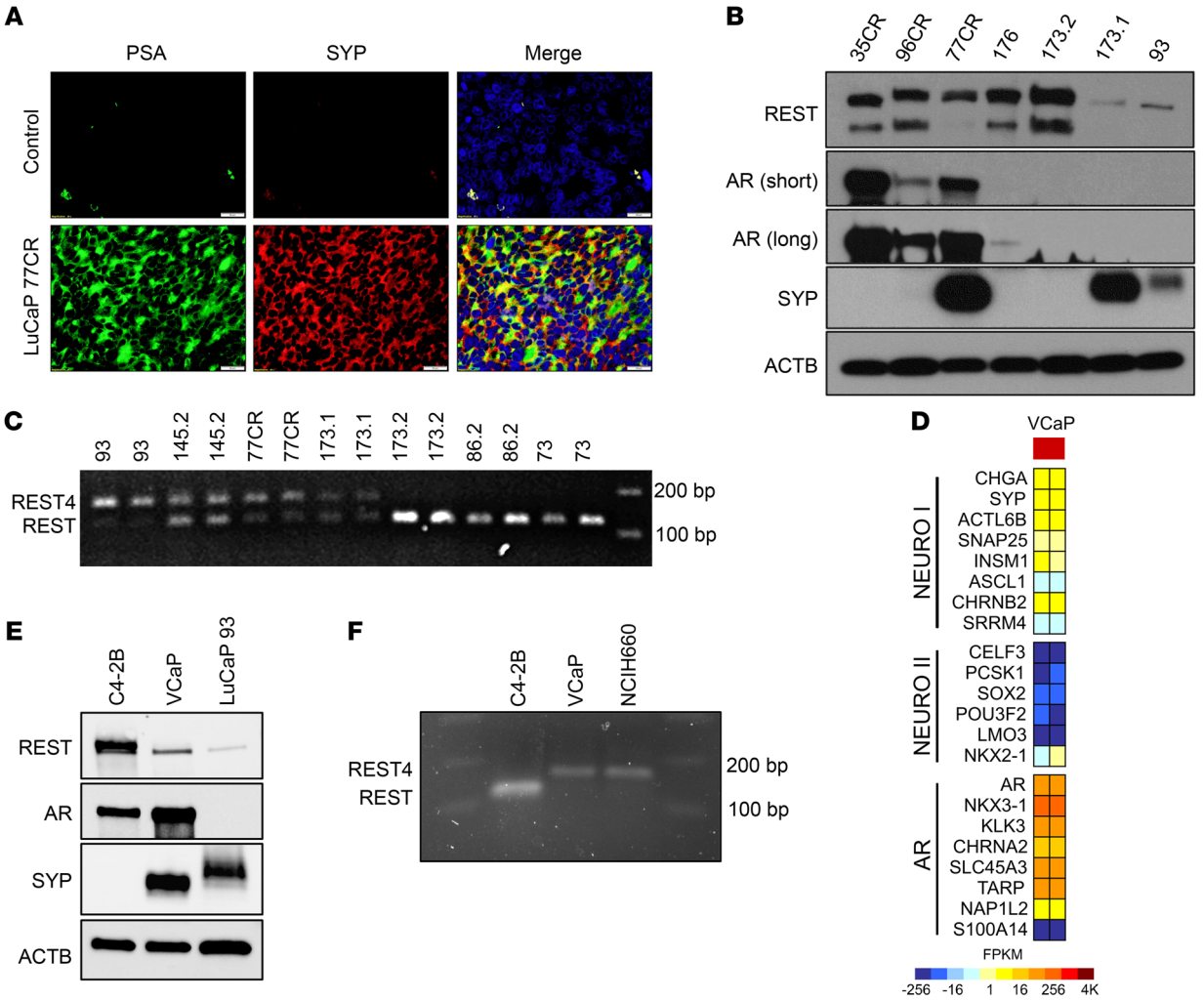


Figure 3. REST splicing occurs in AMPC and SCNPC phenotypes. (**A**) Immunofluorescence of an AMPC LuCaP 77CR tumor using PSA (green) and SYP (red) antibodies. Sections were counterstained with DAPI (blue) and top panels represent LuCaP 77CR PDX sections stained with secondary antibody only. Scale bars: 20 μM. (**B**) Immunoblot of LuCaP PDX specimens probing for REST, AR, and SYP. ACTB was used as a loading control. Short, 10-second film exposure; long, 5-minute film exposure. (**C**) PCR of LuCaP PDX specimens using primers specific to REST shows the REST4 insertion sequence appearing in AMPC (LuCaP 77CR) and SCNPC (LuCaP 93, 145.2, and 173.1) but not in DNPC (LuCaP 173.2) or ARPC (LuCaP 86.2 and 73). (**D**) RNA-Seq heatmap of VCaP cells displaying NE-associated genes (NEURO I and NEURO II) and AR-associated genes. Results are expressed as $\log_2$ FPKM and colored according to scale. (**E**) Immunoblot of C4-2B, VCaP, and LuCaP 93 whole-cell extracts using antibodies against AR, REST, SYP, and ACTB. ACTB was used as a loading control. (**F**) PCR of C4-2B, VCaP, and NCIH660 cells using primers specific to REST. The upper band represents the REST4 splice variant.

(3 cycles) leading to a PSA decline and stable disease for approximately 8 months. He subsequently received 2 cycles of capecitabine and gemcitabine with eventual PSA progression prior to death (Supplemental Figure 4). At autopsy in 2013, we recovered several metastatic tumors that exhibited different phenotypes, including ARPC, ARLPC, and DNPC sites in bone and SCNPC sites in the liver as determined by IHC (Figure 2A). We developed 2 PDX lines representing SCNPC (LuCaP 173.1) and DNPC (LuCaP 173.2) from acquired patient metastases (5). Previous reports have described the transdifferentiation of an AR-expressing adenocarcinoma PC PDX line to SCNPC (20). We therefore questioned whether the DNPC phenotype is a transition stage. We sought to test the hypothesis that sustained tumor growth through serial passaging of the DNPC LuCaP 173.2 PDX line would lead to SCNPC conversion. Indeed, serial passaging in intact mice of LuCaP 173.2 and staining for SYP expression through IHC showed that first passage PDX tumors were negative for SYP expression, whereas SYP-positive cells were detected by passage 4 and were maintained as a minor cell population through passage 9 (Figure 2B). RNA-Seq of LuCaP 173.2 from passages 2, 9, and 12 indicated that the NEURO I and NEURO II panels of genes were expressed at substantially higher levels in the later passages (Figure 2C). Furthermore, the NEURO scores of LuCaP 173.2 from passages 9 and 12 were similar to SCNPC LuCaP 173.1. These data suggest that mCRPC is a disease continuum, and that although the DNPC phenotype is generally stable, a small proportion of DNPC tumor cells possess an intrinsic plasticity that permits conversion to SCNPC.

The amphicrine phenotype and relationship with REST expression. Historically, SCNPC was considered to lack AR activity but recent studies have identified atypical tumors with NE features that express

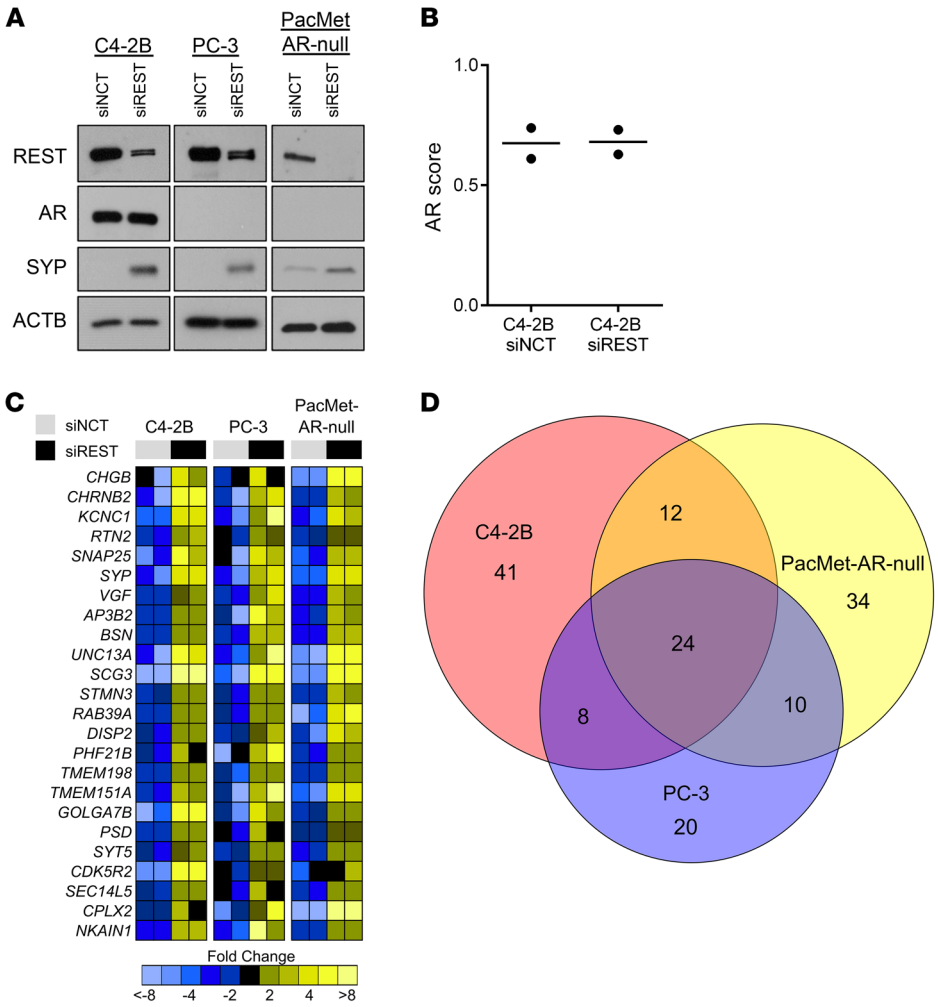


Figure 4. REST knockdown in AR-expressing and AR-null CRPC cell lines. (**A**) Immunoblot of REST, AR, SYP, and ACTB using C4-2B, PC-3, and PacMet AR-null cells transfected with either REST siRNA (siREST) or negative control siRNA (siNCT). (**B**) AR activity scores assessed in C4-2B cells transfected with siNCT ($n = 2$) or siREST ($n = 2$) by RNA-Seq. (**C**) RNA-Seq heatmap of the 24 common upregulated genes (up >3-fold; $P < 0.05$) between C4-2B, PC-3, and PacMet AR-null cells transfected with siREST or siNCT. Log_2 mean-centered ratios of genes are depicted and colored according to scale. (**D**) Venn diagram describing the interrelationships of all upregulated genes (vs. siNCT; up >3-fold; $P < 0.05$) identified through RNA-Seq in siREST transfected cell lines.

AR and exhibit AR-mediated signaling (6). In addition, classification of the AMPC phenotype based on bulk RNA-Seq or IHC using single markers may be due to tumors comprised of multiple cell types (AR^+/NE^- and AR^-/NE^+) or may be due to tumors comprised of individual cells expressing both AR and NE differentiation markers simultaneously. Thus, to establish the existence of AMPC cells in our clinical specimens (i.e., cells with both AR transcriptional output and neuroendocrine features; AR^+/NE^+), we stained LuCaP PDX tumors and patient metastases with immunofluorescent (IF) antibodies to PSA and SYP. AMPC LuCaP 77CR tumors contained numerous cells coexpressing PSA and SYP (Figure 3A). Though PSA and SYP coexpression normally occurred throughout LuCaP 77CR tumors, we also identified a subset of tumors with focal SYP expression (unpublished observations). Furthermore, we used IF to characterize 6 AMPC metastases from 4 patients. The patient tissues used for IF analysis were adjacent to the specimens used for RNA-Seq. Importantly, IF demonstrated clear PSA and SYP coexpression in patient tumor cells. However, patient 13-042 site M3 and patient 17-033 site J1 showed regions that were mixed of distinct populations of ARPC and SCNPC tumor cells (Supplemental Figure 5).

Previously, we interrogated SCNPC patient tumors and PDX lines and determined that SCNPC is associated with loss of REST repressor activity (15). However, the role of REST in other mCRPC phenotypes has not been evaluated. Using representative PDX lines from ARPC (LuCaP 35CR and 96CR), AMPC (LuCaP 77CR), ARLPC (LuCaP 176), DNPC (LuCaP 173.2), and SCNPC (LuCaP 173.1 and 93), we found that full-length REST protein was decreased in both AMPC and SCNPC tumors (Figure 3B). Interestingly, we observed REST species with our REST C-terminus antibody at both approximately 120 KDa and approximately 200 KDa in PDX lysates from ARPC, ARLPC, and DNPC. Full-length REST protein is predicted to be 116 KDa but can be O-glycosylated and readily detected at approximately 200 KDa (21, 22). Additionally, the REST transcript has multiple splice variants that produce truncated proteins (23). Nevertheless, both REST proteins with intact C-terminus repressor domains were diminished in AMPC and SCNPC PDX models. Moreover, AMPC LuCaP 77CR showed robust expression of both AR and SYP protein, whereas ARLPC LuCaP 176 had low AR protein expression (Figure 3B).

Next, we examined alternative splicing of the REST transcript. The RNA splicing factor SRRM4 splices the REST transcript to REST4, resulting in the loss of the C-terminus repressor domain and diminished REST transcriptional repression (15, 24, 25). To examine SRRM4-mediated splicing of REST in mCRPC phenotypes, we conducted PCR using REST primers spanning the SRRM4 splice site and determined that REST4 splicing events occurred exclusively in AMPC and SCNPC LuCaP PDX models (Figure 3C). However, instead of a previously reported 62 bp inser-

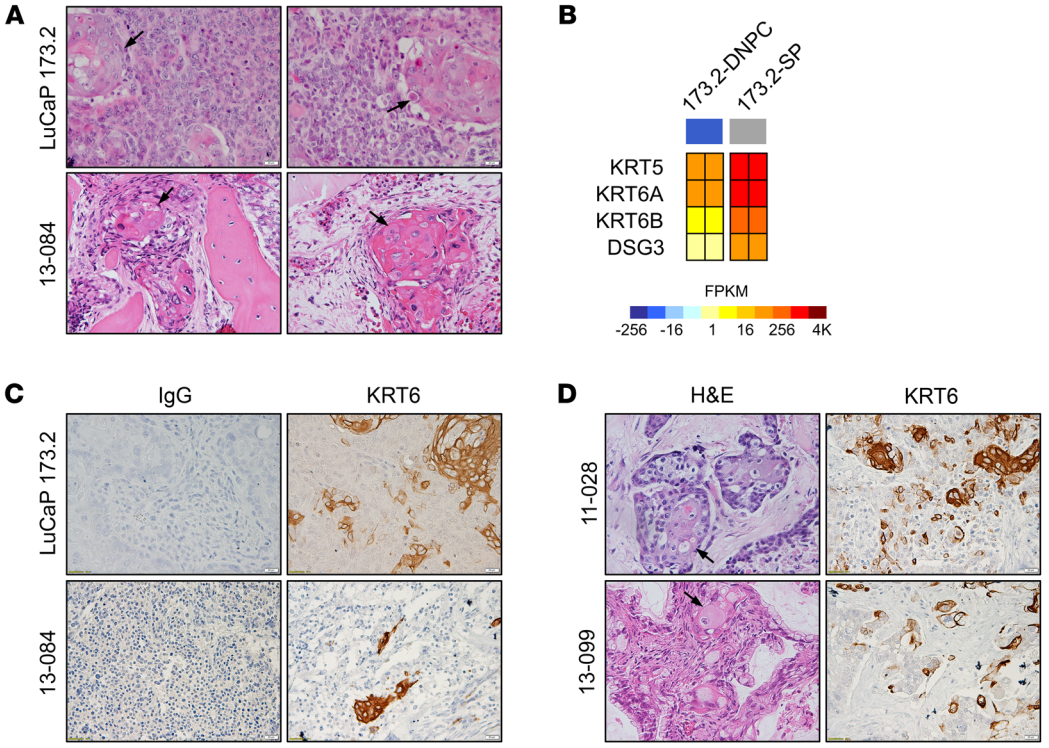


Figure 5. DNPC can convert to a squamous phenotype. (**A**) H&E staining of mCRPC tissues from LuCaP 173.2 and patient 13-084. Black arrows point to squamous pearl structures. (**B**) Expression of squamous cell lung cancer associated genes from RNA-Seq of LuCaP 173.2 DNPC cells and squamous pearl (SP) cells isolated by laser capture microdissection. Results are expressed as $\log_2$ FPKM and colored according to scale. (**C**) IHC of specimens from LuCaP 173.2 and patient 13-084 using KRT6 antibody or IgG as a negative control. (**D**) H&E staining (left panels) and KRT6 IHC (right panels) of DNPC tumor sections from patients 11-028 and 13-099. Scale bars: 20 μM.

tion into the REST transcript (25), band sequencing identified a 50 bp insertion, suggesting a mechanism of REST4 splicing in AMPC and SCNPC phenotypes similar to small cell lung cancer (26). Taken together, these data indicate that the AMPC phenotype arises from the loss of REST transcriptional repression.

To further support the existence of the AMPC phenotype, we interrogated the VCaP PC cell line, which exhibits an amphicrine-like transcript profile. RNA-Seq confirmed that VCaP cells express AR-associated genes and the REST-repressed NEURO I genes but do not express the NEURO II transcription factors that drive the SCNPC phenotype (Figure 3D). Immunoblot analysis determined that VCaP cells express considerable AR and SYP protein and have diminished full-length REST protein expression compared with C4-2B cells (Figure 3E). Immunofluorescence validated that both PSA and SYP are coexpressed in the same VCaP cell (Supplemental Figure 6) and PCR analysis of REST determined that REST transcripts are alternatively spliced to REST4, similar to neuroendocrine NCIH660 cells (Figure 3F). Notably, the growth of VCaP cells is inhibited by ADT or exposure to the AR antagonist enzalutamide (27). In addition, 22Rv1 cells also exhibit features of AMPC as they have attenuated REST expression and appreciable SYP and AR protein expression (28). Taken together, these results confirm the existence of AMPC cells in patient specimens and in CRPC models in vitro and in vivo, and suggest that the AMPC phenotype is still driven by AR activity and is responsive, at least transiently, to AR pathway repression.

REST knockdown in CRPC cells promotes an amphicrine phenotype. To examine the impact of the loss of REST activity in AR-expressing and AR-null cell lines, we conducted knockdown studies using siRNAs directed to REST (siREST) or a negative control (siNCT) in C4-2B, PC-3, and PacMet AR-null cells. PacMetUT1 cells were modified using CRISPR-Cas9–mediated editing to knockout AR expression and were characterized previously (5, 29). REST knockdown led to increases in the NE-associated protein SYP (Figure 4A). Interestingly, REST depletion in AR-expressing C4-2B cells did not alter AR protein expression or the magnitude of AR transcriptional output (Figure 4, A and B). However, this does not rule out the possibility that complete loss of REST could alter the AR transcriptional output. Transcript profiling by RNA-Seq and subsequent GSEA showed that REST ablation in C4-2B, PC-3, and PacMet AR-null cells led to significant upregulation of known REST-repressed genes (up >3-fold; $P < 0.05$). Furthermore, the REST pathway was the top altered pathway from the MSigDB C3-Transcription Factor Target database in all siREST transfected cell lines. Surprisingly, the number of genes significantly upregulated with REST knockdown was relatively low across all cell models and only 24 genes were in common between C4-2B, PC-3, and PacMet AR-null cells (Figure 4, C and D; Supplemental Table 5). The REST-repressed genes with increased expression following REST depletion included *SYP, SNAP25, CHRNB2* (NEURO I Panel) as well as *VGF*, *SCG3*, and *CHGB* (Figure 4C). However, REST knockdown did not significantly alter the expression of transcrip-

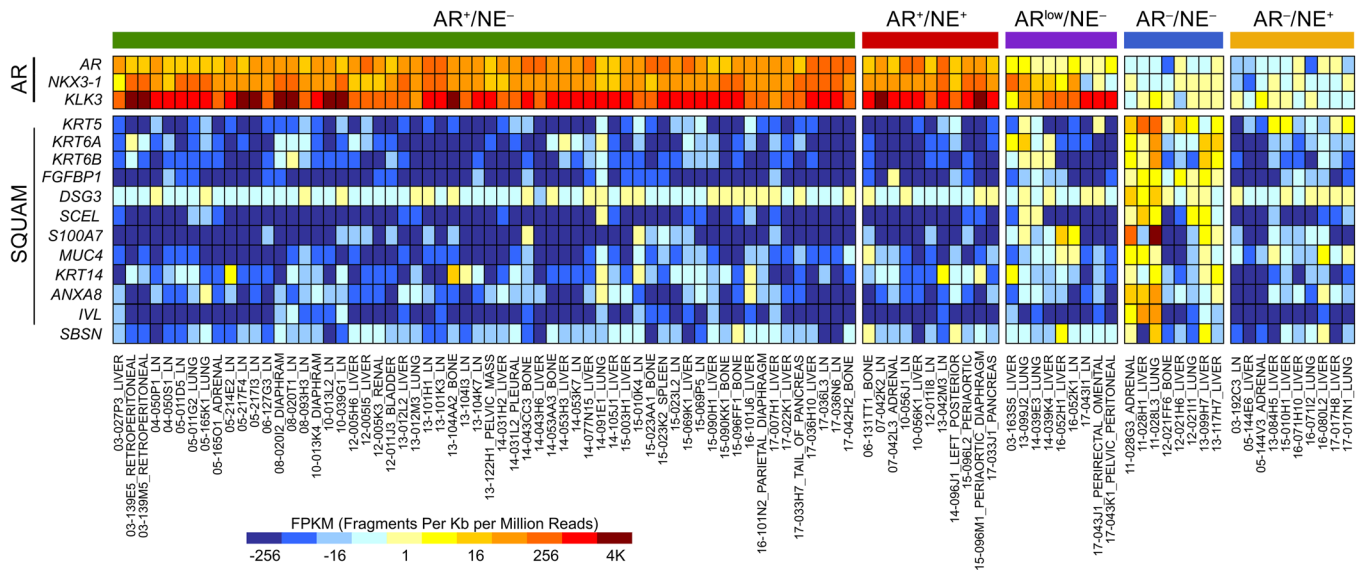


Figure 6. Expression of squamous markers is associated with DNPC and ARLPC. RNA-Seq heatmap of patient specimens (n = 98) highlighting AR-regulated genes and genes associated with squamous pearl cells (SQUAM). Results are expressed as $\log_2$ FPKM and colored according to scale.

tion factors and drivers of SCNPC such as *NKX2-1*, *POU3F2*, and *SOX2* (NEURO II panel) in either AR-expressing or AR-null CRPC cell lines (Supplemental Figure 7). Taken together, we determined that REST loss induces the expression of a limited set of NE-associated genes (NEURO I) and drives PC conversion to the AMPC phenotype with continued evidence of AR activity.

A subtype of mCRPC exhibits features of squamous cell carcinoma. While histologically characterizing the DNPC LuCaP 173.2 PDX model, we observed squamous pearls, which were evidence of focal squamous differentiation (Figure 5A). To determine if the squamous pearls occurred spontaneously during LuCaP 173.2 development or were native to the original malignancy, we evaluated tumors from patient 13-084 and identified squamous pearl structures in adjacent tumor sections of the rib bone metastasis that served as the origin of LuCaP 173.2 (Figure 5A). Squamous pearl cells from LuCaP 173.2 PDX tumors were then isolated using laser capture microdissection and subjected to RNA-Seq and GSEA. Transcriptome analysis determined that 880 genes were upregulated and 29 genes were downregulated in LuCaP 173.2 squamous pearl cells compared with surrounding DNPC tumor cells (FDR < 0.001; Supplemental Table 6). GSEA determined that many of the upregulated genes were enriched in other squamous cancer gene sets, such as RICKMAN_HEAD_AND_NECK (P < 0.0001; ref. 30). Importantly, KRT5, KRT6A, KRT6B, and DSG3 were recently highlighted through ROC curves as biomarkers to differentiate lung adenocarcinoma from lung squamous cell cancer (31). Indeed, our analysis showed that *KRT5*, *KRT6A*, *KRT6B*, and *DSG3* were highly expressed in LuCaP 173.2 squamous pearl cells compared with surrounding DNPC tissue (Figure 5B). IHC using a primary antibody specific to KRT6 in LuCaP 173.2 and 13-084 tumor specimens revealed strong KRT6 staining only in tumor cells with squamous pearl morphology (Figure 5C).

Examination of 4 other patients with DNPC metastases identified squamous pearls with positive KRT6 staining in 2 patients: 11-028 and 13-099 (Figure 5D). Interestingly, patient 11-028 had an adenocarcinoma phenotype in the initial prostate biopsy and was subsequently treated with diethylstilbesterol (DES) for 13 months prior to cystoprostatectomy. At the time of cystoprostatectomy, histology and IHC revealed adenocarcinoma with focal basaloid and squamous differentiation in several sections of the prostate as well as a left axillary lymph node that was consistent with squamous carcinoma. The other 2 patients with KRT6-positive metastases, patients 13-084 and 13-099, had primary prostate cancers with no evidence of squamous differentiation, and subsequent hormone therapy led to the appearance of squamous mCRPC. Although DES and hormone therapies have been linked to the development of squamous cancer in the prostate with subsequent squamous metastases (32–36), this report provides evidence for hormone therapy–mediated conversion of ARPC to squamous DNPC at metastatic sites.

We compared the top significantly (FDR < 0.001) upregulated genes from the LuCaP 173.2 squamous pearl data set with the literature to identify genes with known roles in squamous cell differentiation or other squamous cancers. In addition to *KRT5*, *KRT6A*, *KRT6B*, and *DSG3*, we also found *IVL*, *SBSN*, *FGFBP1*, *SCEL*, *S100A7*, *MUC4*, *KRT14*, and *ANXA8* to be significantly overexpressed in other squamous cell types (37–44). Importantly, RNA-Seq heatmaps show that these genes are strikingly elevated in subsets of both ARLPC and DNPC patient specimens (Figure 6), suggesting that ARLPC and DNPC phenotypes could be transition states to squamous mCRPC. These results indicate that squamous cell conversion is not a rare occurrence in end-stage disease and should be considered an emerging phenotype following resistance to AR-directed therapy.

Transcript signatures define the molecular phenotypes of mCRPC. The variability in expression of any single marker, both at the biological level and technical level makes tumor classification by immunohistochemistry challenging. Transcript panels for tumor

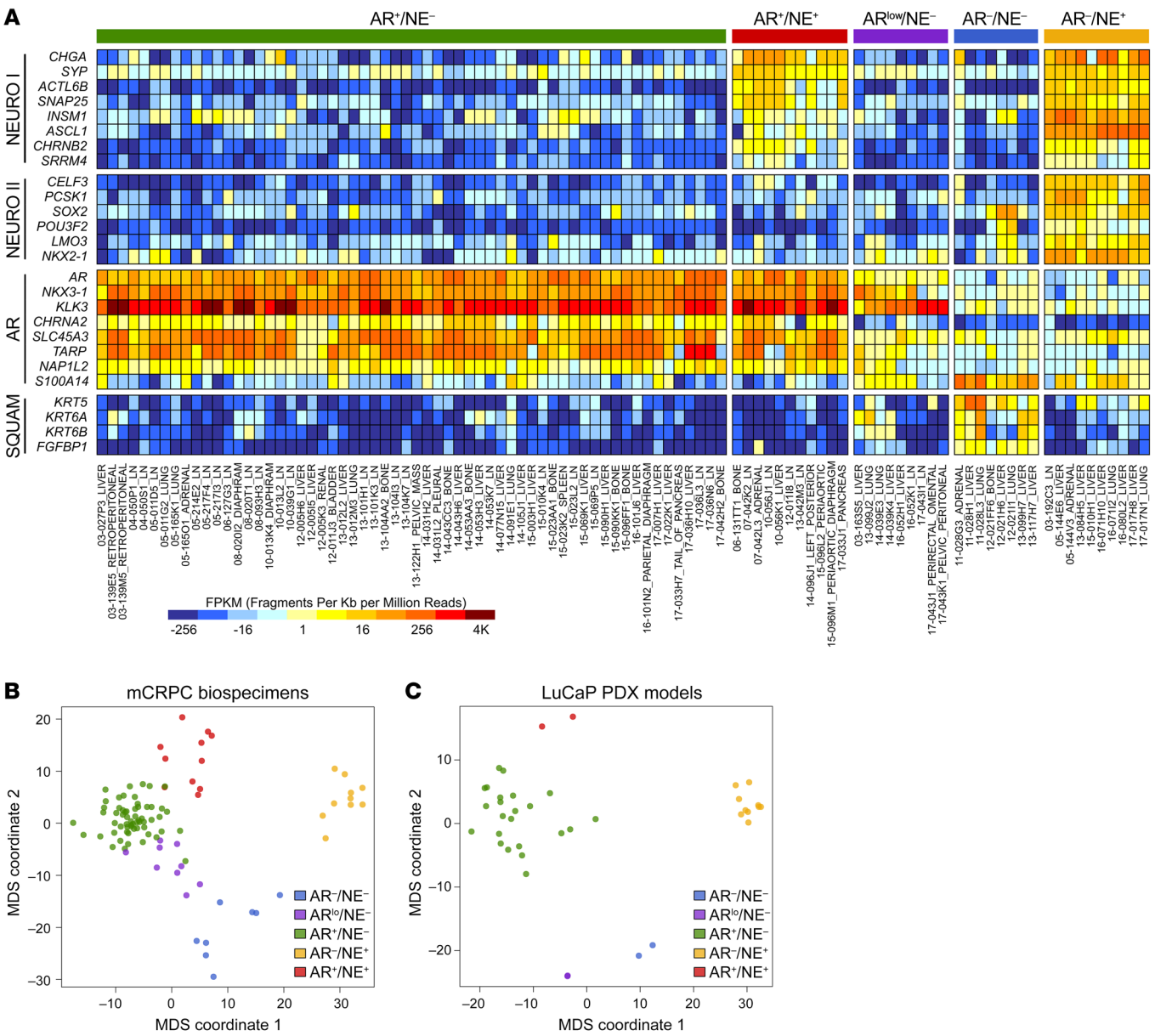


Figure 7. Cluster analysis using AR, NE, and squamous gene expression profiles segregates mCRPC specimens and LuCaP PDX models into the different phenotypes. (**A**) RNA sequencing of mCRPC specimens acquired between 2003–2017 (n = 98; modified from Figure 1B). NE genes listed in the NEURO I and NEURO II panels, AR and AR-regulated genes are listed in the AR panel, and squamous associated genes are shown in SQUAM panel. Results are expressed as $\log_2$ FPKM and colored according to scale. Multidimensional scaling and cluster analysis of (**B**) mCRPC specimens (n = 98) and (**C**) LuCaP PDX models using the 26-gene set depicted in A. The LuCaP analysis was conducted on 18 distinct PDX lines (n = 2 for each line). ARPC (AR^+/NE^-; green), ARLPC (AR^{low}/NE^-; purple), DNPC (AR^-/NE^-; blue), AMPC/mixed (AR^+/NE^+; red), SCNPC (AR^-/NE^+; yellow).

classification have been explored as predictive and prognostic biomarkers for treatment decision-making (45, 46). We leveraged the data generated from the patient metastases and LuCaP PDX models to develop a 26-gene transcriptomic signature for defining treatment-refractory mCRPC phenotypes. Using the aforementioned AR, NEURO I, and NEURO II gene panels, as well as a squamous panel (SQUAM) that includes *KRT5*, *KRT6A*, *KRT6B*, and *FGFBP1*, we conducted multidimensional scaling (MDS) and cluster analysis of the patient metastases and LuCaP PDX models (Figure 7A and Supplemental Figure 3B). The MDS demonstrated clear distinction between the 5 mCRPC phenotypes (ARPC, ARLPC, AMPC, DNPC, and SCNPC) in both patient specimens and LuCaP PDX models (Figure 7, B and C).

We further evaluated our 26-gene signature using PolyA RNA-Seq landscapes from 270 CRPC metastases in the Stand Up To Cancer (SU2C) data set (47). Although the SU2C data set contains RNA-Seq from mCRPC tumors earlier in disease progression and from tumors that are responding to treatment, the transcriptional signature segregated the tumors into the 5 mCRPC phenotypes (Supplemental Figure 8, A and B). Interestingly, we detected expression of the squamous-associated genes in 2 DNPC tumors and 2 ARLPC tumors but also observed marked squamous marker

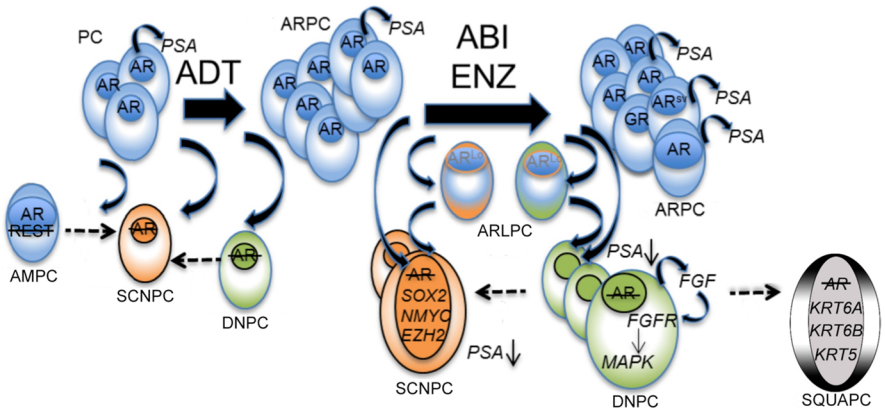


Figure 8. Schematic of the mCRPC disease continuum. The proposed mechanisms, molecular drivers, and cellular differentiation states following AR pathway inhibition therapy. ADT, androgen deprivation therapy; ABI, abiraterone; ENZ, enzalutamide; PC, hormone-sensitive prostate cancer; ARPC, AR-high prostate cancer; ARLPC, AR-low prostate cancer; SCNPC, small cell or NE prostate cancer; DNPC, double-negative prostate cancer; AMPC, amphicrine prostate cancer; SQUAPC, squamous prostate cancer.

expression in 4 ARPC tumors and 1 SCNPC tumor. Thus, removing the squamous genes from the analysis showed a more effective clustering of the tumors into their respective phenotypes (Supplemental Figure 8C). We do not know if the ARPC and SCNPC specimens with squamous aspects represent tumors containing 2 different phenotypes or single phenotypes.

Discussion

The clinical phenotyping of mCRPC has been limited to morphologic and immunohistochemical analyses. Although adenocarcinoma (AR and PSA) and NE (CHGA and SYP) biomarkers have provided some clarity for pathologic classification, the complexity of tumor heterogeneity, and the emergence of new treatment-resistant phenotypes have catalyzed a need for deeper understanding of the mCRPC disease continuum. Moreover, anaplastic tumors or aggressive variants are a clinically defined group of small cell metastatic/CRPC phenotypes with varying degrees of both AR expression (generally AR-null) and NE differentiation (48, 49). The classifications prompted a call for further elucidation of underlying mCRPC biology and more accurate nomenclature that limits confusion between research and medical fields (50). At the transcriptome level, expression signatures for classifying SCNPC have been demonstrated (51), but an encompassing signature that appreciates the spectrum of mCRPC phenotypes has not been identified. In this report, we interrogated end-stage mCRPC patient specimens and treatment-resistant LuCaP PDX models and demonstrated that transcriptome analysis in conjunction with IHC is a powerful method for phenotyping mCRPC in the current era. Our approach led to the characterization of 5 distinct mCRPC phenotypes (AR-high/ARPC, AR-low/ARLPC, amphicrine/AMPC, double-negative/DNPC, and small cell or NE tumors lacking AR expression/SCNPC) and ultimately resulted in a clinically relevant 26-gene transcriptional signature to classify mCRPC biospecimens. Moreover, our data demonstrated that mCRPC is a disease continuum driven by AR, REST, and core SCNPC transcription factor programs; treatment-induced differentiation of DNPC to squamous cell carcinoma is an emerging mCRPC phenotype; AR-low and AR-null phenotypes share common pathways of resistance to AR pathway inhibition that could be exploited for clinical benefit; and loss of REST repressor activity is critical for driving conversion to the AMPC/mixed phenotype but only promotes rather than drives the SCNPC phenotype.

Observations made through our rapid autopsy program support a treatment-induced shift in mCRPC phenotypes with ARI therapies increasing the number of AR-null and AR-low metastases at end-stage disease (5). In addition, our patient, LuCaP PDX, and cell line data suggest that ARPC can transition to ARLPC, AMPC/mixed, DNPC/squamous, or SCNPC to bypass hormone or AR pathway suppression therapies. These results were further verified through our analysis of the SU2C cohort of CRPC metastases (47). Notably, DNPC is a proliferative AR-null intermediate that contains cells with the inherent plasticity and potential to convert to SCNPC or squamous mCRPC (Figure 8 and Supplemental Figure 9). Multiple cell line, murine model, and PDX reports have demonstrated that loss of tumor suppressor proteins, AR-directed therapies, and/or the tumor microenvironment contribute to CRPC cellular plasticity and ARPC to SCNPC transition (16, 20, 52–56). Moreover, Beltran et al. have established that subsets of NE tumors are clonally derived from ARPC (18). Of note, the genomic landscapes of intrapatient CRPC metastases are relatively similar (4). Thus, our analysis indicating that intertumoral phenotypic heterogeneity is not a rare occurrence argues that epigenetic, posttranscriptional, posttranslational, and microenvironment events can contribute to phenotypic diversity in mCRPC. Taken together, our data add further clinical support for the proposed mCRPC disease continuum and demonstrates that treatment-induced selective pressures can change the phenotypic and molecular landscapes of mCRPC.

The analyses of DNPC tumors and the LuCaP 173.2 PDX model unexpectedly revealed the appearance of squamous cell pearls within the mass of DNPC tumor cells. RNA-Seq and staining for KRT6 confirmed the molecular nature of the squamous pearls. We hypothesize that only the most differentiated squamous carcinoma cells stain positive for KRT6 and display a cornified GSEA profile and that there exists a proliferating DNPC/squamous intermediary. Support for this hypothesis comes from RNA-Seq and IHC that shows ARLPC metastases and LuCaP 176 significantly enriched for squamous transcriptional profiles but negative for squamous pearl structures and KRT6 staining. The mechanisms of ARLPC/DNPC to squamous transition remain unclear, but future research examining the parallels between prostate and lung cancer lineage plasticity is warranted. For example, prostate and lung epithelial cells can be reprogrammed to small cell NE cancers through induction of the same transcription factor pathways (19). Moreover, lung ade-

nocarcinomas can transition to squamous cell carcinomas through *LKB1*-loss (57). Our RNA-Seq data show no evidence *LKB1/STK11*-loss across patient samples but other mechanisms of adenocarcinoma-squamous differentiation are likely. We speculate that there are common molecular pathways driving lung and prostate cancer lineage switching. Taken together, our data demonstrate that treatment-induced ARPC-DNPC-squamous conversion is one potential pathway to bypass AR-suppression strategies.

There are currently no standard treatments for SCNPC, DNPC, and ARLPC phenotypes. However, RNA-Seq and GSEA between mCRPC phenotypes revealed biologically relevant pathways that could be further interrogated for therapeutic benefit. Significantly upregulated genes common to the AR-null and ARLPC phenotypes were enriched for cell adhesion processes, and delving into the pathway revealed *CEACAM5* as a top hit. CEACAM5 has been identified as a surface marker of potential utility in directing chimeric antigen T cells in SCNPC (58), and our data reveal that this therapy could also be clinically effective against subsets of ARLPC and DNPC tumors. Moreover, upregulated genes common to ARLPC and AR-null phenotypes are enriched in immune system, inflammatory, and defense responses. Since the phenotype comparisons were relative to ARPC, these data support the notion that the immune cell content of ARLPC and AR-null tumors is strikingly different from that of ARPC tumors. Notably, DNPC-specific immune-related genes included *IL8* and *CXCR1*, which have been reported to promote CRPC metastasis and angiogenesis (59), and genes such as *TGFB* and *RUNX2*, which support tumor growth in bone (60). Whether associated with the tumor cells, immune cells, or stromal cells, the presence of enriched immunomodulatory signaling pathways suggests that ARLPC, DNPC, and SCNPC tumors could be more receptive to immunotherapies.

Our group and others have previously demonstrated that loss of REST repressor activity promotes the SCNPC phenotype (15, 24, 61, 62). Here, we confirmed the existence of AMPC cells in vivo and in vitro and demonstrated that AMPC cells express a limited set of neuronal genes that are REST-repressed (NEURO I panel) and maintain AR signaling. Furthermore, transcriptome analysis of mCRPC and LuCaP PDX tumors and siRNA-mediated knockdown of REST in AR-expressing and AR-null cell lines provided compelling evidence that loss of REST repressor activity is critical for conversion to the AMPC/mixed phenotype but does not necessarily drive the SCNPC phenotype. We realize that siRNA treatments transiently relieve REST-mediated transcriptional repression, and that the impact of sustained REST-ablation remains to be determined. However, we hypothesize that epigenetic factors are preventing the expression of core SCNPC transcription factors (NEURO II panel of genes) that would permit SCNPC transdifferentiation in AR-null and AR-expressing cells with REST knockdown. Indeed, the epigenomes of NE and adenocarcinoma tumors are significantly different and EZH2 inhibitors have been shown to reactivate AR expression in some SCNPC models (18, 63). On the other hand, SRRM4-mediated splicing of REST and other neuronal regulators can drive ARPC-SCNPC transition (24). Our results demonstrated that SRRM4-mediated splicing of REST occurs in both AMPC and SCNPC PDX models and in AMPC VCaP cells, suggesting that SRRM4 expression alone is not sufficient to drive SCNPC conversion in all cases. Concordantly, overexpression of SRRM4 converted DU145 cells to a classical SCNPC phenotype but failed to do so in PC-3, 22Rv1, and LNCaP cells (64), implying that multiple hits to the cellular blueprint are required for complete lineage switching. Furthermore, REST directly represses SRRM4 expression and loss of REST activity has been proposed as a feed-forward mechanism for SCNPC conversion (25, 62). Whether loss of REST activity mediates increased SRRM4 expression or increased SRRM4 activity mediates loss of REST requires further examination. Nevertheless, our data clearly show that the homeostatic regulation of the SRRM4-REST axis is required for epithelial differentiation and function.

In summary, our comprehensive analysis of end-stage mCRPC highlights the use of AR and REST transcriptional programs to categorize mCRPC phenotypes in the abiraterone/enzalutamide era. In addition, the data generated in this report could be exploited through biopsy or blood-based biomarkers in future therapeutic studies to define inclusion criteria. This approach could stratify patients according to mCRPC phenotypes and account for the mCRPC disease continuum to implement targeted therapies.

Methods

Tissue acquisition. Biospecimens were obtained within 8 hours of death from patients who died of metastatic CRPC. Visceral metastases were identified at the gross level, bone biopsies were obtained according to a previously described template (65) from 16–20 different sites, and metastases were identified at a histological level. LuCaP PDX lines were established from specimens acquired at either radical prostatectomy or at autopsy, implanted, and maintained by serial passage in immune compromised male mice (66).

Cell lines. All cells were maintained at 37°C in humidified Steri-Cult CO_2 incubators (Thermo Fisher Scientific). C4-2B (gift from L. Chung, Cedars-Sinai Medical Center, Los Angeles, CA), PC-3 (ATCC), and PacMet AR-null cells (5) were maintained in RPMI-1640 Media (Gibco, Life Technologies) with 10% fetal bovine serum (Atlanta Biologicals). VCaP cells (ATCC) were maintained in DMEM (ATCC) with 10% fetal bovine serum (Atlanta Biologicals).

Transient transfections. Cells were suspended in Nucleofector Solution V (Lonza) and 5 μL of 50-μM ON-TARGETplus pooled REST siRNA or control siRNA (Dharmacon). Cell suspensions were electroporated using the Nucleofector II device (Lonza) and program T-027 and then replated in complete media. Forty-eight hours after transfection, cells were harvested for RNA or protein for subsequent analysis.

Immunohistochemistry. The antibodies used in this study are listed in Supplemental Table 1. Five-micron-thick sections of the TMAs were deparaffinized and rehydrated in sequential xylene and graded ethanol. Antigen retrieval was performed in 10 mM citrate buffer (pH 6.0) in a pressure cooker for 30 minutes. Endogenous peroxidase and avidin/biotin were blocked respectively (Vector Laboratories). Sections were then blocked with 5% normal goat-horse-chicken serum, incubated with primary antibody (Supplemental Table 1), incubated with biotinylated secondary antibody (Vector Laboratories), followed by ABC reagent (Vector Laboratories), and stable DAB (Thermo Fisher Scientific). All sections were lightly counterstained with hematoxylin and mounted with Cytoseal XYL (Richard Allan Scientific). Mouse or rabbit IgG was used as negative control. IHC scores were represented as values between 0–200 and were determined as previously described (15).

Immunofluorescence. Formalin-fixed, paraffin-embedded (FFPE) patient and LuCaP PDX tumors were prepared according to the above methods up to and including antigen retrieval. For cells in culture, VCaP cells were seeded on chamber slides (Nunc Lab-Tek; Thermo Fisher Scientific) in complete media 24 hours prior to fixing. Cells were fixed and permeabilized with ice-cold methanol for 10 minutes and then washed in PBS. Cells and sections were blocked for 1 hour with 5% normal goat-horse-chicken serum, incubated for 1 hour (cells) or overnight (sections) with primary antibodies in blocking buffer, washed, and then incubated with fluorescent secondary antibodies for 45 minutes in the dark. All incubations occurred at room temperature and antibodies used are listed in Supplemental Table 1. Slides were mounted using ProLong Gold Antifade Mountant with DAPI (Thermo Fisher Scientific) and then visualized and imaged at ×20 on an Olympus BX41 Fluorescence Microscope.

Immunoblot analysis. Protein extracts from LuCaP PDXs and cell lines were obtained using the Nuclear Extract Kit (Active Motif) according to the manufacturer's protocols. Quantification of total protein was determined using the ProStain Protein Quantification Kit (Active Motif) according to the manufacturer's protocols. Ten to twenty micrograms of total protein lysate was electrophoresed on 4%–15% Bis-Tris gels (Bio-Rad Laboratories) with 1× Tris/Glycine/SDS Buffer (Bio-Rad Laboratories). The proteins were transferred to PVDF that was blocked with 5% Blotting-Grade Blocker (Bio-Rad Laboratories) in TBS/0.1% Tween-20 and subsequently probed with primary and secondary antibodies (Supplemental Table 1). Proteins were visualized using Clarity Western ECL Substrate (Bio-Rad Laboratories).

RNA isolation. Total RNA was isolated from 98 tissue samples of CRPC metastases, which had been frozen in OCT (Tissue-Tek) with RNA STAT-60 (Tel-Test). Using an H&E-stained slide for each sample for orientation, 1-mm core punches of tumor were obtained. Alternatively, multiple sections enriched for tumor were cut using a Leica CM3050S cryostat. Total RNA was isolated from flash-frozen LuCaP PDX tissues or cell lines with RNA STAT-60 (Tel-Test) followed by purification with RNeasy Mini Kit (Qiagen) using the manufacturer's recommended in-solution DNase digestion (Qiagen). The purity and yield of the RNA were determined on a NanoDrop 2000 (Thermo Fisher Scientific). RNA integrity was assessed on a 2100 Bioanalyzer (Agilent Technologies).

PCR and sequencing. First-strand cDNA synthesis was performed with 1 μg RNA using an Advantage RT-for-PCR Kit (Clontech Laboratories). PCR was performed using either Platinum SYBR Green qPCR SuperMix-UDG (Invitrogen; real-time PCR) or HotStarTaq Plus Master Mix (Qiagen; PCR for sequencing) on a Rotor-Gene Q (Qiagen). PCR primers (Integrated DNA Technologies) specific for *REST* were adapted from Raj et al. (25). The REST 5′ primer-GAGAACGCCCATATAAATGTGAAC and 3′ primer-CGGGTTACTTCATGTTGATTAGAG were used. The PCR reaction parameters were as follows: 50°C for 2 minutes and 95°C for 2 minutes (one cycle), followed by 30 cycles (standard gels) or 40 cycles (band sequencing) at 95°C for 10 seconds, annealing/extension at T(m) for 30 seconds, and 72°C for 30 seconds; the final extension was 72°C for 7 minutes. *REST* and *REST4* PCR products were visualized after electrophoresis on a 1.2% agarose gel. For sequencing, PCR product bands were dissected out and purified using the QIAquick Gel Extraction Kit (Qiagen). The purified product was then sequenced by Eurofins Genomics using their Standard Read sequencing chemistry.

RNA sequencing. RNA-Seq libraries were constructed from 1 μg total RNA using the Illumina TruSeq Stranded mRNA LT Sample Prep Kit according to the manufacturer's protocol. Barcoded libraries were pooled and sequenced on the Illumina HiSeq 2500 generating 50 bp paired end reads. Sequencing reads were mapped to the hg38 human using TopHat v2.1.0 (67). For PDX samples, sequences were also aligned to the mm10 mouse genome and those derived from potential contamination with mouse tissue were removed from the analysis as previously described (68). Gene level abundance was quantified from the filtered human alignments in R using the GenomicAlignments Bioconductor package (69). Differential expression was assessed using transcript abundances as inputs to the edgeR Bioconductor package in R (70). For edgeR analysis, genes filtered for a minimum expression level of at least 1 count per million reads (CPM) in at least 2 samples were used to calculate expression differences using an exact test with a negative binomial distribution, applying a significance level of 0.05 with Benjamin-Hochberg false discovery rate (FDR) adjustment. The RNA-Seq data from this report can be accessed through GEO at GSE126078 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE126078).

Pathway analysis. Gene expression results were ranked by their edgeR statistics and used to conduct Gene Set Enrichment Analysis (GSEA) to determine patterns of pathway activity in different treatment groups. We used the curated pathways from within the MSigDBv6.1. Gene ontology (GO) enrichment of Venn diagram groups was computed using GOrilla with default parameters (71). The target and background list option was used and gene sets with enrichment of $P < 0.001$ were considered significant.

Multidimensional scaling (MDS) plots. Specimens were classified according to expression of NEURO I, NEURO II, AR, and SQUAM gene signatures. ARPC and ARLPC phenotypes were differentiated based on AR or KLK3 expression (RNA-Seq) with ALRPC possessing an AR $\log_2$ FPKM value less than 4.0 or a KLK3 $\log_2$ FPKM value less than 2.0. Phenotypic groups were visualized using classical multidimensional scaling (MDS) calculated with the cmdscale function in R using the expression profiles of the 26 genes from the combined lists of NEURO I, NEURO II, AR, and SQUAM gene signatures. The distance metric was euclidean calculated by dist function on the columns (samples). The RNA-Seq data from the Stand Up To Cancer mCRPC cohort were accessed using dbGaP accession phs000915.v2.p2.

Statistics. Sample size for each experiment is indicated in the figure legends. Experiments were repeated a minimum of 2 times. Statistical analyses for RNA sequencing, pathway analyses, and MDS were performed as indicated using R software. The enrichment scores were calculated in R using the GSVA package using the 14 genes in the NEURO I and NEURO II gene sets for NEURO scores and a previously published set of AR-regulated genes for AR-activity scores (5, 72). Mean AR-activity scores in transfected C4-2B cells were graphed using GraphPad Prism software.

Study approval. All rapid autopsy tissues were collected from patients who had signed written informed consent under the aegis of the Prostate Cancer Donor Program at the University of Washington (73). The IRB of the University of Washington approved this study. All patient-derived xenograft experiments were approved by the University of Washington IACUC.

Author contributions

MPL, LGB, PSN, and CM conceived and designed the project. IMC, RC, and AK performed sequencing and bioinformatics analyses. MPL, LGB, LK, BL, YCY, and ACH conducted molecular and cell biology experiments. LDT and RMG provided pathology evaluation. HMN, EC, and CM provided biospecimens and patient-derived xenograft models. CSH, EYY, HHC, EAM, BM, MTS, DWL, and PSN consented patients for the rapid autopsy program and/or provided clinical expertise. MPL, PSN, and CM wrote the manuscript, and all authors reviewed and edited the manuscript.

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Germline Genetic Testing in Advanced Prostate Cancer; Practices and Barriers: Survey Results from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium

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Abstract

More than 10% of patients with advanced prostate cancer carry inherited genetic mutations that might amplify their response to targeted therapies, but barriers, including a shortage of genetic counselors, limit patient access to testing that would enable targeted therapy. This study of practices in nineteen US comprehensive cancer centers showed that a shortage of genetic counselors and 4 other barriers limit adoption of this important advance. Herein we also catalogue germline genetic testing practices and illuminate initiatives that might expand testing availability.

Background: Germline genetic testing increasingly identifies advanced prostate cancer (PCa) patients who are candidates for precision therapies. The Prostate Cancer Clinical Trials Consortium (PCCTC) established the Germline Genetics Working Group to provide guidance and resources to expand effective use of germline genetic testing. **Materials and Methods:** A 14-item questionnaire was e-mailed to academic oncologists at 43 PCCTC sites to collect information on germline genetic testing patterns, including patients considered, choice of assays, barriers slowing adoption, and actions to overcome barriers. **Results:** Twenty-six genitourinary oncologists from 19 institutions responded. Less than 40% (10 of 26) reported referring patients to a genetics department, whereas the remainder take personal responsibility for genetic testing and counseling; 16 (62%) consider testing all metastatic PCa patients,

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whereas 3 (12%) consider testing all patients with high-risk local disease; and 7 (27%) use multigene comprehensive pan-cancer panels, and 14 (54%) use smaller or targeted cancer gene panels. Barriers to widespread use are: (1) delayed or limited access to genetic counseling; (2) no insurance coverage; (3) lack of effective workflows; (4) insufficient educational materials; and (5) time and space constraints in busy clinics. The primary limitation was the <50% (19 of 43) response from PCCTC sites and no coverage of nonacademic cancer treatment facilities. **Conclusion:** Joint efforts by urologists, oncologists, genetics counselors, insurers, and cancer centers can accelerate implementation of integrated germline genetic services for personalized treatment and clinical trial eligibility for PCa patients.

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Introduction

A significant number of prostate cancer (PCa) cases have a heritable component. Germline DNA damage repair (DDR) defects are present in >10% of patients who develop metastatic PCa (mPCa), with defects in breast cancer *(BRCA2)* found in more than 5% and defects in *BRCA1*, ataxia-telangiectasia mutated *(ATM)*, and checkpoint kinase 2 genes each found in 1% to 2%. Prevalence of germline mutations in DDR genes in men with mPCa exceeded the observed 5% prevalence in men with localized PCa and 3% prevalence in men without a known cancer diagnosis.[1,2] In recent years, the treatment landscape for mPCa has been refined by the discovery of DDR deficiency as predictive biomarkers for response to targeted therapies. For example, the presence of homologous recombination deficiency might predict response to poly (adenosine diphosphate-ribose) polymerase inhibitors as well as to other DNA-damaging chemotherapy agents (platinum chemotherapy).[3-6] Similarly, the presence of germline mutations in mismatch repair (MMR) genes might identify candidates for treatment with immune checkpoint inhibitors.[7-10] Thus, it has become progressively important to assess practice patterns and needs regarding germline genetic testing and counseling for men with PCa. Urologists are increasingly ordering germline testing for their PCa patients in light of recent evidence that *BRCA1/2* and *ATM* mutation status is associated with grade reclassification or PCa patients undergoing active surveillance.[11] Urology involvement in germline genetic testing will grow as the area evolves to include high-risk localized (HRL) and earlier disease states.[12-14]

The Germline Genetics Working Group (GGWG) of the Prostate Cancer Clinical Trials Consortium (PCCTC) was established in June 2017 in response to the need to better inform and advise clinicians of the increasing evidence that germline alterations in DDR genes might identify additional options for PCa therapy. The objectives of the GGWG are to work together with clinicians and researchers around topical challenges of treatment selection and eligibility for trials of investigational therapeutics, and to enable more streamlined and effective use of germline genetic testing in PCa patients in the face of a rapidly evolving genetics-informed therapeutic landscape.

In June 2018, the GGWG produced a white paper that presented a framework to address unique challenges and therapeutic opportunities regarding germline testing for precision therapy in patients with advanced PCa and identified areas of future research.[15] In the white paper the GGWG recommended that clinicians: (1) consider expanding germline genetic testing beyond cancer risk assessment to inform treatment selection and eligibility for clinical trials; (2) work with genetic counselors to ensure pretest informed decision-making through education or counseling and post-testing counseling; and (3) where appropriate, ensure mechanisms for offering cascade germline genetic testing to family members. However, barriers and challenges to broader implementation of these recommendations require attention.

To elucidate practice patterns and challenges in germline genetic testing of PCa patients in oncology, the GGWG surveyed medical oncologists from institutions who were members of the PCCTC. Herein, we report survey data from responding oncologists from 19 PCCTC cancer centers identifying commonalities and differences in practice patterns. The survey results were used to support recommendations for addressing barriers to germline testing for men with PCa and are placed in the context of current National Comprehensive Cancer Network (NCCN) guidelines for genetic testing of PCa patients.

Materials and Methods

Survey

A 14-question survey was developed by the GGWG to capture data on the practice patterns and needs of oncologists at PCCTC institutions. The survey was refined after pilot testing and then distributed to oncologists at their institutions using RedCap, a Web-based survey tool, with an e-mail (December 20, 2017) asking members to complete the survey and to ask other investigators at their institutions to respond. A reminder e-mail was sent on January 16, 2018 to GGWG members who had not completed the survey. PCCTC principal investigators were reminded of the survey during 2 sequential monthly conference calls that took place between the 2 e-mail survey distributions (December 21, 2017 and January 8, 2018).

The survey questions offered multiple choice answer selections on personal practices around genetics services, on patient characteristics oncologists consider for germline testing (metastatic disease, advanced stage, family history), on cascade genetic testing processes, and on gene panels. The remainder were free-form questions asking for clarifications of answers to the multiple-choice questions and also asking participants to describe their approaches to integrating

Table 1 Cancer Centers Providing Germline Genetic Testing Survey Responses

Cancer Center	Responses
Fred Hutchinson Cancer Research Institute	3
Johns Hopkins Sidney Kimmel Comprehensive Cancer Center	3
Lurie Comprehensive Cancer Center	2
Rush University Medical Center	2
Weill Cornell Medical College	2
Beth Israel Deaconess Cancer Center	1
Carbone Cancer Center	1
Dana-Farber Cancer Institute	1
Duke Comprehensive Cancer Center	1
Jonsson Comprehensive Cancer Center	1
Lineberger Comprehensive Cancer Center	1
Masonic Cancer Center	1
Memorial Sloan Kettering Cancer Center	1
Moores Cancer Center	1
Oregon Health and Science University Knight Cancer Institute	1
Sidney Kimmel Cancer Center at Thomas Jefferson University	1
University of Chicago Medicine Comprehensive Cancer Center	1
Wayne State Karmanos Cancer Institute	1
Yale Cancer Center	1

germline testing with therapeutic clinical trials and to cascade testing. The full survey is shown in Supplemental Appendix 1 in the online version).

Analysis

Data were gathered in the RedCap package and exported to a comma-separated value file. Data were imported into Excel (Version 16.18, Microsoft Corp, Redmond, WA), where they were summarized, tabulated, and graphed.

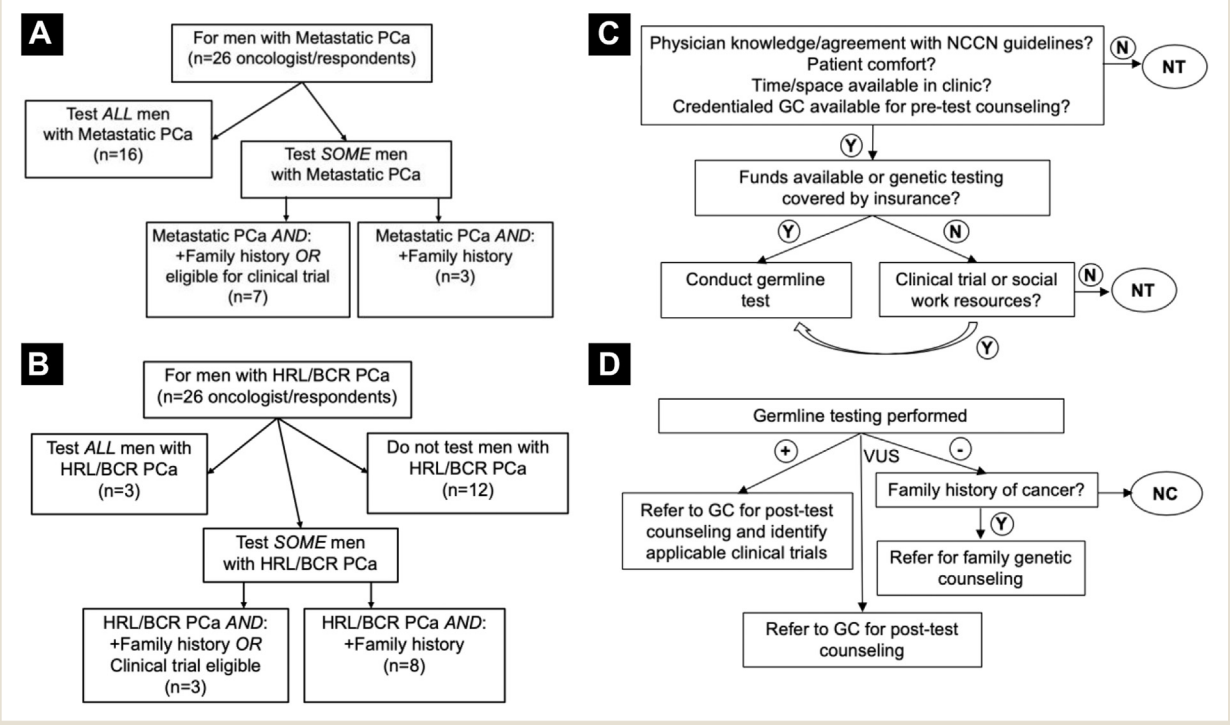
Results

Between December 20, 2017 and April 3, 2018, representatives of the 43 PCCTC participating and affiliate sites received the germline genetic testing current practice survey and an e-mail encouraging redistribution to institutional colleagues, and 26 PCa oncologists from 19 sites (44%) completed the survey (Table 1).

Personal Practices of PCa Oncologists Regarding Genetics Services for PCa Patients

Whereas 10 of 26 (38%) participating oncologists reported that they refer patients to a separate department for genetic testing and counseling, more than half reported taking personal responsibility for some or all genetic education and testing of their patients. Four (15%) reported personally performing pretest counseling, ordering germline testing, and performing post-test counseling. Those who reported using a combination of approaches generally referred to

Figure 1 Provider Considerations of Germline Testing Among Men With Prostate Cancer. (A) Men With Metastatic Prostate Cancer (PCa) Considered for Germline Testing. (B) Men With High-Risk Localized (HRL) and Biochemically Recurrent (BCR) PCa Considered for Germline Testing. (C) Factors Affecting Decision to Test. (D) Factors Affecting Decisions on Results



Abbreviations: + = positive results; GC = genetic counselor; N = no; NC = no post-test genetic counseling; NCCN = National Comprehensive Cancer Network; NT = no germline genetic testing; VUS = variant of uncertain significance; Y = yes.

Table 2 Approaches to Germline Cancer Predisposition Testing

General Approach to Germline Cancer Predisposition Testing[a]	Respondent																									
	11	6	10	17	21	1	22	18	20	16	19	13	2	8	12	3	15	7	24	5	25	26	23	4	9
Comprehensive, Pan-Cancer Panel	•	•	•	•	•	•	•	•																	
Expanded Cancer Panel (eg, Lynch and *BRCA1/2* and Hereditary Breast and Ovarian Cancer Genes)	•								•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Limited Prostate Cancer-Specific Panel																							•		
Specific Individual Genes (eg, *BRCA1, BRCA2*)																								•	•
Clinical Trial-Focused Panel	•																								

[a]Sites that listed multiple approaches (eg, comprehensive and limited) explained that lack of insurance or limited patient capacity to pay sometimes causes them to select a more limited panel.

genetic counselors for post-test counseling. Variation in practice appears to depend on factors such as: (1) patient's insurance coverage for genetic testing and counseling; (2) availability of testing and counseling resources within the oncology group; (3) testing and counseling resources in a separate genetics department; and (4) wait times for referrals.

Patients Considered for Germline Genetic Testing

Metastatic PCa. All 26 participating oncologists reported considering some mPCa patients for germline genetic testing: 16 (62%) reported considering all mPCa patients; 7 (27%) considered testing mPCa patients with a family history and/or who were eligible for clinical trials; and 3 (12%) considered testing only for patients with a family history for germline genetic testing (Figure 1A).

High-Risk Localized PCa Patients and Non-mPCa. More than half of the participating oncologists, 14 of 26 (54%), considered germline genetic testing for some PCa patients with HRL or non-mPCa (nmPCa), whereas 12 (46%) did not consider germline testing for these patients. Three (12%) reported testing all HRL/nmPCa patients; 3 (12%) reported considering testing only for patients with a family history for germline genetic testing; and 8 (31%) reported considering testing only those with a family history of cancer (Figure 1B).

Operational Barriers Faced by Oncologists Considering Germline Genetic Testing for PCa Patients

On the basis of participant responses and free text comments, 5 barriers in streamlining genetic testing were identified: access to genetic counselors, insurance coverage and cost, clinic workflow, time and space availability, and access to resources for provider and patient education. Figure 1C shows the role of those operational barriers and the flow of considerations on whether to conduct germline genetic testing reported by responding oncologists, whereas Figure 1D shows how referral decisions are made on the basis of those results.

Reported Germline Testing Approaches

Participating oncologists reported their approaches for germline cancer predisposition testing. Seven of 26 (27%) reported using only "comprehensive pan-cancer panels," whereas 14 (54%) listed only "expanded cancer panels (eg, Lynch and *BRCA1/2* and hereditary breast and ovarian cancer genes)," and 4 others (15%) reported using more than 1 type of panel. One participant did not answer this question (Table 2).

Resources for Patients and Family Members Regarding Genetic Testing

The GGWG aggregated a list of Web sites that it has found valuable for educating patients and their families about germline genetic testing for PCa (Table 3). Two participants reported they are developing local resources (a video and an information sheet for patients).

Discussion

The relevance of germline genetic testing in PCa is emerging today as it did in breast cancer 3 decades ago, although in PCa it is

Table 3 Web Resources for Educating PCa Patients and Families About Germline Genetic Testing

Source	URL	Content
Color	https://www.color.com/learn/can-cancer-be-inherited	Patient-friendly discussion and data about cancer due to inherited (germline) genetic mutations
Dana Farber	https://www.dana-farber.org/cancer-genetics-and-prevention/videos/	Videos explaining topics in cancer genetics and testing
Invitae	https://www.invitae.com/en/patients/genetic-diagnosis/	Brief descriptions of genetic testing
Memorial Sloan Kettering	https://www.mskcc.org/cancer-care/risk-assessment-screening/hereditary-genetics/genetic-counseling/inherited-risk-prostate	Very brief discussion of inherited risk of PCa
National Society of Genetic Counselors	https://www.nsgc.org/	Comprehensive guidance for patients, including help finding counselors
Prostate Cancer Foundation	https://www.pcf.org/news/genetic-screening-guidelines-for-prostate-cancer/	High-level overview of genetics-related knowledge helpful to patients with PCa and their families
	https://www.pcf.org/patient-resources/family-cancer-risk/genetic-testing-prostate-cancer/	Recommendation to speak with physician about whether patients need genetic testing, with 5 more detailed subpages
Sidney Kimmel Cancer Center of Thomas Jefferson University	https://prostategenetics.jeffersonhealth.org/	PCa-focused and patient-friendly, Web-based resource explaining genetic counseling, genetic testing, family history, genes, and cancer risks

Abbreviation: PCa = prostate cancer.

accompanied by concurrent therapeutic relevance. These rapid and exciting changes have resulted in challenges illustrated by the 2018 PCCTC GGWG survey of medical PCa oncologists at academic institutions in the PCCTC consortium, around their practices in germline genetic testing of PCa patients. The survey identified common themes across 19 institutions as well as substantial

Table 4 Therapeutic and Delivery Model Clinical Trials in PCa With Relevance for Germline Genetic Eligibility Criteria

Phase	Title	Disease State	Abbreviated Title	Clinicaltrials.gov
Therapeutic Trials				
III	Study of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men With Metastatic Castration-Resistant Prostate Cancer (PROfound Study)	mCRPC	PROFOUND	NCT02987543
III	A Study of Rucaparib Versus Physician's Choice of Therapy in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency	mCRPC	TRITON3	NCT02975934
II	An Efficacy and Safety Study of Niraparib in Men With Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies	mCRPC	GALAHAD	NCT02854436
II	A Study of Rucaparib in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency	mCRPC	TRITON2	NCT02952534
II	A Study of Talazoparib in Men With DNA Repair Defects and Metastatic Castration-Resistant Prostate Cancer	mCRPC		NCT03148795
II	Olaparib in Men With High-Risk Biochemically-Recurrent Prostate Cancer Following Radical Prostatectomy, With Integrated Biomarker Analysis	BCR		NCT03047135
II	Abiraterone/Prednisone, Olaparib, or Abiraterone/Prednisone + Olaparib in Patients With Metastatic Castration-Resistant Prostate Cancer With DNA Repair Defects	mCRPC	BRCAaway	NCT03012321
Pilot	Docetaxel and Carboplatin in Treating Patients With Metastatic, Castration Resistant Prostate Cancer Containing Inactivated Genes in the BRCA 1/2 Pathway	mCRPC	ABCD	NCT02598895
II	Docetaxel and Carboplatin for Patients With mCRPC and DNA-Repair Deficiencies	mCRPC	V-ABCD	NCT02985021
II	Trial of Rucaparib in Patients With Metastatic Hormone-Sensitive Prostate Cancer Harboring Germline DNA Repair Gene Mutations	mHSPC	TRIUMPH	NCT03413995
Delivery Model Trials				
NA	Evaluating an Alternative Clinical Genetics Cancer Care Delivery Model: A Pilot Study of Patient Outcomes	PCa		NCT02917798
NA	Genetic Evaluation of Men (GEM)	PCa	GEM Registry	NCT03076242
NA	Genetic Counseling Processes and Outcomes Among Males With Prostate Cancer (ProGen)	PCa	ProGen	NCT03328091
NA	Genetic Testing for Men With Metastatic Prostate Cancer	mPCa	GENTleMEN	NCT03503097

Abbreviations: BCR = biochemical recurrence; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; mPCa = metastatic prostate cancer; PCa = prostate cancer.

variation in those practices. Five barriers to obtaining genetic testing were identified: lack of timely access to genetic counselors, lack of insurance coverage or high patient out-of-pocket costs, lack of integrated clinic workflow, time and space constraints, and insufficient resources for provider and patient education. Our survey showed that more than half of oncologists reported taking part or full responsibility for germline genetic testing and education/counseling, despite the fact that most oncologists are not trained in genetic counseling.[16] Nearly 40% (10 of 26) of the participating oncologists reported that among mPCa patients, they considered germline genetic testing mainly for patients with a family history of cancer and those who were eligible for a clinical trial with genetic eligibility criteria, rather than all mPCa patients. Germline testing results are increasingly important for consideration of clinical trial eligibility. PCCTC sites reported 10 therapeutic trials for PCa patients with relevance to germline mutations and 4 trials testing new models of genetics delivery in PCa (Table 4). Similarly, a little more than half of respondents reported considering germline genetic testing for patients with HRL PCa and nmPCa. These responses might reflect a period of limited resources and substantial logistical barriers and the need for triaging and prioritization of genetic counseling and testing until barriers can be better addressed.

At the time the survey was distributed, the NCCN guidelines did not include recommendations for germline testing for most PCa patients. On the basis of recent data of germline mutations in men with PCa, before all GGWG survey responses were returned, NCCN prostate guidelines (version 4.2018) were expanded to recommend consideration of germline genetic testing for most metastatic and HRL PCa patients.[17] Thus, the survey captured change in action.

The current guidelines recommend consideration of germline testing for all patients with high-risk and very high-risk local disease, regional disease, and metastatic disease. Further, with more sensitive techniques for early identification of metastatic disease such as prostate specific membrane antigen, fluciclovine,[18] and choline,[19,20] more patients might be classified as metastatic than in the past, further increasing the numbers of patients to be considered for germline genetic testing. This expansion of patient populations to be considered for genetic testing, together with the barriers reflected in our findings, highlight the need for dedicated education and training for radiation oncologists, urologists, and medical oncologists. In the localized disease setting with risk levels that are very low, low, favorable intermediate, and unfavorable intermediate, the NCCN prostate guidelines suggest consideration for germline testing on the basis of a strong family history of PCa and/or other primary cancers, or for patients with a relative with a known familial cancer risk syndrome.

The current NCCN prostate guidelines also suggest that patients whose tumor testing is positive for microsatellite instability-high or deficient-MMR (indicating potential use of pembrolizumab in treatment for metastatic castration-resistant PCa (mCRPC), also be referred for genetic counseling to assess for the possibility of Lynch syndrome. Finally, the current NCCN guidelines recommend that physicians consider testing tumors of patients with mCRPC for germline and somatic mutations in *BRCA1*, *BRCA2*, *ATM*, partner and localizer of *BRCA2* and Fanconi anemia complementation group A genes.

Approximately half of survey participants indicated that they would refer patients for genetic counseling and dedicated confirmatory germline testing if a tumor mutation was potentially germline in nature (thus with family counseling implications[21]) consistent with the recommendation in the GGWG white paper.[15] As tumor sequencing for targeted treatment opportunities increase in PCa, the likelihood of identifying mutations that are potentially germline might increase, raising the need for distinct workflows to address this specific clinical scenario.

Several respondents noted that patient willingness to undergo germline genetic testing could be affected by concerns about genetic discrimination for life, disability, and long-term care insurance. The Genetic Information Nondiscrimination Act (GINA) of 2008[22] provides protection from genetic discrimination in health insurance and employment in most employment scenarios, but does not cover life insurance, long-term care, disability insurance, Indian Health Service, federal employees enrolled in the Federal Employee Health Benefits Plan, and other specific Veterans Administration or US military plans. Because of these gaps in protection by the GINA law and potential changes over time, patients approached about germline testing need to consider these issues and their own financial situations before proceeding with germline testing. Thus, providers and patients can benefit from educational and practice-ready resources to help address the need to discuss genetic discrimination laws.

There are some limitations to consider in our results. Urologists were not surveyed, because metastatic disease has been a key driver of genetic testing up to the present time. However, because guidelines for testing are expanding to earlier-stage disease, including urologists in future surveys will add important information. Our analysis does not account for institutional limitations that might have informed physician decisions regarding whom to test. In addition, there were site-specific differences in clinical trial availability with germline genetic eligibility criteria, including in the nmPCa setting which would have influenced consideration of genetic testing for that group. Another limitation is the response rate (oncologists from only 19 of 43 PCCTC sites responded), and the composition of respondents being largely oncologists with specific focus on PCa in academic centers. Nevertheless, we believe that the general concepts around the clinical need for better integration of germline genetic testing in PCa care and the current barriers to implementation will be broadly applicable across oncology practice settings.

Conclusion

The NCCN and other professional organizations advocate informed decision-making for patients in the pretest setting.[23-27] Research to improve delivery of pretest education and optimization of informed decision-making is key to streamlining genetic testing for men with PCa. In the post-test setting, discussion with a genetic counselor is important for patients with germline mutations,

variants of uncertain significance, and with no mutations but with a family history of cancer to ensure understanding of results and appropriate follow-up with regard to additional cancer screening and cascade testing recommendations. Physicians ordering genetic testing need to be well versed in cancer risk guidelines for screening, genetic results interpretation, GINA laws, and population-level cancer screening guidelines. Although referral to a genetic counselor is preferred when possible, there is a recognized shortage of genetic counselors that is predicted to worsen,[28,29] suggesting a role for subspecialty oncologists with training in genetics as well as for genetics training for oncology providers who perform aspects of genetic counseling themselves.[30] Registries that include germline data, family history, treatments, and outcomes such as those being developed in the GEM (Genetic Evaluation of Men), GENTLeMEN (Genetic Testing for Men With Metastatic Prostate Cancer), and ProGen (Genetic Counseling Processes and Outcomes Among Males With Prostate Cancer) trials, along with systems to address barriers to genetic testing, will help inform future guidelines and facilitate integrated genetic testing and counseling services into busy clinical practices.

Clinical Practice Points

- In the context of an evolving therapeutic landscape for men with mPCa and expanding NCCN guidelines for germline testing for patients with earlier stage disease, oncologists and urologists will increasingly need to consider incorporating genetic education, counseling, and germline testing for men with PCa.
- Providing guideline-concordant care now requires that practices and institutions prioritize including germline genetic testing as part of optimal care delivery.
- Physicians, advanced practice providers, genetic counselors, practice managers, and other team members must work in a concerted manner to overcome these barriers in practice- and resource-specific ways for this evolving care model.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

The supplemental appendix accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2019.04.013.

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Supplemental Appendix 1

Survey Questions and Germline Genetic Testing-Related Therapeutic Clinical Trials

1. What are your current personal practices around genetics services?
2. If you practice a combination of approaches, very briefly, how would you describe your general approach for an individual patient?
3. What prostate cancer patient population(s) are you currently considering for germline genetic testing? Select all that apply.
   a. Men with metastatic PCa (all)
   b. Men with metastatic PCa (trial candidates)
   c. Men with metastatic PCa (with family history of cancer)
   d. Men with high-risk localized or nonmetastatic PCa (all)
   e. Men with high-risk localized or nonmetastatic PCa (trial candidates)
   f. Men with high-risk localized or nonmetastatic PCa (with family history of cancer)
   g. PCa patients with family history of PCa and other cancers
   h. Other criteria (see next question)
4. If you are testing a combination of the groups listed above, very briefly, how would you describe your decision process for an individual patient?
5. What is your personal/institutional mechanism or system to integrate germline results with therapeutic clinical trials?
6. What is your personal/institutional mechanism for cascade testing of pathogenic/likely pathogenic germline mutation carriers?
7. Cascade genetic testing refers to offering genetics referral to relatives such as siblings and children of patients found to carry a germline mutation (pathogenic variant) in a cancer risk gene. This might provide valuable information for family members regarding their own risk and options for cancer screening and prevention. Is the cascade genetic testing process in your practice systematized to attempt to capture screening for other cancers and to facilitate cascade testing of family members?
8. What is your general approach to germline cancer predisposition testing? (If you select more than one, please explain further in the question that follows.)
   a. Specific individual genes (eg, *BRCA1*, *BRCA2*)
   b. Limited prostate cancer-specific panel
   c. Expanded cancer panel (eg, Lynch and *BRCA1/2* and hereditary breast and ovarian cancer genes)
   d. Comprehensive, pan-cancer panel
   e. Clinical trial-focused panel
   g. Reflex, single-site if tumor sequencing suggests germline finding
9. Please add any comments or details about your approach here.
10. Do you have any clinical trials around the delivery of genetic testing at your institution open or anticipated? (See Responses in Table 4.)
11. Do you have suggestions for patient/family resources to recommend to patients for more information?
12. What would be most immediately helpful to you as a resource for germline genetics that the PCCTC Working Group can help develop?
13. List any specific concerns, frustrations, worries, barriers, and challenges you would like to share around germline genetics and prostate cancer.
14. What is your name/institution?

Germline and Somatic Mutations in Prostate Cancer for the Clinician

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ABSTRACT

It is increasingly important for clinicians involved in the management of prostate cancer to understand the relevance of heritable (germline) mutations that, for select patients, affect prostate cancer risk and cancer biology, and acquired (somatic) mutations that occur in prostate cancer cells. In the advanced disease setting, mutations in homologous recombination repair genes (eg, *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *PALB2*) suggest candidacy for platinum chemotherapy and PARP inhibitor trials. Similarly, microsatellite instability and mismatch repair deficiency, which may arise in the setting of *MLH1*, *MSH2*, *MSH6*, and *PMS2* mutations, suggest potential vulnerability to PD-1 inhibitors. Germline genetic testing has potential importance in the treatment and assessment of familial risk, and tumor-directed somatic sequencing may guide treatment decision-making. This review provides clinicians with knowledge of basic genetic terminology, awareness of the importance of family history of cancer (not limited to prostate cancer), contrasts between the different but potentially related objectives of germline versus somatic testing of tumor tissue, and indications for genetic counseling. Specific clinical scenarios, objectives of testing, and nature of the assays are reviewed. Germline and somatic mutations of known and potential relevance to prostate cancer are discussed in the context of treatment options, and algorithms to assist clinicians in approaching this area are proposed.

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Expansion of genomic technologies and declining costs of next-generation sequencing (NGS) have led to rapid changes in germline and somatic genetic testing that must be considered in everyday clinical practice. Similar technology is used in direct-to-consumer "recreational" testing for understanding genealogic origins from an individual's DNA. Tests for primary prostate cancer to determine risk of recurrence and inform decisions regarding active surveillance are addressed elsewhere.[1–3] This review focuses on testing ordered by medical providers to determine heritable risk of cancer and guide treatment options in the advanced disease setting, provides a framework for understanding current options and uses for genetic testing, and considers data supporting genetic testing recommendations in the latest version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, version 2.2019 (in this issue).[4]

Germline DNA refers to the constitutional DNA of an individual resulting from the unique combination of genetic material, half from mother (egg) and half from father (sperm). (A list of key terms and definitions is provided in supplemental eTable 1, available with this article at JNCCN.org). Germline DNA is present in every cell of the body, and specific genetic changes have a 50/50 chance of being passed on to biologic children. Germline genetic testing can identify presence of inherited pathogenic variants (also called *mutations*) in genes associated with cancer risk. Testing can be performed on lymphocyte DNA from blood or a combination of lymphocyte and buccal cells from saliva, because germline DNA is nearly identical in all nucleated cells of an individual. Identification of a germline mutation associated with cancer susceptibility should involve a genetic counselor to ensure that medical, psychologic, legal, and ethical consequences for the patient and relatives are explained. Germline testing also can have important implications regarding treatment options for some patients with cancer.

In prostate cancer, the percentage of patients with germline mutations in DNA repair genes ranges from


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4.6% in localized disease to 11.8% to 16.2% in metastatic disease.[5,6] Patients with a strong pattern of cancers found on a comprehensive family history should be evaluated by a genetic counselor, who may recommend specific tests (Figure 1). In addition, if a germline mutation is identified, genetic counselors ensure appropriate education and testing for family members who may also carry the same gene mutation, a process known as "cascade genetic testing."

Sequencing DNA for tumor-acquired genetic changes (also referred to as *somatic mutations*) requires prostate tumor material: cancer-containing biopsies, surgical material, or, in some cases, circulating tumor cells or circulating tumor DNA (ctDNA) in the blood. Testing of tumor tissue from primary or metastatic sites or blood may help guide treatment options in the advanced disease setting. A number of specific mutations are summarized in Table 1, although the base of knowledge is evolving rapidly.

Somatic mutations observed in tumor tissue may change over time due to genetic instability and selective pressure from therapy. Thus, repeat testing of tumor DNA may be appropriate during the disease course. Findings in archival primary tissue obtained years earlier may differ from those in a metastatic site, although detection of certain relevant mutations is possible early in tumorigenesis. Other potential limitations include

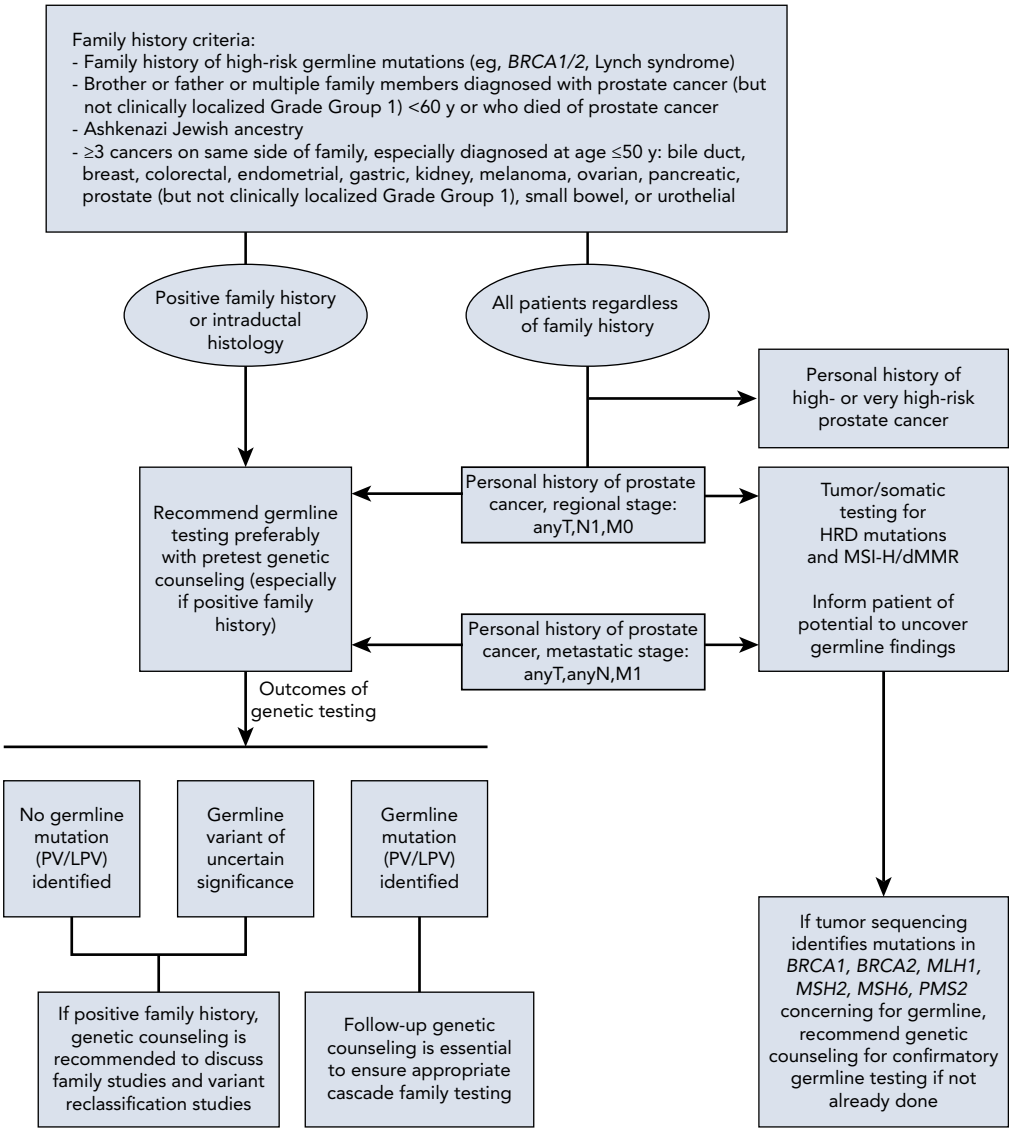


Figure 1. Algorithm for inherited/germline and tumor/somatic mutation testing in men diagnosed with prostate cancer.
Abbreviations: dMMR, mismatch repair deficiency; HRD, homologous recombination DNA repair; MSI-H, microsatellite instability-high; PV/LPV, pathologic variant or likely pathologic variant.

Table 1. Genes With Established or Emerging Potential Clinical Actionability, Germline vs Somatic

Gene	Association With Increased PC Risk	Prevalence of Germline Mutations in mPC[5]	Prevalence of Germline Mutations in PC With Clinical Suspicion[11]	Consideration of DNA-Damaging Agents: PARPi Trials, Platinum[40]	Consideration of Immune Checkpoint Inhibitors: PD-1 Inhibitors
ATM	X	1.6%	2.0%	X	
ATR		0.3%	Not evaluated		
BRCA1	X	0.9%	0.7%	X	
BRCA2	X	5.4%	4.7%	X	
BRIP1		0.2%	0.3%		
CDK12 (somatic only)		—	—		X
CHEK2	X	1.9%	2.9%	X	
FAM175A		0.2%	Not evaluated		
FANCA		—	Not evaluated	X	
HOXB13 (germline only)	X	Not evaluated	1.1%		
MLH1	X	—	0.06%		X
MRE11A		0.14%	Not evaluated		
MSH2	X	0.14%	0.69%		X
MSH6	X	0.14%	0.45%		X
NBN	[a]	0.3%	0.32%	X	
PALB2	[a]	0.4%	0.56%	X	
PMS2	X	0.3%	0.54%		X
RAD51C		0.14%	0.21%		
RAD51D		0.4%	0.15%		

Abbreviations: mPC, metastatic prostate cancer; PARPi, PARP inhibitors; PC, prostate cancer.
[a]Emerging/Limited data.

variance in tumor content and purity, and sensitivity and specificity of detecting tumor-specific mutations. Tumor-based testing has the potential to identify germline mutations that have implications for inherited cancer predisposition.[7,8] Tumor testing should never be used to substitute for germline testing because of the risk for false-positives and false-negatives due to variation in bioinformatics and reporting between commercially available tests. If somatic testing identifies a mutation in a gene associated with cancer predisposition (eg, *BRCA2*), referral to a genetic counselor for dedicated, confirmatory germline testing is indicated.

Family and Personal History of Cancer

Family history of cancer remains a foundation of genetic risk assessment, and inquiring about prostate and non-prostate cancers is critical to a complete assessment for possible inherited cancer risk (supplemental eTable 2).[5] In particular, cancers of the breast (especially in men or those diagnosed at a young age), ovary, pancreas, and melanomas should be noted, given their known association with mutations in *BRCA1/2*.[9] However, other cancers, such as mesothelioma, should also be noted.[10] Importantly, family history is necessary but not sufficient for identifying all germline carriers.[5]

In a recent study of 3,607 men diagnosed with prostate cancer who underwent genetic testing between 2013 and 2018, 17.2% were found to have germline mutations and 37% would not have met criteria for testing from the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.[9] However, the dates spanned a period when guidelines were changing (consideration of genetic testing in individuals with a personal history of metastatic prostate cancer was not incorporated until 2017), and therefore the tested population was likely influenced by clinical suspicion based on family history even if they did not meet contemporaneous testing guidelines.[11] The argument that all men with prostate cancer should be tested is thought-provoking, but cost-effectiveness and actionability of widespread genetic testing in early, low-risk prostate cancer settings without other risk factors remain unclear, and short-term unintended consequences include clinical confusion and low-yield depletion of limited genetic counseling resources.

In contrast, clinical predictors of germline status, such as metastatic stage[5] or intraductal histology,[12,13]

emerging data about ductal histology,[14,15] and/or history of second or multiple primary cancers at younger age[16] may help prioritize candidates for testing, because each has been independently associated with the presence of germline DNA repair mutations. The biochemically recurrent population is heterogeneous, although application of advanced modern imaging such as C-11 choline and F-18 fluciclovine PET scans may help distinguish patients with indolent versus occult metastatic disease. Figure 1 illustrates the interaction between clinical disease features, family history, and pathology to determine who should be offered germline and/or somatic testing and genetic counseling.[4]

Genetic Counseling

Genetic counselors play an essential role in many aspects of the genetic testing process, but particularly in educating patients and family members, deciding on appropriate testing when there is strong family history, guiding accurate communication of medical information to family, and addressing psychosocial aspects of testing.

Risk assessment and pretest genetic counseling have been performed traditionally by genetic counselors, but access and long wait times can hamper time-sensitive testing that may inform treatment options in advanced disease. Ongoing studies are exploring novel delivery models for genetic services to balance time sensitivity with responsibility for informed consent, pretest education, and posttest follow-up (ClinicalTrials.gov identifiers: NCT02987543, NCT3328091, and NCT03503097).

Figure 1 illustrates the points in care at which genetic counseling is essential: (1) when there is a strong family history of cancer to ensure appropriate testing is ordered and that posttest communication to family is accurate; (2) after a germline pathogenic variant (mutation) is identified to ensure cascade testing; (3) when somatic testing uncovers a mutation that is potentially germline in nature; or (4) if the patient displays any indication of stress, distress, or unanswered questions. Providers should work closely with their genetics colleagues to develop systems that address patient needs with thoughtful stewardship of local genetics resources.

Genetic Testing

Choice of which germline test to use is beyond the scope of this review, although a number of commercial tests are available and typically use blood or saliva. There is variation in insurance coverage and out-of-pocket costs, although with assistance programs and competitive pricing, patient costs can often be limited to several hundred dollars or less. If genetic testing is being performed in the context of advanced prostate cancer, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, and *PMS2* should be included due to potential treatment implications, although this list is expected to be refined over time. In specific research or clinical contexts, a larger gene panel may be appropriate. For example, *HOXB13* is a prostate cancer risk gene that does not have clear therapeutic implications in advanced disease at this time, but which should be included if heritable prostate cancer risk is part of the question.[4] Similarly, the gene list to consider may be larger for a somatic tumor gene panel and extend beyond cancer risk genes.

Potential outcomes for germline testing include identification of a mutation (pathogenic or likely pathogenic variant), which may suggest additional prostate cancer treatment options and clinical trials and inform risk of other cancers. This result would also indicate a 50/50 chance that first-degree relatives inherited the same risk gene and thus would prompt a recommendation for the patient to share this information (including a copy of test results) with relatives and for referral of family members to genetic counseling for cascade genetic testing. Single-site testing for a specific mutation is typically covered by insurance and is less expensive.

Another potential outcome is a variant of uncertain significance (VUS), which indicates that available data in the field were insufficient to characterize the finding as either benign or pathogenic at the time of test interpretation. A VUS result should not be used to direct clinical management. Research studies are available to help reclassify VUS, and these can be discussed with a genetic counselor.[17] In one study, 7.7% of VUS results were reclassified: 91% as benign/likely benign and 9% as pathogenic/likely pathogenic.[18]

An outcome could also be that no mutations were identified (a benign result). Failure to identify a single, inherited cancer risk–associated mutation does not obviate an increased risk of prostate cancer to family members if there is a strong family history. If testing is negative (benign, with no mutations) or identifies a VUS, the clinical family history should be used to guide cancer screening for family members. Although tempting, VUS—including and especially in *BRCA1/2*—should not be used for medical management, although follow-up with genetic counseling and consideration of research opportunities, such as registries and variant reclassification studies, are encouraged.

Individuals found to have germline pathogenic (or likely pathogenic) variants must see a genetic counselor for counseling, guidance on communication to family, and appropriate cascade genetic testing that extends genetic testing to other family members (https://www.nsgc.org/findageneticcounselor). Providers should also be aware that telehealth-, phone-, and new technology-based genetic counseling services may be an additional option for patients.

Genes With Germline and Somatic Actionability

Prostate Cancer Risk

For germline *BRCA2* mutation carriers, the relative risk of developing prostate cancer by age 65 years is estimated to be 2.5- to 8.6-fold compared with noncarriers.[19] In a recent study, lifetime risk of prostate cancer by age 80 years was reported between 19% and 61%, and 7% and 26% for carriers of *BRCA2* and *BRCA1* mutations, respectively.[20] Retrospective studies have shown that men with *BRCA2* mutations present at a younger age with higher Gleason grade tumors, higher rates of nodal involvement and distant metastases at diagnosis, and higher prostate cancer–specific mortality.[21,22] *BRCA1*,[23] *ATM*,[24] *CHEK2*,[25,26] and *PALB2*[27] also are involved in homologous recombination DNA repair and have been associated with increased prostate cancer risk, although these germline mutations have fewer data available and suggest less apparent relative risk of developing prostate cancer compared with *BRCA2*.[5,28] Germline mutations in the mismatch repair (MMR) genes *MLH1*, *PMS2*, *MSH2*, and *MSH6* are associated with Lynch syndrome, an inherited condition that predisposes individuals to an increased risk of developing many different types of cancers, including colorectal, endometrial, and gastrointestinal, often at a young age.[29] Several studies suggest a modest increased risk of prostate cancer in patients with Lynch syndrome,[30,31] and germline MMR gene mutations have been seen in the metastatic setting.[5] *HOXB13* G84E is a germline variant associated with increased risk of developing prostate cancer, but this variant is not clearly associated with increased disease aggressiveness nor should it influence treatment decision-making.[32–34] Emerging data suggest that *NBS1* (also called *NBN*),[35] *FANCA*,[36] and other DNA repair genes are associated with increased prostate cancer risk and choice of treatment, but further studies are needed before clinical action is warranted.

Screening Recommendations for Carriers of Pathogenic Germline Mutations

Screening recommendations have not been established for men with pathogenic germline mutations associated with increased prostate cancer risk. The ongoing IMPACT study is evaluating the role of targeted prostate-specific antigen (PSA) screening in men with *BRCA1/2* mutations (ClinicalTrials.gov identifier: NCT00261456). Preliminary results support yearly PSA screening in men with *BRCA2* mutations aged 40 to 69 years.[37] NCI's recently opened Men at High Genetic Risk for Prostate Cancer trial incorporates annual PSA testing and regular digital rectal examination and prostate MRI (NCT03805919). If clinical trial participation is not available, annual PSA measurement for carriers of high-risk mutations should begin at age 40 years (Figure 2). Men with PSA levels greater than the median age-adjusted PSA ranges[3,38,39] may consider prostate biopsy, which may be MRI/ultrasound fusion–guided.

Therapeutic Implications of Genetic Testing

Prostate tumors can now be sequenced for mutations that may offer molecularly targeted therapeutic options.[4] Archival tissue from the primary is often considered acceptable for studies of targeted agents when the biomarker in question is present, but archival tissue from a patient who has had multiple therapies may not reflect current tumor DNA status. Contemporary sampling of metastatic disease sites or cell-free ctDNA or circulating tumor cells may be more informative, although uninformative somatic testing, false-negatives, and limitations due to tumor purity must also be considered. Studies suggest that concordance with metastatic tissue can be good,[40] and that clinical selection and the timing of ctDNA draw at progression may improve diagnostic yield.[41]

Recent studies have resulted in major changes to consideration of germline testing in some patients with prostate cancer.[5,6,13,15] Germline genetic testing is now recommended for all men with a family history of prostate cancer or intraductal histology and/or high- or very high-risk regional or metastatic prostate cancer.[4] The decreasing cost of germline panel testing has made it more feasible to follow these guidelines for testing, although substantial issues remain regarding disparities in insurance coverage and access to genetic counseling.

The standards for somatic testing and reporting are less established than those for germline testing. Rapid changes in assays and clinical trials in progress make it difficult to recommend specific assays. A number of NGS sequencing panels are available and FDA-approved for somatic testing

For men with personal history of *BRCA1/2* mutation, Lynch syndrome, or mutations (ie, pathogenic variants) in prostate cancer-associated risk genes:

- Begin screening at age 40 y.
- Annual PSA and DRE.
- Men with a PSA level above the median for their age group are at higher risk for prostate cancer and aggressive prostate cancer. The higher above the median, the greater the risk.
- If PSA level is below age-adjusted median and no other indication for biopsy, repeat screening in 12 months.
- If PSA level is above age-adjusted median, recheck PSA in 6–12 months; if increased, consider extended pattern biopsy with mpMRI or TRUS-guidance.
- Upper limit age-adjusted median range PSA[38,39]:
  - Aged ≤49 y, PSA >1.5 ng/mL
  - Aged 50–59 y, PSA >2.0 ng/mL
  - Aged 60–69 y, PSA >2.5 ng/mL

Figure 2. Recommendations for prostate cancer early detection in carriers of high-risk mutations.

Abbreviations: DRE, digital rectal examination; mpMRI, multiparametric MRI; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.

in CLIA-certified laboratories. Currently, somatic testing for homologous recombination gene mutations and microsatellite instability (MSI) and MMR deficiency (dMMR) should be considered due to potential treatment implications. In addition, some somatic NGS assays may also report alterations that, although investigational, may inform clinical trial candidacy: androgen receptor amplifications, *PTEN* deletions, PI3K/Akt/mTOR pathway alterations, and *TMPRSS2-ERG* gene fusions.

The definition of actionability for specific gene mutations in prostate cancer is emerging, and currently at least 2 classes of gene mutations should be considered (Table 1). Tumor and/or germline mutations in genes such as *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, and *CHEK2* may suggest candidacy for early use of platinum-based chemotherapy[42,43] or enrollment in clinical trials testing PARP inhibitors,[44] such as olaparib and rucaparib, which have been granted breakthrough designation by the FDA. Ongoing clinical trials are evaluating a number of PARP inhibitors for metastatic castration-resistant prostate cancer (mCRPC) and earlier disease states (ClinicalTrials.gov identifiers: NCT02854436, NCT02975934, NCT02987543, and NCT03148795). Retrospective and prospective studies to date have not shown that any FDA-approved treatment of mCRPC should be withheld from men with advanced prostate cancer and germline mutations.[45–47]

Tumor DNA evaluation for high MSI (MSI-H) or dMMR can be determined using immunohistochemistry or NGS methods demonstrating loss of function of *MLH1*, *MSH2*, *MSH6*, or *PMS2*, and is ideally validated for prostate cancer.[48,49] Identification of tumor MSI-H or dMMR indicates potential eligibility for pembrolizumab in later lines of therapy for advanced disease.[4]

Importance of the Molecular Tumor Board

Because approaches to NGS testing of tumors have changed and continue to evolve quickly, interpretation of results for the busy clinician may be challenging. Many institutions have instituted molecular tumor boards in which relevant clinical information is presented alongside results of germline and/or somatic testing and is reviewed by a multidisciplinary team. These tumor boards should include expert interpretation of data by a molecular pathologist, medical oncologist with disease-specific expertise, and genetic counselor, and may also include radiation and surgical oncologists. Such molecular tumor boards are increasingly available at comprehensive cancer centers with consultation for or participation by outside physicians because molecular pathology expertise is not yet widely available.

Conclusions

A summary of important points is available in eTable 3. Information about heritable (germline) and tumor-acquired (somatic) mutations has increasing importance in the management of men with prostate cancer. Germline data can inform both patient and family risk for prostate and other cancers and drive more aggressive screening in men at high risk of developing prostate cancer. Somatic testing is performed to determine whether the tumor has actionable targets for therapy, and prior knowledge of germline mutations can help in the interpretation of the results. Molecular tumor boards are needed to best interpret results and to direct clinical management and trial opportunities for providers and patients. Partnership with genetic counselors is needed to assist patients and relatives with decisions regarding genetic testing, interpretation, and follow-up cascade testing for family members. Clinicians should be aware of how to integrate genomic testing into treatment paradigms, because this field is rapidly evolving.

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eTable 1: Key Terms and Definitions
eTable 2: Obtaining a Comprehensive Family History of Cancer
eTable 3: Take-Home Points

eTable 1. Key Terms and Definitions
Cascade testing: Genetic counseling and testing in blood relatives of individuals who have been identified with specific genetic mutations; may include screening, counseling, or referral for a patient with a relative who has tested positive for a genetic mutation.
CTC: Circulating tumor cells. Tumor cells from the circulation (blood) that can be enumerated, measured, and/or evaluated.
ctDNA: Circulating tumor DNA. Typically measured from cell-free DNA in the plasma.
DDR: DNA damage response pathways. Includes homologous recombination, MMR, base excision repair, and others.
dMMR: Deficiency in mismatch repair. Refers to the inability to use a mechanism of correcting errors in DNA by detecting and replacing bases in the DNA that are paired incorrectly (mismatched bases). dMMR in the tumor may be associated with susceptibility to treatments, such as immune checkpoint inhibitors.
Genetic counseling: The evaluation and understanding of a family's risk for an inherited medical condition. A genetic counselor is a healthcare professional with specialized training in medical genetics and counseling.
Genetic testing: Laboratory methods to evaluate DNA of an individual to identify increased risks of specific conditions (eg, cancer), select treatment, or determine response to treatment.
Germline DNA: Constitutional DNA that is inherited from mother and father, present in nucleated cells of the body, such as lymphocytes, and may be passed on to children. Some genes may be shared with siblings.
HRD: Homologous recombination deficiency. Refers to the inability to use a common mechanism of repairing harmful breaks that occur on both strands of DNA, known as doublestrand breaks, through genetic recombination. Examples: *BRCA2, BRCA1, PALB2.*
MSI-H: Microsatellite instability. MSI-high refers to microsatellite instability, a measure of dMMR. Can result from defects in genes such as *MLH1, MSH2, MSH6, or PMS2.*
NGS: Next-generation sequencing. High-throughput DNA sequencing technologies. Millions or billions of DNA strands can be sequenced in parallel to yield more throughput. Practically, this allows multiple genes to be tested at the same time in gene "panels."
Pathogenic variant: A genetic alteration that increases an individual's susceptibility or predisposition to a certain disease or disorder (eg, prostate cancer). Development of prostate cancer is more likely, but not certain, when such a variant (or mutation) is inherited.
Somatic DNA: Acquired mutations and genetic changes to the germline DNA. Often refers to tumor-associated genetic changes that are not heritable.
VUS: Variant of uncertain significance. Typically refers to a genetic change in germline DNA where there is insufficient information available to know if it causes an increased susceptibility to cancer or not.

Abbreviations: CTC, circulating tumor cells; ctDNA, circulating tumor DNA; dMMR, mismatch repair deficiency; HRD, homologous recombination deficiency; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability–high; NGS, next-generation sequencing; VUS, variant of uncertain significance.

eTable 2. Obtaining a Comprehensive Family History of Cancer

Detailed family history includes:

- Parents
- Children
- Siblings/Half siblings
- Grandparents and great-grandparents (specify maternal or paternal)
- Nieces and nephews
- Aunts and uncles (specify maternal or paternal)
- Cousins (specify maternal or paternal)
- Ethnicity/Country of origin
- Consanguinity

Minimal data for each cancer-affected relative:

- Current age and age at diagnosis (if not known exactly, decades can be helpful)
- Age at and cause of death (especially if cancer-related)
- Type of cancer (note multiple primaries)
- Results of any prior genetic testing

Resources for collecting family history:

- CDC My Family Health Portrait, https://phgkb.cdc.gov/FHH/html/index.html
- Cancer.net, https://www.cancer.net/sites/cancer.net/files/cancer_family_history_questionnaire.pdf
- NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (see algorithm page HRS-A; available online at NCCN.org).

Abbreviation: CDC, Centers for Disease Control and Prevention.

eTable 3: Take-Home Points
• Germline DNA is inherited from both biologic parents and is present in all cells in the body. It does not change over time, therefore repeat testing will typically be of limited value.
• Somatic (tumor) DNA is comprised of germline genetic material with additional acquired mutations; however, somatic testing platforms may or may not report suspected germline mutations (pathogenic variants).
• Tumor testing may suggest the need for, but should never replace, dedicated germline testing.
• Tumor evolution over time means repeat somatic testing may be of value.
• Germline testing can identify increased risk for heritable cancers.
• Germline DNA may have therapeutic implications for some patients.
• Tumor sequencing can be performed to find actionable mutations that may have therapeutic implications in advanced disease.
• Germline mutation testing should be offered to patients with a family history of prostate other cancers, or those with a personal history of high- and very high-risk localized prostate cancer, regional, or metastatic disease.
• All patients with pathogenic germline mutations should be referred to a genetic counselor.
• When there is a strong family history, genetic counseling is recommended before genetic testing whenever possible.
• If germline testing is negative or inconclusive (ie, there is no known cancer associated with the identified mutation) but there is a strong family history for cancers, referral to genetic counseling is indicated.
• Variants of uncertain significance (VUS; including in *BRCA1/2*) should not be used for medical management.
• Tumor DNA analysis should be performed at a time when a new therapy is under consideration.
• Intraductal histology has a higher association with actionable tumor and germline mutations.
• Genetic counselors can be found at https://www.nsgc.org/findageneticcounselor.
• Carriers of the *BRCA1/2* mutation are at increased risk of prostate cancer before age 65 years, and prostate cancer in men with germline *BRCA2* mutations occurs earlier and is more likely to be associated with prostate cancer mortality.
• Men with germline *BRCA1/2* mutations may consider beginning shared decision-making about PSA screening at age 40 years and at annual intervals, factoring in age-adjusted median PSA values. Early detection clinical trials are recommended whenever possible.

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Original Research

Radium-223 in combination with docetaxel in patients with castration-resistant prostate cancer and bone metastases: a phase 1 dose escalation/randomised phase 2a trial

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KEYWORDS
Castration-resistant prostate cancer;
Radium 223 dichloride;
Docetaxel;
Combination treatment

Abstract ***Purpose:*** Radium 223 dichloride (radium-223) is an alpha particle–emitting bone-directed therapy that prolongs overall survival in men with bone-predominant metastatic castration-resistant prostate cancer (mCRPC). Docetaxel is an antimicrotubule cytotoxic agent that improves survival in mCRPC. We investigated whether combining these potentially cross-sensitising agents to dually target tumour and bone would be safe and effective.
Patients and methods: Phase 1 was a dose escalation study to define a recommended phase 2 dose (RP2D) of docetaxel and radium-223. In phase 2a, patients were randomised 2:1 to the recommended combination regimen or docetaxel at a dose of 75 mg/m^2 every 3 weeks (q3w). Patients with bone-predominant mCRPC were eligible. End-points were safety, efficacy and treatment-related changes in serum and imaging biomarkers.
Results: Twenty patients were enrolled in phase 1; 53 patients were randomised in phase 2a: 36 to combination treatment and 17 to docetaxel alone. The RP2D for the combination was radium-223 55 kBq/kg every six weeks × 5 doses, plus docetaxel 60 mg/m^2 q3w × 10 doses. Febrile neutropenia was dose limiting. A higher rate of febrile neutropenia was seen in the docetaxel monotherapy arm (15% vs 0%); the safety profile of the treatment groups was otherwise similar. The combination arm had more durable suppression of prostate-specific antigen (median time to progression, 6.6 vs 4.8 months, respectively), alkaline phosphatase (9 vs 7 months) and osteoblastic bone deposition markers.
Conclusions: Radium-223 in combination with docetaxel at the RP2D was well tolerated. Exploratory efficacy data suggested enhanced antitumour activity for the combination relative to docetaxel alone. Comparative studies with end-points of clinical benefit are warranted. ClinicalTrials.gov number: NCT01106352.
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1. Introduction

Prostate cancer is bone-tropic, rendering it particularly susceptible to treatments that target bone formation and osteoblastic activity. The cancer-induced abnormal bone metabolism that places patients at risk of death and morbidity can also be leveraged to deliver life-prolonging therapy.

Radium 223 dichloride (radium-223), a calcium mimetic alpha particle–emitting radiopharmaceutical, targets hydroxyapatite. It selectively accumulates in areas of increased bone turnover that surround metastatic lesions, where it emits four high-energy, short-range (<100 μm) alpha particles with resulting minimal radiation effects on the adjacent bone marrow [1,2]. In preclinical models, it reduces abnormal bone production, tumour burden and dysregulated bone deposition [3,4]. Clinically, radium-223—given at a dose of 55 kBq/kg every 4 weeks for 6 doses—prolongs life and the time to first symptomatic skeletal event in patients with bone-predominant metastatic castration-resistant prostate cancer (mCRPC) and no known visceral metastases [5].

Docetaxel is a chemotherapeutic agent that interferes with microtubule dynamics and has a radiosensitising effect [6]. Docetaxel given at a dose of 75 mg/m^2 every 3 weeks (q3w) in combination with prednisone prolongs life in patients with mCRPC [7].

We hypothesised that combining bone-targeted alpha radiation therapy with chemotherapy in patients with mCRPC might be an effective treatment approach, predicated on the concepts of multicompartment targeting and possible cross-sensitisation in bone lesions [8]. We conducted a phase 1/2a study to investigate this combination.

2. Patients and methods

2.1. Patients

Eligible patients had progressive mCRPC with ≥2 bone metastases, testosterone ≤50 ng/dL, Karnofsky Performance Status of ≥70%, life expectancy of ≥6 months and adequate organ functionality (white blood cell count ≥3 × 10^9/L, with an absolute neutrophil count ≥1.5 × 10^9/L, a platelet count ≥100 × 10^9/L and haemoglobin ≥10.0 g/dL; total bilirubin level ≤ upper limit of normal (ULN) and aspartate aminotransferase and alanine aminotransferase concentrations ≤1.5 × ULN; creatinine ≤1.5 × ULN and albumin >30 g/L). The patients needed to have had two consecutive prostate-specific antigen (PSA) increases at least one week apart, with a minimum value of 2 ng/mL at screening, or two or more new bone lesions when analysed by bone scintigraphy. Those patients on a first-generation androgen inhibitor needed to progress through a 4-week withdrawal. The exclusion criteria included the following: visceral metastases, defined as >2 lung metastases and/or liver metastases that were ≥2 cm in size, symptomatic nodal disease and malignant lymphadenopathy >3 cm in short-axis diameter. Patients should not have received >10

previous docetaxel doses or previous treatment with a bone-seeking radiopharmaceutical.

2.2. Study design

This two-part phase 1/phase 2a study, conducted at eight centres, seven in the United States and one in France, aimed to establish a recommended phase 2 dose (RP2D) of radium-223 in combination with docetaxel and to investigate safety and exploratory efficacy end-points at the RP2D.

In phase 1, between 9 and 18 patients were to be enrolled and treated according to a 3 + 3 design. The dose escalation scheme is shown in Fig. 1A. Dose-limiting toxicity (DLT) was assessed during the 6-week period after the first radium-223 injection. DLT was defined as absolute neutrophil count $<0.5 \times 10^9$/L for >7 days without fever despite granulocyte-colony stimulating factor support, grade ≥3 febrile neutropenia (after a protocol amendment), platelet count $<25 \times 10^9$/L for >7 days, grade ≥3 diarrhoea despite optimal medical management, grade ≥4 vomiting or constipation.

Radium-223 was started at a dose of 27.5 kBq/kg (according to the National Institute of Standards and Technology [NIST] 2016 update [9]), every six weeks (q6w), and could be escalated to 55 kBq/kg (according to NIST 2016 update [9]). The starting dose of docetaxel was 75 mg/m^2 q3w, with a planned reduction to 60 mg/m^2 in the event of DLT. We prioritised achieving full-dose radium-223 over full-dose chemotherapy in the dose escalation scheme, given that there are survival data using docetaxel as part of combination therapy at its step-down dose but no survival data using a lower dose of radium-223 [10]. Radium-223 was administered every other chemotherapy dose rather than monthly to optimise the likelihood of patient acceptance and compliance by having only one day of treatment per cycle, at a dosing interval known to have favourable clinical effects [11]. The number of doses was capped at five in an abundance of caution to protect long-term marrow integrity in the event of enhanced toxicity that would not be detected by blood count assessments during treatment. In all cohorts, docetaxel was to be administered every 3 weeks and was to be continued in the absence of progressive disease or unacceptable toxicity. Docetaxel and radium-223 were administered on the same day, with docetaxel administered first, followed by radium-223 as soon as practically feasible. Prednisone 5 mg was given orally twice daily, continuously. Dexamethasone premedication was given before docetaxel dosing as per each institution's practice. Growth factor support was allowed only as secondary prophylaxis.

In phase 2a, using a schedule generated by an independent statistician, patients were randomly assigned centrally 2:1, using a block randomisation scheme (block size of three), via an interactive voice response system, to combination therapy or docetaxel alone, respectively. A preplanned early stopping rule applied in the event of significant toxicity in the combination arm. The treatment period was a maximum of 30 weeks (10 doses of docetaxel), followed by 22 weeks of follow-up.

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation E6, Good Clinical Practice. The protocol and all amendments were approved by the independent ethics committee/institutional review boards at each site, and written informed consent was obtained from the patients before any assessments were performed.

2.3. Assessments

Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities version 13.0. Severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. The safety assessment period for AEs was from the start of study treatment to 6 weeks after the end of study treatment (8 weeks for serious AEs [SAEs]). Data on marrow sequelae and any second malignancies were collected up to 12 months after the start of study treatment. Exploratory efficacy assessments included on-treatment changes in bone alkaline phosphatase (bALP), total ALP (tALP), urinary C-telopeptide of type 1 (uCTX-1), N-terminal propeptide of procollagen type 1 (P1NP), pyridinoline cross-linked carboxyterminal telopeptide (ICTP), PSA and circulating tumour cells (CTCs).

2.4. Statistical considerations

The primary objectives were to establish a recommended dose of radium-223 combined with docetaxel and to investigate safety and explore efficacy at this dose level. The safety population included all patients who received treatment. To examine the antitumour effect of treatment in this exploratory study, the efficacy population comprised patients who received ≥40% (2 infusions) of the specified number of radium-223 doses (combination arm) or docetaxel doses (docetaxel arm) and had no major protocol violations (per protocol population). No formal statistical testing was planned.

Exploratory efficacy end-points included time to PSA progression, time to bALP progression, time to tALP progression, time to first radiographic or clinical progression based on Response Evaluation Criteria in Solid Tumours (RECIST) [12] version 1.1 and Prostate Cancer Working Group 2 (PCWG2) [13] definitions and overall survival. Time-to-event end-points were measured from the first dose of study treatment. For this report, progression-free survival (PFS) events are defined as radiographic or clinical progression or death. Medians

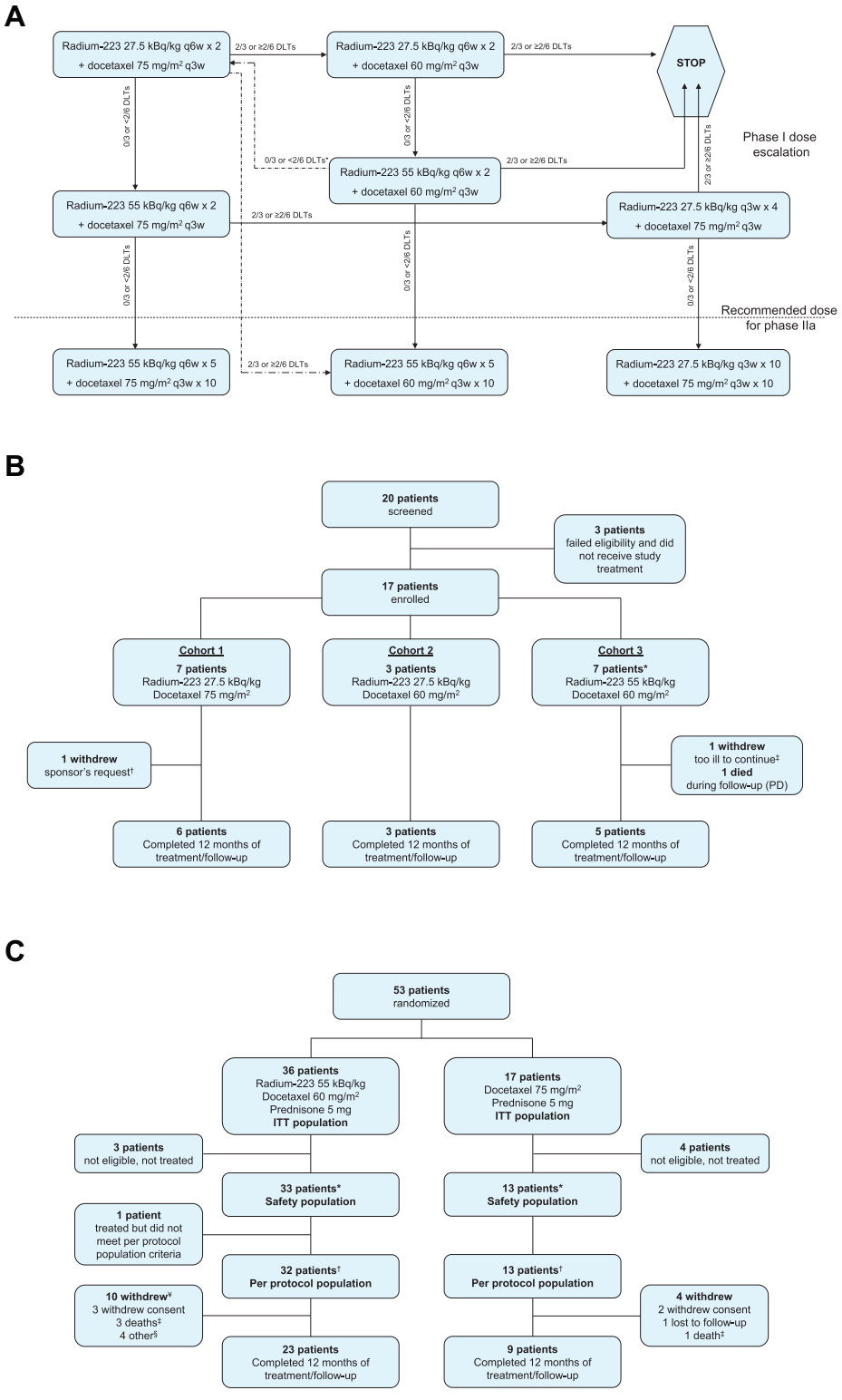


Fig. 1. Study profile. (A) Dose escalation scheme.*A return to the very first dose cohort could be considered in the event of 0/3 or <2/6 DLTs at 55 kBq/kg radium-223 + 60 mg/m^2 docetaxel q3w. If then 2/3 or ≥2/6 DLTs occurred at docetaxel 75 mg/m^2, the chosen regimen for the phase 2a cohort was to be radium-223 50 kBq/kg × 5 + docetaxel 60 mg/m^2 q3w × 10. (B) Phase 1 dose escalation cohorts. *One patient was replaced, unable to receive both combined doses of radium-223 and docetaxel because of docetaxel hypersensitivity. †Withdrew before receiving both doses of radium-223 to receive another treatment deemed necessary by the study sponsor. ‡Withdrew after receiving both doses of radium-223, too ill to attend the 12-month follow-up visit. (C) Phase 2a safety and efficacy cohort.*25 patients in the combination arm received all planned radium-223 doses, 20 patients in the combination arm and 5 patients in the docetaxel arm received all planned docetaxel doses; the dose for 4 patients in the docetaxel arm was stepped down to 60 mg/m^2. The study was completed through 12 months of follow-up from the start of treatment with 23 (70%) patients in the combination arm and 9 (69%) in the

for time-to-event variables were estimated using the Kaplan–Meier method. Changes in biomarkers over time were computed as the area under the bone marker curve. Based on the Lehmann alternative power function for a two-sided 0.05-level test, the planned 42 patients were to be randomised. Assuming for a given marker that the odds were 3:1 that a patient in the combination group had a greater area under the bone turnover curve relative to a patient in the docetaxel group, the power of the test was 0.78. *P* values for exploratory efficacy end-points have not been corrected for multiplicity of testing and are provided for information only.

3. Results

3.1. Phase 1 dose escalation

Seventeen patients were treated in the phase 1 dose escalation cohort, including three with visceral disease; patient disposition and baseline characteristics are summarised in Fig. 1B and Supplementary Table 1. No DLTs occurred among the first three patients treated at full-dose chemotherapy and half-dose radium-223 (27.5 kBq/kg), but two developed febrile neutropenia, which was not then specified as a DLT. The cohort was expanded to six patients; no DLTs or additional febrile neutropenia events were seen. Owing to febrile neutropenia in two of six patients, the docetaxel dose was reduced to 60 mg/m^2 in the second cohort, which also used radium-223 at a dose of 27.5 kBq/kg. No DLTs were seen in the first three patients enrolled in this cohort. Because it appeared that the docetaxel dose at 75 mg/m^2 was accounting for the neutropenic fevers, the radium-223 dose was escalated to 55 kBq/kg in the third cohort, holding the docetaxel dose at 60 mg/m^2. No DLTs were seen in the first three patients enrolled at this dose level. However, one patient developed grade 3 neutropenia and another developed grade 4 neutropenia, both without fever or infection. After reviewing the safety data, it was decided to add three more patients to this cohort. No DLTs occurred in these patients. The third cohort dose (55 kBq/kg radium q6w × 5 and 60 mg/m^2 docetaxel q3w × 10) was consequently selected as the RP2D to be administered over 30 weeks. Haematological treatment-emergent AEs (TEAEs) occurring in phase 1 are shown in Supplementary Table 2.

3.2. Phase 2a cohort

3.2.1. Patients and treatment

Between December 19, 2012, and April 7, 2014, 53 patients were randomly assigned to receive combination therapy with docetaxel 60 mg/m^2 and radium-223 55 kBq/kg q6w × 5 (n = 36) or docetaxel alone, at a standard dose of 75 mg/m^2 q3w × 10 (n = 17, Fig. 1C, Supplementary Fig. 1); seven patients were found not to be eligible and were not treated. Baseline characteristics were similar between treatment groups (Table 1). Seven (15%) of 46 eligible patients had visceral metastases at baseline, five in the combination arm and two in the docetaxel arm.

3.2.2. Treatment exposure

The patients in the combination arm received a cumulative median of 1187 mg of docetaxel (range, 250–1520), versus 1270 mg (range, 643–1600) in the docetaxel monotherapy arm. The median number of docetaxel doses was 10 (range, 2–11) in the combination arm and 9 (range, 4–10) in the monotherapy arm. The median number of radium-223 doses in the combination arm was 5 (range, 1–5).

In the combination therapy arm, radium-223 and docetaxel administration was delayed in two patients because of TEAEs (cellulitis and osteoporosis), with docetaxel administration delayed in a further five patients (because of back pain, pain in extremity; oral abscess; pneumonia; toothache; diarrhoea, dehydration, pleural effusion, acute respiratory failure and pneumonia). There were three dose delays because of TEAEs in the docetaxel arm (hypotension; influenza-like illness, cough and melaena; cellulitis). In the combination arm, radium-223 and docetaxel were discontinued in 4 of 33 (12%) patients because of TEAEs (unilateral blindness; cerebrovascular accident; pneumonitis; asthenia and back pain), and docetaxel was discontinued in a further two (6%) patients (peripheral neuropathy; asthenia). In the docetaxel arm, 3 of 13 (23%) patients discontinued treatment because of TEAEs (febrile neutropenia; interstitial lung disease; peripheral neuropathy).

3.2.3. Safety

TEAE and TESAE incidence in the phase 2a safety population is summarised in Table 2 and Supplementary Table 3. Notably, there was less toxicity of any grade seen with combination therapy than docetaxel alone for neutropenia, febrile neutropenia, fatigue, dyspnoea, arthralgia and nausea. However, combination therapy was associated with more diarrhoea and back pain. The incidence of grade 3 or 4 TEAEs was low in both arms (Table 2), with the exception of neutropenia. Febrile neutropenia occurred in two patients (one grade 3 and one grade 4) in the docetaxel arm and none in the combination arm; growth factors were used to prevent or resolve neutropenia in four patients in the combination arm and two

docetaxel arm. †Received at least 40% of drug dose, no protocol violation. ¥Including the one patient who was excluded from the per protocol population. ‡All deaths occurred during follow-up and were due to disease progression. §3 patients entered hospice, and 1 had disease progression. PD, progressive disease; DLT, dose-limiting toxicity; ITT, intention to treat; q3w, every 3 weeks; q6w, every 6 weeks.

Table 1
Baseline characteristics (phase 2a cohort).

Characteristic	Radium-223 + docetaxel $N = 33$	Docetaxel $N = 13$
Age, median (range), years	68 (49–82)	67 (55–82)
Weight, median (range), kg	87 (61–120)	78 (69–132)
Karnofsky Performance Status, median %, (range)	90 (70–100)	90 (70–100)
Albumin, median, g/L	43.0	43.0
Haemoglobin, median, g/L	122.0	121.0
PSA		
>ULN, *N* (%)	32 (97)	13 (100)
Median (range), µg/L	99 (3–1000)	43 (4–1042)
Total ALP		
>ULN, *N* (%)	20 (61)	10 (77)
Median (range), U/L	167 (62–1016)	186 (74–472)
Bone ALP		
>ULN, *N* (%)	23 (70)	11 (85)
Median (range), µg/L	36 (10–331)	47 (16–164)
LDH		
>ULN, *N* (%)	6 (18)	2 (15)
Median (range), U/L	191 (123–418)	190 (124–328)
Patients with visceral metastatic lesions, *N* (%)		
Any	5 (15)	2 (15)
Lung	1 (3)	1 (8)
Liver	0	0
Other	4[a] (12)	1[b] (8)
Extent of disease (number of bone lesions), *N* (%)		
2–4	4 (12)	0
5–9	7 (21)	3 (23)
10–20	9 (27)	4 (31)
>20	13 (39)	6 (46)
Time since initial diagnosis, median (range), months	73 (7–292)	45 (12–274)
Time since bone metastases, median (range), months	23 (1–58)	10 (0–92)
Prior anticancer therapies, *N* (%)		
Hormonal therapies		
Abiraterone + prednisone	25 (76)	8 (62)
Enzalutamide	3 (9)	5 (38)
Chemotherapy		
Docetaxel	2 (6)	0
Immunostimulants		
Sipuleucel-T	6 (18)	4 (31)
Bone-modifying agents, *N* (%)		
Bisphosphonates	13 (39)	5 (38)
Denosumab	12 (36)	3 (23)
Other, *N* (%)		
Radiation	24 (73)	9 (69)

ALP, alkaline phosphatase; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; ULN, upper limit of normal.
[a] Adrenal (2 patients), pleura, pancreas.
[b] Adrenal.

patients in the docetaxel arm. There were no TEAEs of thrombocytopenia reported in either arm during the treatment period, and median platelet laboratory values were similar for both treatment groups between baseline and day 8 (Supplementary Fig. 2). There were no grade 5 TEAEs. No fractures were observed.

3.2.4. *Efficacy*

PSA declines of >50% occurred in 61% of patients in the combination arm and 54% of patients in the docetaxel arm (Supplementary Fig. 3A). Plots of PSA level relative to baseline from week 4 to end of treatment show similar profiles for both arms, but PSA suppression was more pronounced with the combination arm (Supplementary Fig. 4A, Supplementary Table 4). A longer time to PSA progression was also observed with the combination arm (Fig. 2A; median, 6.6 vs 4.8 months).

The median PFS was 12.0 months in the combination arm and 9.3 months in the docetaxel arm (Fig. 2D). Twelve-month overall survival rates were similar (89% and 90%, respectively), although the high level of censoring precluded meaningful analysis. Disease progression based on RECIST and PCWG2 criteria is shown in Supplementary Table 5.

Changes in bone marker levels indicated a greater suppression of osteoblastic activity in the combination

Table 2
TEAEs in the phase 2a treatment period (any grade and grade 3 or 4): safety population.

TEAE	Any grade		Grade 3 or 4	
	Radium-223 + docetaxel $N = 33$	Docetaxel $N = 13$	Radium-223 + docetaxel $N = 33$	Docetaxel $N = 13$
Any	33 (100)	13 (100)	16 (48)	8 (62)
Haematological[a]				
Neutropenia	10 (30)	5 (38)	10 (30)	5 (38)
Anaemia	3 (9)	1 (8)	1 (3)	0
Leucopenia	2 (6)	2 (15)	2 (6)	2 (15)
Lymphopenia	1 (3)	0	1 (3)	0
Febrile neutropenia	0	2 (15)	0	2 (15)
Non-haematological[b]				
Fatigue	17 (52)	9 (69)	0	0
Nausea	16 (48)	8 (62)	0	0
Diarrhoea	15 (45)	5 (38)	1 (3)	0
Back pain	13 (39)	4 (31)	2 (6)	0
Alopecia	12 (36)	7 (54)	0	0
Peripheral oedema	12 (36)	5 (38)	0	1 (8)
Constipation	11 (33)	5 (38)	0	0
Decreased appetite	11 (33)	4 (31)	0	0
Peripheral neuropathy	10 (30)	4 (31)	0	0
Dysgeusia	7 (21)	8 (62)	0	0
Arthralgia	7 (21)	6 (46)	0	0
Dyspnoea	2 (6)	5 (38)	0	0
Gastrointestinal reflux disease	1 (3)	4 (31)	0	0

TEAEs, treatment-emergent adverse events.
Data are number of patients (%).
[a] Selected because of their relevance to radium-223 and chemotherapy.
[b] Any grade occurring in ≥25% of patients in either treatment group.

arm (Supplementary Fig. 3B, 3C, 4B, C, Supplementary Table 4). For both tALP and bALP, a longer median time to progression was observed for combination arm patients than docetaxel arm patients (9.0 vs 6.9 and 9.3 vs 7.4 months, respectively; Fig. 2B and C).

P1NP showed a decline pattern favouring the combination similar to that for bALP (Supplementary Fig. 3D, 4D). The weighted median area under the time–activity curve for P1NP was substantially smaller for the combination arm (25.0 *v* 46.2 μg*day/L), reflecting greater suppression of this marker (Supplementary Table 6).

Markers of osteoclastic activity, uCTX-1 and ICTP, showed similar patterns of decrease during treatment for combination arm and docetaxel arm patients (Supplementary Fig. 3E, 3F, Fig. 4E, F, Supplementary Table 6).

An antitumour treatment effect in both arms was suggested by the decrease in CTCs (Supplementary Table 7).

4. Discussion

To our knowledge, this trial is the first to explore the concept of dual targeting of osteoblastic bone and cancer cells using two concurrent agents, radium-223 and docetaxel, both of which prolong survival in patients with mCRPC. The concept of targeting bone and tumour is not novel. Prior studies have examined docetaxel in combination with bone-targeting agents that are not known to prolong survival, namely, strontium-89 and rhenium-188-hydroxyethylidine diphosphonate [14,15]. These studies only used one or two doses of the bone-seeking radiopharmaceutical, rather than as a repetitively dosed regimen integrated with chemotherapy. Neither of these studies yielded data sufficiently promising to warrant advancement to phase 3. This study, however, used only life-prolonging agents in a regimen in which patients were exposed to both agents throughout the treatment. Although the combination arm used the step-down dose of docetaxel commonly applied in clinical practice, the cumulative exposure to docetaxel in the two arms of the phase 2a cohort was similar, and the combination was associated with less neutropenia, fatigue, and certain gastrointestinal toxicities. Another factor that may have contributed to the safety profile of the combination is that we administered five doses of radium q6w, rather than six doses every four weeks. Combination therapy appeared to increase the proportion of patients with substantial

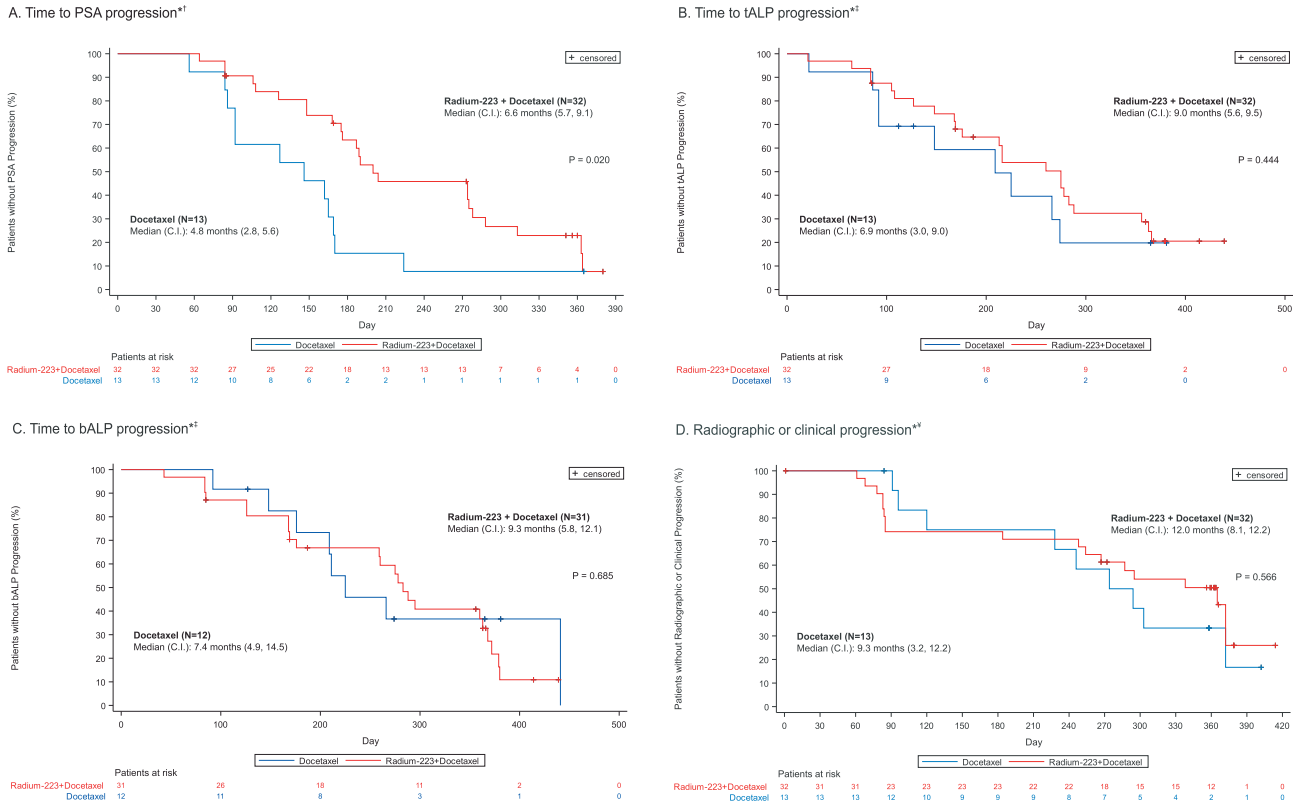


Fig. 2. Kaplan–Meier plots for (A) time to PSA progression; (B) time to tALP progression; (C) time to bALP progression and (D) radiographic or clinical progression-free survival. *Per protocol population; intent-to-treat patients who received ≥40% of specified number of radium-223 injections or docetaxel, per dose escalation study results, and have no major protocol violations. †As per Prostate Cancer Working Group 2 (PCWG2). PSA progression for patients with an initial PSA decline from baseline is defined as a PSA increase ≥25% and ≥2 ng/mL above nadir, confirmed ≥3 weeks later; for those with no PSA decline from baseline, progression is defined as a PSA increase ≥25% and ≥2 ng/mL above baseline after 12 weeks. ‡tALP/bALP progression for patients with an initial decline in tALP/bALP from baseline was defined as a tALP/bALP increase ≥25% above the nadir, confirmed ≥3 weeks later; for patients with no tALP/bALP decline from baseline, progression was defined as a tALP/bALP increase ≥25% above the baseline after 12 weeks. ¥Time to radiographic or clinical progression is a composite end-point encompassing time to first radiographic or clinical progression or death. bALP, bone alkaline phosphatase; CI, confidence interval; PSA, prostate-specific antigen; tALP, total alkaline phosphatase.

declines in levels of PSA and bone formation biomarkers relative to docetaxel alone and appeared to delay time to progression of these markers.

The safety of this combination is increasingly clinically relevant. Patients generally receive abiraterone or enzalutamide as first-line therapy for mCRPC, with chemotherapy reserved for second-line or beyond. After abiraterone or after enzalutamide therapy, patients frequently manifest both bony disease and soft tissue disease [16,17] and remain sensitive to chemotherapy despite the presence of molecular changes that may render tumours resistant to further androgen receptor (AR)–directed therapy [18]. We therefore have an increasing clinical need for a regimen that is non-AR directed and delivers potent therapy both systemically to the cancer cells and also to the osteoblasts surrounding metastatic bone lesions. Radium-223 and docetaxel appear to fulfil these criteria well. This trial suggests that such an approach is safe, with patients followed up for 1 year without the emergence of long-term safety concerns. It is unknown whether the combination prolongs overall survival compared with radium-223 or docetaxel alone, thus warranting further investigation.

5. Conclusions

This study showed that radium-223 (55 kBq/kg q6w) plus docetaxel (60 mg/m^2 q3w) was well tolerated and presented no greater safety concerns than docetaxel alone (75 mg/m^2 q3w). Exploratory efficacy data suggested enhanced antitumour activity in the combination arm. Based on these results, the radium-223/docetaxel combination will be further explored in a phase 3 trial in patients with bone metastatic CRPC (NCT03574571).

Role of the funding source

The study was designed by the funder in conjunction with the coordinating investigator (M.J.M.). The funder collected, analysed and interpreted the study data in collaboration with the authors and commissioned

medical writing support for the drafting of the report. M.J.M. had the final responsibility for the decision to submit for publication.

Conflict of interest statement

M.J.M. discloses consultancy/advisory roles with Astellas Pharma, Bayer, Endocyte and Advanced Accelerator Applications and has received travel/accommodation expenses from Bayer and Endocyte, and his institution has received research funding from Bayer, Endocyte, Progenics and Sanofi; Y.L. discloses consultancy/advisory roles with Astellas Pharma, AstraZeneca, Janssen, Merck Sharp & Dohme, Pfizer, Roche, Seattle Genetics and Sanofi, and his institution has received research funding from Sanofi; C.J.S. declares stock ownership in relation to Leuchemix, consultancy/advisory roles with Astellas Pharma, AstraZeneca, Bayer, Genentech/Roche, Janssen Biotech, Pfizer and Sanofi and intellectual property interests in relation to Leuchemix and Exelixis, and his institution has received research funding from Astellas Pharma, Bayer, Janssen Biotech, Sanofi and Sotio; K.F. has received honoraria from Bayer and Sanofi, discloses consultancy/advisory roles with Amgen, Astellas Pharma, Bayer, Janssen and Sanofi and has received travel/accommodation expenses from Amgen; C.J.R. has received honoraria from Astellas Pharma, Bayer and Janssen Oncology, discloses consultancy/advisory roles with Bayer, Ferring and Millennium and has received research funding from BIND Biosciences, Karyopharm Therapeutics and Novartis; D.H.S. declares participation in speakers' bureau for Bayer; E.S.A. has received honoraria from Astellas Pharma, AstraZeneca, Clovis Oncology, Dendreon, ESSA, Janssen Biotech, Medivation, Merck and Sanofi, discloses consultancy/advisory roles with Astellas Pharma, AstraZeneca, Clovis Oncology, Dendreon, ESSA, Janssen Biotech, Medivation, Merck and Sanofi, has an intellectual property interest in relation to Qiagen and has received travel/accommodation expenses from Dendreon, Medivation and Sanofi, and his institution has received research funding from Aragon Pharmaceuticals, Astellas Pharma, AstraZeneca, Clovis Oncology, Constellation Pharmaceuticals, Dendreon, Exelixis, Genentech, Janssen Biotech, Johnson & Johnson, Merck, Millennium, Novartis, Sanofi and Tokai Pharmaceuticals; N.P-.T. has nothing to disclose; D.D. has received travel/accommodation expenses from Bayer Healthcare and General Electric, and her institution has received research funding from Bayer Healthcare; H.A.J. has received honoraria from Astellas Pharma, Bayer Healthcare and Ipsen and has an intellectual property interest in relation to Cambridge University Press, and her institution has received research funding from GTx and Siemens Healthineers; H.V. discloses a consultancy role with MIM Software, outside the submitted work; O.P. is an employee of Bayer; C.L. is an employee of Bayer and owns company stock; J.A.C. discloses a consultancy/advisory role with Y-mAbs Therapeutics and Bayer and research support from Genentech, Regeneron, Gilead Pharmaceutical and Morphotek; C.S.H. has received honoraria from Genentech, discloses consultancy/advisory roles with Asana BioSciences, Astellas Pharma, Bayer, Blue Earth Diagnostics, Clovis Oncology, Dendreon, Endocyte, Ferring, Myriad Genetics, Orion Corporation and Tolmar Pharmaceuticals, has received travel/accommodation expenses from Asana Biosciences, Astellas Pharma, Bayer, Blue Earth Diagnostics, Clovis Oncology, Dendreon, Endocyte, Ferring, Genentech, Menarini, Orion Pharma GmbH, Myriad Genetics and Pfizer and has an immediate family member who is employed by, has a leadership role in and holds stock in CTI BioPharma, and her institution has received research funding from Aragon Pharmaceuticals, Astellas Pharma, AstraZeneca, Bayer, Dendreon, Emergent BioSolutions, Genentech, Medivation, Pfizer and Roche.

Data availability statement

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA 'Principles for responsible clinical trial data sharing'. This pertains to scope, time point and process of data access.

As such, on request from qualified scientific and medical researchers, Bayer commits to sharing patient-level clinical trial data, study-level clinical trial data and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014.

Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymised patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study sponsors section of the portal.

Data access will be granted to anonymised patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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Appendix A. Supplementary data

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Clinical Cancer Research

The Role of Lineage Plasticity in Prostate Cancer Therapy Resistance

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Abstract

Lineage plasticity has emerged as an important mechanism of treatment resistance in prostate cancer. Treatment-refractory prostate cancers are increasingly associated with loss of luminal prostate markers, and in many cases induction of developmental programs, stem cell–like phenotypes, and neuroendocrine/neuronal features. Clinically, lineage plasticity may manifest as low PSA progression, resistance to androgen receptor (AR) pathway inhibitors, and sometimes small cell/neuroendocrine pathologic features observed on metastatic biopsy. This mechanism is not restricted to prostate cancer as other malignancies also demonstrate lineage plasticity during resistance to targeted therapies. At present, there is no established therapeutic approach for patients with advanced prostate cancer developing lineage plasticity or small cell neuroendocrine prostate cancer (NEPC) due to knowledge gaps in the underlying biology. Few clinical trials address questions in this space, and the outlook for patients remains poor. To move forward, urgently needed are: (i) a fundamental understanding of how lineage plasticity occurs and how it can best be defined; (ii) the temporal contribution and cooperation of emerging drivers; (iii) preclinical models that recapitulate biology of the disease and the recognized phenotypes; (iv) identification of therapeutic targets; and (v) novel trial designs dedicated to the entity as it is defined. This Perspective represents a consensus arising from the NCI Workshop on Lineage Plasticity and Androgen Receptor-Independent Prostate Cancer. We focus on the critical questions underlying lineage plasticity and AR-independent prostate cancer, outline knowledge and resource gaps, and identify strategies to facilitate future collaborative clinical translational and basic studies in this space.

Introduction

Lineage plasticity is a biological process that occurs during normal development and later as a mechanism that promotes cell survival when adapting to their environment, evading stress, or repairing tissues. Plasticity may manifest as reversible or irreversible changes in cellular "identity," whereby cells take on an alternative morphologic, phenotypic, or epigenetic state (1). In cancer, lineage plasticity facilitates carcinogenesis, metastasis, and treatment resistance (2). During therapy-related lineage plasticity, differentiated tumor cells acquire new phenotypes, in some cases reverting back to a more "stem-like" state followed by redifferentiating toward an alternative "cell fate" in order to bypass therapeutic pressure. This versatility of cellular state is particularly prominent in cancer types with effective therapies that target major growth programs and lineage-directing factors (e.g., BRAF-mutant melanoma, EGFR-mutant lung cancer, AR-driven prostate cancer). In these cases, early "targetable" genomic alterations are often retained, but expression of the pressured target is suppressed. Despite preserving a molecular memory of their differentiated cancer cell precursor, alternative lineage programs facilitate subsequent tumor progression.

Prostate cancer is a malignancy driven by androgen receptor (AR) signaling, and AR-targeted therapies are commonly used to treat patients at all stages of the disease. Prostate tumors most frequently

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Lineage plasticity associated with loss of androgen receptor signaling dependence and the acquisition of alternative lineage programs occurs in up to 20% of advanced prostate cancer patients as a mechanism of treatment resistance, with important clinical and therapeutic implications. We discuss our current understanding of mechanisms underlying this process and outline a path toward the development of novel biomarkers and trials for this molecularly distinct subset of patients.

display an adenocarcinoma morphology reminiscent of normal luminal prostate architecture, with higher levels of disorganization associated with advanced tumor grade. Downstream markers of canonical AR activity, such as PSA, are used as clinical biomarkers to confirm a diagnosis of prostate cancer and for disease monitoring. Although several prostate cancer drugs are effective at lowering androgen levels and/or blocking the AR directly, metastatic prostate cancers universally develop treatment resistance (3). Acquired resistance is typically due to reactivation of AR signaling mediated, in part, by genomic mutation, amplification, or structural rearrangement of the *AR* gene itself. However, loss of AR expression and/or downstream signaling occurs in an estimated 15% to 20% of castration-resistant tumors (4–6). In extreme cases, tumors may reprogram toward alternative pathways adopting features of neuroendocrine, neuronal, or other lineages. Clinically, these cancers are notable for attenuated AR signaling and a range of histologies of which the most common exhibit small cell neuroendocrine carcinoma characteristics. At present, the definition and mechanistic underpinnings of this subset remain ill-defined, and there are no established therapeutic approaches for small cell/NEPC or other phenotypes. Few clinical trials address lineage plasticity, and the outlook for patients remains poor.

To address the challenges resulting from lineage plasticity, the NCI organized a Workshop focused on Lineage Plasticity and Androgen Receptor-Independent Prostate Cancer. Five working groups were assembled prior to the workshop to formulate questions underlying basic, translational, and clinical knowledge gaps and to develop approaches to address them (Supplementary Information). This Perspective generated as a result of the workshop summarizes concepts, data, deficiencies, and opportunities that drive critical questions underlying lineage plasticity and AR-independent prostate cancer.

Gap 1: A Fundamental Understanding of How Lineage Plasticity Occurs

Lineage plasticity is a term that implies that cells are capable of reprogramming their identity by acquiring an alternative lineage state and that this process is at some point plastic, or reversible. Whether AR-independent treatment resistance is mediated through an intermediate stem-like state, an "epithelial–mesenchymal transition" (EMT), or through direct transdifferentiation to acquire new characteristics and the extent of the reversibility of these processes are not well understood. Tumors with mixed or overlapping features expressing both AR and AR pathway genes as well as neuroendocrine markers ("hybrid" or "amphicrine" tumors), or those lacking both AR and neuroendocrine markers ("double negative" tumors) may further represent distinct disease states or a continuum (Fig. 1). Lineage programs such as gastrointestinal, squamous, and others have also been described (7). Identifying subsets within AR-independent disease provides expanding insights into the unique biology of AR-independent therapy resistance as well as potentially distinct therapeutics, such as the preferential activation of fibroblast growth factor signaling in "double negative" castration-resistant prostate cancer (CRPC; ref. 4).

The transition of prostate cancer away from a luminal epithelial phenotype is facilitated by genomic loss of the tumor suppressors *RB1* and *TP53*, leading to changes in stem cell, developmental, and EMT programs, mediated in part by the lineage pluripotency transcription factor SOX2 (8–10). Downregulation of REST (a transcription factor that normally silences the expression of neuron-specific genes in nonneuronal cells) through splicing

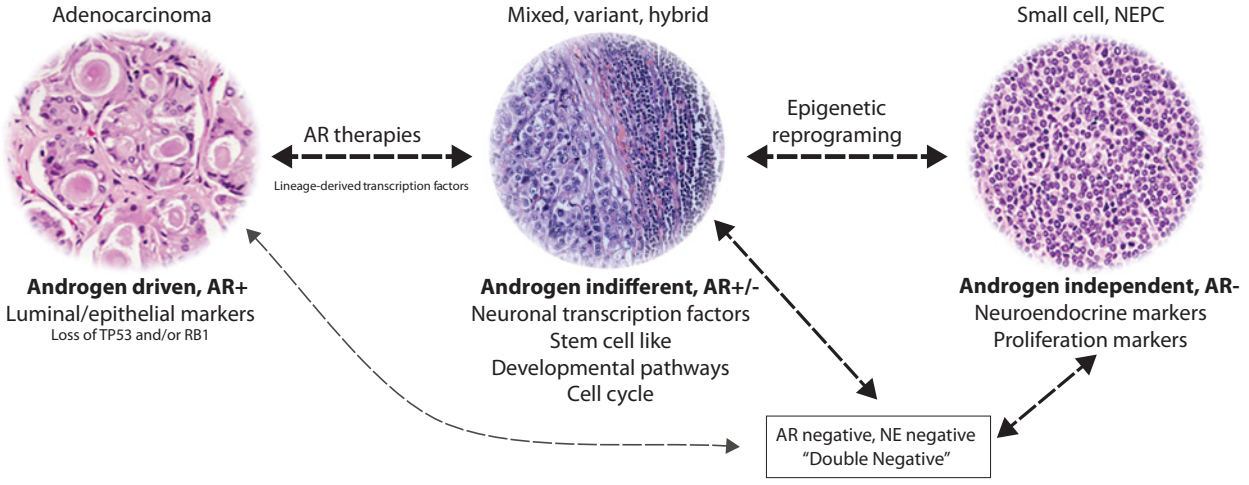


Figure 1.
Schematic of the proposed molecular events and transition states underlying lineage plasticity that occurs during CRPC progression from an AR-positive, AR-driven prostate adenocarcinoma (luminal phenotype) toward an AR-negative, AR-independent cellular state (e.g., small cell/neuroendocrine).

regulated by SRRM4 (11, 12), as well as activation of lineage-associated transcription factors such as N-myc (13, 14), Onecut2 (15, 16), and BRN2 (17), and derepression of developmental genes such as PEG10 (18) also occur. These changes in cellular programs associate with an increase in cellular proliferation and amplification or overexpression of cell-cycle regulators (e.g., aurora kinase, polo-like kinase; refs. 13, 19), leading to aggressive tumor growth and often visceral metastatic spread. Lineage tracing studies (20) have supported a luminal cell of origin of neuroendocrine prostate cancer cells that arise upon potent androgen blockade, supporting a "transdifferentiation" process. Important questions concerning the timing, cooperation, and feedback of the drivers of transdifferentiation processes and their relationships to oncogenic programs and AR silencing remain to be addressed. Further, identification of noncanonical AR programs associated with AR-positive, PSA low tumors as well as genes derepressed by AR inhibition could provide biological insights into other potential early mediators of lineage plasticity. Epigenetic modifications including changes in DNA methylation and upregulation of the polycomb complex gene enhancer of zeste 2 (EZH2) also play a role in silencing the luminal program and in reprogramming lineage (8, 10). Targeting epigenetic programs may result in some degree of reversibility or reversion back to a more luminal state. Metabolic shifts mediated in part by loss of PKCλ/ι (21), which support proliferation and epigenetic changes, as well as changes in tumor hypoxic state (15) are also observed during NEPC progression. A better understanding of the fundamental cellular and molecular interactions that drive lineage plasticity and the role of the tumor microenvironment, metabolic alterations, and changes in epigenetic state requires further focus and study. This will help to further refine the working definition of this cellular state in prostate cancer.

Working definition of lineage plasticity in prostate cancer

A progressive state of CRPC associated with the loss of AR-regulated lineage characteristics and in some situations the acquisition of new phenotypes (e.g., neuroendocrine features). Plasticity is driven by intrinsic and/or acquired alterations in the biological activities of tumor cells and the tumor microenvironment that involve metabolic, genetic, and epigenetic changes. The consequences of these changes comprise a gene expression profile/phenotype consistent with AR/androgen independence and sustained proliferation.

Open questions

- Is loss of canonical AR signaling equivalent to AR independence? For instance, could the presence of AR in cases with low AR signaling still drive a noncanonical program to sustain tumor growth?
- How many lineages are there and how do we best recognize and define them?
- What degree of reversibility underlies lineage plasticity? Could targeting epigenetic alterations completely revert back toward a luminal state, and/or do genetic factors "fix" tumors in an alternate state?
- What are the mechanisms and mediators of tumor microenvironment regulation that underlie lineage plasticity—aging, senescence, inflammation, metabolism, oncogenic, and nononcogenic biological processes; and the cellular dynamics of immune cells, fibroblasts, adipocytes, endothelial, and neuronal cells that effect this process?
- How do lineage determining transcription factors interact or cooperate during prostate cancer progression?
- What extent do factors related to the metastatic environment (e.g., liver, bone) and/or oncogene-associated or therapy-induced senescence contribute to lineage plasticity?

Gap 2: Determining the Temporal Contribution and Cooperation of Emerging Drivers

How AR-directed therapies affect clonal evolution, clonal selection, and the evolutionary bottlenecks that shape lineage plasticity is not well established. Mapping these processes have important clinical implications for biomarkers and therapeutics. For instance, hormone-naïve high-grade localized prostate cancers with low PSA levels may express neuroendocrine genes and harbor lower AR signaling (22), which may represent a high-risk patient population for developing lineage plasticity when later treated with AR pathway inhibitors. *RB1* loss, with or without *TP53* mutation or deletion, also occurs in a subset of prostate adenocarcinomas along the disease spectrum (23, 24), and may identify patients for aggressive surveillance and/or early intervention therapeutic strategies. The timing and cooperation of lineage-derived transcription factors further shape downstream programs as well as the epigenetic landscape. Whether intermittent AR inhibition, potentially alternating with therapies that target these alterations to induce differentiation, could delay the onset of lineage plasticity or prevent its emergence due to reconstitution of the tumor ecosystem with luminal lineage cells is intriguing and requires further study.

Understanding how mixed CRPC tumors that express both AR and neuroendocrine (or other) markers respond to AR therapies, and whether double-negative and small cell NEPC share treatment vulnerabilities such as sensitivity to platinum chemotherapy have important clinical implications for therapy selection. Assessment of the impact of emerging therapies (and combination approaches) on the prevention or reversal of phenotype or for their impact on tumor kill will help refine treatment goals; the readouts from targeting epigenetic alterations or alternative splicing, for instance, may differ from the goals of targeting proliferation or downstream effects of fixed genomic events. Serial metastatic biopsies or liquid biopsies will be useful for understanding the sequence of aberrations in patients and, when combined with clinical features such as PSA trends and sites of radiologic progression, have the potential to improve the diagnosis of patients progressing through the various biological disease states and to help refine clinical endpoints. One proposed translational research strategy for identifying the context and impact of RB1 alterations is highlighted in Box 1.

Open questions

- What are the relationships between lineage drivers and oncogenic programs?
- Does the presence of *RB1* and/or *TP53* aberrations in *prostate adenocarcinoma* predispose patients toward developing lineage plasticity and small cell/neuroendocrine features?
- Is there an intermediate clinical state where intervention may be effective in preventing or reversing lineage plasticity?
- Do PSA dynamics adequately reflect AR signaling in patients?

Box 1. One of the proposed translational research strategies developed at the workshop to address the role and cooperation of *RB1* and *TP53* in driving lineage plasticity in prostate cancer and other Rb1-deficient tumors (e.g., small cell lung cancer, SCLC) and an approach toward the development of novel biomarker-driven therapeutics.

What are the vulnerabilities in NEPC versus SCLC and other RB-deficient cancers?

Aim 1: Develop a series of collaborating institutions with large clinical volumes of CRPC patients and clinical databases to determine clinical parameters associated with RB loss ± TP53 loss and type of alteration (mutation; copy loss). Compare with other dual RB/p53 loss cancer types (SCLC).

Aim 2: Develop tissue and blood-based markers (IHC/ISH/transcriptional/proteomic/metabolic signatures) that detect/identify and associate with specific RB1 ± TP53 aberrations.

Aim 3: Develop isogenic models of RB ±TP53 deficiency in prostate cancer backgrounds [cell lines, patient-derived xenograft (PDX), organoids] to assess: (i) molecular consequence for E2F and TP53 signaling, (ii) biological impact, and (iii) relevance for reflecting clinical observations as per Aim 1.

Aim 4: Utilize models developed in Aim 3 to screen for vulnerabilities/synthetic lethality using high-throughput strategies (e.g., CRISPR screening, FDA-approved compound screening) with the goal of establishing the foundation for the next phase of clinical testing

Aim 5: Refine strategies for accurately assessing RB and TP53 status in liquid biopsy, and develop longitudinal studies to determine the impact on progression from prostate cancer to CRPC to NEPC.

- How and when is the AR lost in the context of disease progression and how do specific therapeutics influence resistance pathways?
- Are there strategies to maintain cell differentiation and AR dependency while still restraining tumor growth?
- Do increased DNA damage response gene activities, or other specific transcriptional signatures contribute to the lineage plasticity program, and can these activities be exploited therapeutically?
- Are there synthetic lethal therapeutic approaches that may be exploited to target lineage plasticity and AR-independent prostate cancer?
- What degree of intratumoral heterogeneity is seen within and across metastases in individual patients?

Gap 3: Preclinical Models That Recapitulate Biology of the Disease and the Recognized Phenotypes

Preclinical models that represent the prostate cancer disease spectrum are essential for understanding biology and for the

Box 2: Glossary

AR signaling (canonical): androgen receptor signaling that occurs through ligand (androgen)-mediated or ligand-independent means, resulting in activation of downstream programs critical for prostate growth, development, and function

AR signaling independent or AR indifferent: sustained growth of prostate tumor cells that is not driven by or reliant on downstream canonical AR signaling

Cellular identity or differentiation: a means of classifying cells based on their phenotype or physiologic function

Cellular determination: the process by which a cell becomes specialized to perform a specific function

Clonality: cells that share a common ancestry

Differentiation: the process by which a stem cell or progenitor cell matures into a cell with a specific identity. Dedifferentiation is when a differentiated cell loses its matured cellular identity to become less mature and more stem-like

Double-negative prostate cancer: a subset of castration-resistant prostate cancer that does not express the AR and also does not express neuroendocrine markers

Epigenome/epigenetics: changes in gene expression and cellular phenotype caused by mechanisms other than changes in DNA

Epithelial–Mesenchymal Transition: a process by which epithelial cells lose their cell–cell adhesion and gain migratory and invasive properties to become more like mesenchymal cells, which may facilitate cancer growth and metastatic spread

Embryonic stem cells: pluripotent stem cells that have the potential to differentiate into multiple cell types and are capable of self-renewal

Lineage determining transcription factors: proteins that bind to DNA, either alone or in cooperation with other partners, to control transcriptional output of a cell type to regulate its phenotype and functional characteristics

Lineage reprogramming: the conversion of a mature, terminally differentiated cell type into another mature cell type with or without undergoing dedifferentiation

Lineage tracing: A method that delineates all progeny produced by a single cell or a group of cells

Multipotent: Potential of a cell to form different lineages

Plasticity: Ability of a cell to convert from one cell type to another. This may refer to the potential of a differentiated cell to dedifferentiate and then redifferentiate into a new state

Progenitor: ancestor cell that gives rise to a specific type of differentiated cell

Neuroendocrine: cells that are neural and endocrine in structure or function. In the pathologic classification of neoplasms, this designation is typically based on tumor morphology rather than function. Well-differentiated neuroendocrine tumors (e.g., carcinoids) and poorly differentiated neoplasms (e.g., small cell carcinoma) have distinct biology and may arise in various anatomic sites

Pluripotent: A cell that is capable of developing into any cell type

Small cell carcinoma: morphologic definition based on pathologic review of tumor hematoxylin and eosin–stained slides demonstrating small blue cells, high-grade features, scant cytoplasm, and distinct nuclear features (i.e., fine chromatin,

lacking prominent nucleoli). Protein expression of classical neuroendocrine markers such as chromogranin or NSE may be present but is not required

Stem-like: cells that possess characteristics similar to normal stem cells, such as the ability to give rise to other cell types within a tumor

Transdifferentiation: reprogramming of a differentiated cell of one lineage into a differentiated cell of another lineage

development of novel therapeutics. Currently, the number and types of cell lines that recapitulate lineage plasticity are limited, though there are PDX and organoid models of AR-negative and neuroendocrine prostate cancer that have been described and characterized (refs. 25–29; Table 1). Dynamic *in vivo* models, such as a PDX model that changes phenotype from an AR-positive adenocarcinoma to an AR-negative NEPC (30), and xenografts that lose AR signaling dependence during enzalutamide resistance (17) have been used to capture the lineage plasticity process. Genetically engineered mouse models such as the TRAMP model and others designed to alter key molecular events, including loss

Table 1. Preclinical models

Model	Source	Pathologic and molecular features
NCI-H660 cell line	Lymph node metastasis	Small cell carcinoma; AR-negative; PSA-negative; TMPRSS2-ERG gene fusion-positive; synaptophysin, CD56, NSE-positive
LuCAP 49, 93, 145.1, 145.2 patient derived xenograft (PDX) and PDX–organoid models	Omental metastasis (LuCAP 49), TURP (LuCAP 93), liver (LuCAP 145.1), lymph node (LuCAP 145.2)	Neuroendocrine histology; AR-negative; synaptophysin-positive
MDA PCa 144-4, 144-13, 155-2, MDA PCa 177-0, MDA PCa 189-1 PDX models	Salvage pelvic exenteration (MDA 144, MDA 155-2), prostate (MDA 177, MDA 189-1)	Small cell and large cell carcinoma; Aggressive variant clinical features; TMPRSS2-ERG gene fusion positive (MDA 144)
LTL352 and LTL370 PDX models	Urethral (LTL352) and penile (LTL370) metastasis	Small cell carcinoma; AR-negative; PSA-negative; synaptophysin, NSE-positive
LTL331 transdifferentiation PDX model	Primary prostate cancer (LTL331) PDX model that develops castration-resistant NEPC *in vivo* (LTL331R)	Primary high-grade adenocarcinoma (LTR331) and neuroendocrine prostate cancer histology (LTL331R); TMPRSS2-ERG fusion-positive; LTR331: AR-positive; LTL331R: AR-negative, PSA-negative, Synaptophysin-positive, chromogranin-positive, CD56-positive
Enzalutamide-resistant LNCaP (42D, 42F)	Cell lines developed from enzalutamide-resistant LNCaP xenograft tumors	AR-positive; PSA low; chromogranin, synaptophysin-positive
MSK-PCA4 Patient-Derived Organoids	Pleural effusion	Neuroendocrine features; AR low; Synaptophysin-positive
WCM Patient-Derived Organoids	Metastatic lesions liver (155), bone (154), lymph node (1,078), soft tissue (1,262)	Small cell carcinoma; AR-negative; PSA-negative; synaptophysin, NSE, chromogranin-positive
TRAMP mouse	C57BL/6 mice expressing the rat probasin driving expression of SV40 large and small T antigens in prostatic epithelial cells	Adenocarcinoma to small cell carcinoma; Rb1 and Tp53 loss; Visceral metastases
$p53^{PE-/-}Rb^{PE-/-}$ mouse	Conditional knockout of p53 and Rb ($p53^{PE-/-}$; $Rb^{PE-/-}$) from the epithelium of all lobes of the mouse prostate	Small cell carcinoma; Rb1 and Tp53 loss
N-Myc-myrAKT1 mouse	Human prostate basal cells overexpressing NMYC and AKT1 implanted subcutaneously in NOD-SCID-IL2Rγnull (NSG) mice	Neuroendocrine features; AR low; chromogranin, synaptophysin-positive
$Pten^{f/f}$;LSL-$MYCN^{+/+}$ mouse	GEMM mice carrying *MYCN* gene integrated into the ROSA26 (*LSL-MYCN*) locus, a Tmprss2-driven tamoxifen-activated Cre recombinase and a *Pten* conditional knockout allele	Divergent differentiation Neuroendocrine features; AR low/AR-negative; chromogranin, synaptophysin-positive; visceral metastases with castration
PBCre4:*Pten*$^{f/f}$:*Rb1*$^{f/f}$ (DKO), PBCre4:Ptenf/f:Rb1f/f:Trp53f/f (TKO)	GEMM mice, PBCre4 transgene is used to delete floxed alleles specifically in prostate epithelium	Neuroendocrine features with metastases; AR-positive/AR low; Synaptophysin-positive
NPp53 mice	GEMM mice, inducible *Nkx3.1*^{CreERT2} driver to delete PTEN and TP53 genes in adult prostate epithelium	Abiraterone-resistant; neuroendocrine features- transdifferentiation (lineage tracing); AR low/AR-negative; Synaptophysin-positive
Ptenf/f-Prkcif/f-PbCre4+ mice (DKO)	GEMM mice, Ptenf/f-PbCre4+ mouse line (PTEN KO) with PTEN specifically deleted in the prostate epithelium, crossed with Prkcif/f mice	Neuroendocrine features; AR low/AR-negative; chromogranin, synaptophysin-positive

NOTE: Table of preclinical models that display lineage plasticity, small cell /NEPC histologic or molecular features, and/or AR-signaling indifference.

of *PTEN*, *TP53*, and *RB1*, and/or gain of *MYCN*, are also useful tools to study the cooperation and timing of emerging tumor suppressors and oncogenes (9, 10, 14, 20, 21, 31). Optimizing and sharing protocols for model development and optimization was discussed as an unmet need, especially as fresh tumor biopsies are more commonly performed clinically and may be used for patient-derived model generation.

Open questions

- What are the preclinical models that can be manipulated in such a way to reflect transition from androgen-dependent to -independent states and further transitions that encompass new differentiation programs such as neuroendocrine phenotypes?
- Are the genomics, transcriptomics, epigenetics, and metabolomics of these model systems representative of advanced human prostate cancer? Do they change over time or with conditions?
- Can we develop a series of paired PDX–organoids with morphologic and molecular information of organoids, PDXs, and human tumor of origin representing the complex molecular landscapes of prostate cancer?
- How do we use model systems to assess reversibility and thereby understand the degree of plasticity?
- What are "the human models" that can be utilized to compare and contrast with the animal models (e.g., rapid autopsies, CTCs, cfDNA, etc.)?

Gaps 4 and 5: Identification of Therapeutic Targets and Novel Trial Designs Dedicated to the Entity as It Is Defined

Given the relatively high reported frequency of small cell NEPC post AR-directed therapy, the National Comprehensive Cancer Network (NCCN) guidelines now recommend consideration of metastatic biopsy for any CRPC patient to look for small cell transformation. If found, patients could be considered for platinum-based chemotherapy based on extrapolation of clinical data for small cell lung cancer and supported by recent platinum-chemotherapy studies in aggressive variant prostate cancer (32). Although these practice guidelines have recently changed, the diagnosis of lineage plasticity remains a clinical challenge due to a lack of standardized or widely accepted clinical or pathologic criteria. Although pure small cell carcinoma defined by morphology is most often congruent between pathologists, those with mixed/hybrid or with varied degrees of neuroendocrine differentiation are often subject to interobserver variability (33).

The diagnosis of other phenotypes may require more detailed studies that involve IHC or other measures of gene expression. There are no standard criteria for when to perform ancillary studies such as IHC for classical neuroendocrine markers (e.g., chromogranin, synaptophysin), AR protein, PSA, or other markers (34, 35). There are also times when AR is expressed in NEPC, but the canonical AR transcriptome (including downstream targets like PSA) is low; identification of downstream genes that may be activated by AR in this setting would be informative and potentially help refine definitions. The incidence of AR-negative or AR-low CRPC without NEPC features or alternative lineage CRPC and the degree of heterogeneity within this spectrum are also not known. The workshop discussed a path toward the standardization of tumor morphology nomenclature and systematic prioritization of ancillary testing in metastatic CRPC (Table 2).

Table 2. Pathology morphology and available ancillary testing

Morphology
%tumor
%glandular
%small cell
Protein studies (**bold** indicates existing CLIA-validated biomarkers)
Molecular/Cell cycle
• **Rb** (Rb function: cyclin D1/p16)
• **P53** (p53 function: p21)
• **Ki-67** (discovery for threshold)
Lineage markers
• **Chg** (Canonical)
• **Syp** (Canonical)
• **CD56**
• **FOXA2**
• **INSM1**
• ASCL
• **Cytokeratin—Cam5.2**
• **Neurofilament**
Androgen signaling
• **AR** (canonical)
• AR-v7
• **PSA**

NOTE: Prioritization of pathology assessment when lineage plasticity is suspected. Tissue should be evaluated for morphologic characteristics that may support small cell carcinoma, neuroendocrine differentiation, or other histologies. Possible ancillary protein studies to consider performing by IHC are listed, with markers in **bold** indicating existing Clinical Laboratory Improvement Amendments (CLIA) grade tests.

Given the current challenges of performing tumor biopsies and the variability in morphologic features that occur after therapy, platinum-based chemotherapy trials have been conducted for patient with aggressive clinical features even in the absence of tumor biopsy (32). Notably, these patients defined by clinical features suggestive of AR independence often harbor combined somatic tumor alterations involving *PTEN*, *TP53*, and/or *RB1*, similar to what has been observed in small cell NEPC (29).

With a loss of AR expression, tumors may also lose other related proteins including prostate-specific membrane antigen (PSMA). This manifests clinically as PSMA-negative lesions on PSMA PET imaging. Low or heterogeneous PSMA PET-CT combined with FDG positivity identifies patients with poor prognosis (36), therefore representing a potential noninvasive means to identify AR-independent resistance. However, there are still many unknowns regarding PSMA regulation and PSMA imaging characteristics along prostate cancer progression and therapy resistance. Multi-institutional collaborative studies combining PSMA with FDG PET imaging, in combination with tumor biopsies of discordant lesions and liquid/tissue molecular assessment, were designed at the workshop.

There is no known effective next-line therapy for patients with small cell NEPC especially after platinum chemotherapy. Although second-line SCLC regimens may be considered, their data in prostate cancer are scarce. Notably, although loss of AR activity eliminates the AR pathway as a therapeutic target, the acquisition of new characteristics that associate with NEPC and other phenotypes exposes new targets and vulnerabilities. Available drugs targeting the AURKA/MYCN or AURK/RB1 axis, LSD1,

EZH2, DLL3, and approaches to target the immune landscape (e.g., vaccine, TGFβi, IL8i, and immune checkpoint inhibitors) are in development for NEPC, as well as drugs targeting FGF/MAPK for double-negative CRPC. The design of rational combination or cotargeting strategies, such as EZH2 inhibition in combination with AR pathway inhibitors or immunotherapy, may also have value. Ultimately, defining the appropriate inclusion criteria and endpoints for trials focused on lineage plasticity will be critical. Trials will require multicenter collaboration and molecularly based biomarker inclusion and careful patient selection. Incorporation of emerging molecular biomarkers in combination with clinical features may help distinguish subcategories of AR-independent CRPC and inform the development of liquid and imaging biomarker approaches for clinical trial design.

Open questions

- What are the clinical and pathologic differences between small cell carcinoma and CRPC with neuroendocrine differentiation? Are IHC markers required and do they capture AR activity?
- Is the increased detection of small cell/NEPC due to increased awareness or is this due to more potent AR-directed therapies? Will the incidence of NEPC increase with recent approvals of potent AR-targeted drugs earlier in the disease (i.e., metastatic castrate-sensitive prostate cancer and nonmetastatic castration-resistant prostate cancer)?
- How well does loss of PSMA or PSMA heterogeneity on imaging in combination with FDG PET-CT noninvasively identify patients developing lineage plasticity? What other radiologic or radiomic (i.e., subvisual tools) may be applied for the early detection of lineage plasticity?
- Platinum sensitivity is also mediated by germline or somatic alterations involving DNA repair genes, which occurs in approximately 20% of CRPC independent of histology. What is the degree of overlap between DNA repair deficiency and lineage plasticity?
- Is reversal of phenotype or tumor kill the primary goal of therapy? What clinical endpoints may be used to assess these outcomes?
- What would a multiarm clinical trial design look like for patients developing lineage plasticity and AR-independent prostate cancer? Which clinical or molecular features are ready to use as inclusion criteria?

Lessons from Other Cancer Types (the Scope of the Problem)

Similar to prostate cancer, malignancies arising from other anatomic sites, tissues, and cell types also develop lineage plasticity as a mechanism of therapy resistance. For instance, 5% to 15% of *EGFR*-mutant lung adenocarcinomas transform to SCLC histology during acquired resistance to EGFR-targeted therapies with retention of the original *EGFR* mutation (37). Cases of small cell transformation in lung cancer have also been reported after immunotherapy (38). *RB1* and *TP53* genomic alterations are universally present in both *de novo* and transformed SCLC and rarely present in unselected lung adenocarcinomas other than those that later develop histologic transdifferentiation (39–41). Whether preexisting *RB1* and *TP53* loss may be used as biomarkers to identify high-risk lung adenocarcinoma patients for alternative treatments is yet to be determined. Understanding whether this predisposition for lineage plasticity is also the case for the subset of castration-resistant prostate adenocarcinomas and localized prostate cancers that harbor *TP53*/*RB1* loss has important implications for the early detection and management. In melanoma, phenotypic switching with distinct cellular populations (e.g., invasive vs. proliferative) and developmental cell states (i.e., MITF low or high) frequently coexisting and dynamically regulated plays a central role in metastasis and therapy resistance (42–44). This switching is hypothesized to be largely regulated by epigenetic modifiers, hypoxia, and the tumor microenvironment, but specific factors remain to be fully elucidated. Similar to prostate cancer, much is still to be learned in melanoma plasticity regarding the number and types of phenotypic states that coexist and their interface with the genetics of the tumor (i.e., do some genomic lesions make the cells more or less responsive to plasticity signals?). In pancreatic ductal adenocarcinoma, lineage heterogeneity associates with poor outcomes; lineage tracing studies have pointed to an acinar cell of origin of neuroendocrine cells, and this is regulated by MYC and epigenomic changes in response to environmental signals (45). A subset of breast cancers also develop lineage plasticity, and in some cases, the luminal phenotype and/or estrogen receptor expression are lost with disease progression; this process may be mediated in part by subpopulations of cells with stem-like properties (46). Given these disease parallels, emerging mechanisms underlying plasticity, stemness, and cellular reprogramming during therapy resistance are pointing to shared mechanisms and potential targets across malignancies.

Summary

It is increasingly recognized that a subset of prostate cancers evades AR-targeted therapies through the development of lineage plasticity. This is associated with loss of AR or AR signaling, frequent *RB1*/*TP53* loss of function, and activation of alternative lineage programs including neuronal, neuroendocrine, stem-like, and developmental pathways. In some instances, lineage plasticity occurs directly through transdifferentiation processes, whereas in other situations, tumor cells dedifferentiate to a stem-like state followed by reprogramming to a new phenotype. Continued tumor evolution under treatment pressures may occur through clonal selection. Although there are many open questions, recent studies have identified newly relevant biological pathways and actionable targets. Addressing the outlined gaps in knowledge will ultimately accelerate the translation of new biologic discoveries into the clinic.

Disclosure of Potential Conflicts of Interest

H. Beltran is a consultant/advisory board member for Janssen, Sanofi Genzyme, and Astellas. H.I. Scher is a consultant/advisory board member for Amgen and Janssen. E.Y. Yu is a consultant/advisory board member for Amgen, Dendreon, Bayer, Merck, AstraZeneca, QED, Incyte, Tolmar, EMD Serono, Pharmacyclics, Seattle Genetics, and Janssen. A. Dicker holds ownership interest (including patents) in Oncohost, is a consultant/advisory board member for Roche, Oncohost, Google, Dreamit Ventures, EMD Serono, Janssen, Cybrexa, and Self Care Catalysts, and reports receiving other remuneration from Wilson Soncini. R. White is a consultant/advisory board member for N-of-One, Inc. E.J. Small holds ownership interest (including patents) in Fortis Therapeutics and Harpoon Therapeutics, and is a consultant/advisory board member for Janssen, Fortis Therapeutics, Tolero Pharmaceuticals, and Beigene Therapeutics. T. Lotan

reports receiving other commercial research support from GenomeDx and Roche, and is a consultant/advisory board member for Janssen. C.L. Sawyers holds ownership interest (including patents) in Novartis, Enzalutamide, and Apalutamide, and is a consultant/advisory board member for Novartis, Agios, Beigene, Blueprint, Column Group, Nextech, Housey Pharma, Foghorn, KSQ, PMV, ORIC, and Petra. C.M. Rudin reports receiving commercial research grants from Daiichi Sankyo, and is a consultant/advisory board member for AbbVie, Amgen, Ascentage, Astra Zeneca, Bristol-Myers Squibb, Celgene, Daiichi Sankyo, Genentech/Roche, Ipsen, Loxo, Pharmamar, Vavotek, Bridge Medicines, and Harpoon Therapeutics. M.A. Rubin reports receiving commercial research grants from Janssen and Eli Lilly, speakers bureau honoraria from Roche and Novartis, and holds ownership interest (including patents) in in the field of NEPC. P.S. Nelson is a consultant/advisory board member for Janssen, Astellas, and Roche. No potential conflicts of interest were disclosed by the other authors.

Supplementary Information

Pre-meeting document with Working Group summaries and questions

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Genomic Characterization of Prostatic Ductal Adenocarcinoma Identifies a High Prevalence of DNA Repair Gene Mutations

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Abstract

PURPOSE—Ductal prostate cancer (dPC) is a rare variant of prostatic adenocarcinoma associated with poor outcomes. Although its histopathologic features are well characterized, the underlying molecular hallmarks of this aggressive subtype are not well described. We sought to provide a comprehensive overview of the spectrum of mutations associated with dPC.

METHODS—Three case series across multiple institutions were assembled. All patients had a diagnosis of dPC, and histopathologic classification was confirmed by an expert genitourinary pathologist. Case series 1 included men who were prospectively enrolled in a tumor sequencing study at the University of Washington (n = 22). Case series 2 and 3 included archival samples from men treated at Johns Hopkins Hospital (n = 21) and University of Calgary (n = 8), respectively. Tumor tissue was sequenced on a targeted next-generation sequencing assay, UW-OncoPlex, according to previously published methods. The frequency of pathogenic/likely pathogenic mutations are reported.

RESULTS—Overall, 25 patients (49%) had at least one DNA damage repair gene alteration, including seven (14%) with a mismatch repair gene mutation and 16 (31%) with a homologous repair mutation. Germline autosomal dominant mutations were confirmed or suspected in 10

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patients (20%). Activating mutations in the PI3K pathway (n = 19; 37%), WNT pathway (n = 16; 31%), and MAPK pathway (n = 8; 16%) were common.

CONCLUSION—This study strongly suggests that dPCs are enriched for actionable mutations, with approximately 50% of patients demonstrating DNA damage repair pathway alteration(s). Patients with dPC should be offered next-generation sequencing to guide standard-of-care treatment (eg, immune checkpoint inhibitors) or triaged toward an appropriate clinical trial (eg, poly [ADP-ribose] polymerase inhibitors).

INTRODUCTION

Ductal prostate cancer (dPC) is a rare prostate cancer variant characterized by large glands lined by tall, pseudostratified, columnar, neoplastic epithelial cells, typically arranged over fibrovascular cores or cribriform glands and associated with an aggressive clinical course.[1–3] Outcomes for dPC generally mirror those of Gleason score 4 + 4 = 8 carcinomas, and tumors with at least 10% ductal morphology have been found to associate with a higher stage and suboptimal response to androgen deprivation.[2,3] Overall, approximately 3% of all prostate cancers have some component of ductal histology.[2,4]

Although the histologic features of dPC are well described, there is relatively little information regarding the underlying molecular alterations associated with this prostate cancer subtype. Fluorescence in situ hybridization studies have found that *TMPRSS2:ERG* fusions are present in 10% to 50% of patients with dPC, and ERG protein expression (consistent with *TMPRSS2:ERG* fusions) is also present in this range.[5–8] Limited gene expression profiling studies have found similarities between dPC and patients with acinar tumors, and there is molecular evidence that concurrent ductal and acinar tumors are clonally related.[4,9,10] More recent immunohistochemical profiling studies have demonstrated that positive phospho–mammalian target of rapamycin staining correlated with risk of biochemical recurrence in patients with ductal carcinoma.[11] In a separate study, it was found that loss of PTEN protein expression occurred more frequently in dPC compared with acinar adenocarcinoma, again, potentially implicating mammalian target of rapamycin signaling pathway in the pathobiology of dPC. However, these data remain controversial, because other studies have suggested a lower rate of PTEN protein loss in ductal carcinomas compared with Gleason score 8 acinar carcinomas.[6] More recently, a study evaluating genomic and transcriptomic differences between foci of ductal and acinar prostatic carcinoma from the same individual found enrichment for mutations in *CTNNB1* and *PTEN* within the ductal foci, with associated WNT- or PI3K- pathway activation.[9]

Given the rarity of dPC and the relative lack of information regarding the associated molecular features, we compiled a multi-institutional, international cohort of patients with dPC for targeted next-generation sequencing (NGS). We previously reported the NGS results from a small series characterizing patients with dPC at our institution (University of Washington [UW]).[12] In that preliminary study, we observed a high rate of DNA damage repair (DDR) mutations, including loss-of-function mutations in mismatch repair (MMR) genes. Building from our initial case series, we now report sequencing results from an expanded multiinstitutional collaborative cohort of 51 patients with dPC.

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METHODS

Study Populations

We assembled three case series comprising 51 patients with dPC from institutions in the United States and Canada (Data Supplement). Histopathologic classification of all tumors was confirmed by an expert genitourinary pathologist at each institution. All tumor tissue was sequenced on the targeted NGS assay UW-OncoPlex according to previously published methods.[12,13]

Case series 1 consisted of prostate cancer specimens (radical prostatectomies and needle biopsies of prostate and metastatic tumors) from 22 men actively receiving treatment at the University of Washington/Seattle Cancer Care Alliance who were prospectively identified as having a diagnosis of dPC. Tissue used for sequencing was acquired between January 2015 and March 2017. Preliminary sequencing results from this series have been previously published.[12] All men provided informed consent to have their tissue sequenced as part of this study.

Case series 2 included 21 radical prostatectomy samples. A subset was obtained from a tissue microarray composed of primary prostatectomy specimens from men with either dPC (n = 51) or Gleason pattern 4 acinar prostatic adenocarcinoma (n = 75) treated at Johns Hopkins Hospital (JHH) between 1984 and 2004. Details regarding this tissue microarray have been previously published.[14] Additional patients with a ductal carcinoma in the dominant nodule were procured from consecutive radical prostatectomies performed at JHH. Case series 3 included archival tissue from eight men treated by transurethral resection of the prostate at the University of Calgary.

Blinded Morphologic Evaluation

To reevaluate the morphologic classification of all patients in a blinded manner, an expert genitourinary pathologist (J.I.E.) examined scanned digital images of a representative slide from each patient corresponding to the formalin-fixed paraffin-embedded (FFPE) block that was macrodissected for sequencing. Each patient was scored for percentage of the tumor that had ductal morphology overall, as well as the percentage of several described morphologic subtypes of ductal carcinoma: cribriform, papillary, gland-like, prostatic intraepithelial neoplasia–like and solid.

Macrodissection of Tumor Tissue

All tissue was previously FFPE. Hematoxylin and eosin– stained sections served as templates for either macro-dissecting the dPC component from 10-micron sections or obtaining 5.0-×−0.6-mm punches from regions with the highest percentage of dPC.

Next-Generation Sequencing

For all patients, DNA was extracted from macrodissected FFPE samples and sequenced using the targeted NGS platform UW-OncoPlex, as that which interrogates approximately 1.8 Mb of DNA encompassing 262 genes. Briefly, genomic libraries were made from 500 ng of genomic DNA extracted from prostate tumor FFPE tissue and a custom Agilent (Santa

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Clara, CA) SureSelect XT capture set used for target enrichment and sequenced on an Illumina (San Diego, CA) NextSEquation 500 instrument with paired-end 101 bp reads. A custom bioinformatics pipeline detects single nucleotide variants, indels of all sizes, structural rearrangements, *PMS2* pseudogene disambiguation, and copy number changes. Sequencing interpretation was performed by an expert molecular pathologist (C.C.P.). Reported alterations were limited to those deemed pathogenic or likely pathogenic (eg, loss of function mutations in tumor suppressors, activating mutations in genes involved in oncogenic signaling pathways).

All 262 genes in UW-OncoPlex were thoroughly reviewed for potential pathogenic germline mutations by an expert in clinical germline cancer predisposition testing (C.C.P.). All reported confirmed or suspected germline variants were carefully vetted by a team expert in variant classification comprising at least three individuals, per the usual clinical process. Of 18 suspected pathogenic germline mutations, 13 were confirmed in nontumor tissue. Of the five suspected germline mutations that did not have matched nontumor DNA, one additional patient was felt to represent a germline mutation after expert molecular pathologist review through cross-referencing against the ClinVar database and by multivariable analysis of the variant allele fraction in the context of tumor content, ploidy, and loss of heterozygosity status.[15,16]

RESULTS

Patient Characteristics

Across the three cohorts (N_{total} = 51), the median age at the time of diagnosis/tissue acquisition was 67.5 years. The majority of patients with data on tumor stage (23 of 40; 57.5%) had T3 or higher disease. For patients with clinical follow-up (UW and University of Calgary, n = 28), seven (25%) were deceased, and 12 (43%) had developed metastatic disease during long-term follow-up. Additional demographics details are listed in Table 1.

dPC Genomics

Overall, our combined cohort of patients with dPC demonstrated a high number of recurrent genomic alterations (Fig 1; Data Supplement). These included alterations in genes involved in DDR repair (n = 24; 47%), PI3K pathway (n = 19; 37%), WNT-signaling pathway (n = 16; 31%), and MAPK signaling (n = 8; 16%). A large number of patients also had mutations in *FOXA1* (n = 17; 33%), *TP53* (n = 9; 18%), and *SPOP* (n = 6; 12%).

Recurrent DDR alterations.—Twenty-five (49%) of 51 patients had at least one alteration in a DDR pathway gene. Overall, seven of 51 patients (14%) had evidence of MMR alterations, six of whom had evidence of hypermutation (ie, ≥ 10 mutation per megabase), consistent with deficient MMR (one patient with monoallelic loss of *MSH2* was not hypermutated). Three patients with MMR alterations also had concurrent secondary mutations in homologous recombination (HR) pathway genes. Sixteen patients (31%) had an HR mutation in the absence of a concurrent MMR mutation. An additional patient with a hotspot *POLD1* mutation was ultramutated (ie, > 100 mutations per megabase).[17,18] There were 10 patients (20%) with evidence of a pathogenic autosomal dominant germline

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alteration in a DDR gene, which is significantly higher than reported by The Cancer Genome Atlas for patients with primary prostate cancer (20% *v* 5%; *P* <.001) and numerically higher than unselected patients with metastatic prostate cancer (20% *v* 12%; *P* = .105).[19,20] Of note, two individuals in our dPC cohort were carriers of recessive germline alterations in DDR pathway genes—one with an *ERCC2* alteration and the other with an *MUTYH* alteration. Neither had evidence that the second allele was affected in tumor tissue. Compared with published genomic data from men with localized and castration-resistant prostate cancer (CRPC), our combined cohort of men with dPC was significantly enriched for mutations in DDR genes (both MMR and HR genes), as well as other genes of interest (Table 2).[20,21]

Additional recurrent genomic alterations.—Similar to localized and metastatic CRPC, mutations in *FOXA1* were frequently observed (n = 17; 33%).[20,21] Interestingly, mutations in genes involved in WNT signaling were also frequent (n = 16; 31%). This includes activating/stabilizing mutations in *CTNNB1* (n = 4), as well as inactivating mutations in *APC* (n = 12), a negative regulator of WNT pathway activation. Similar to a prior report, we found that *PTEN* alterations were generally mutually exclusive of mutations in genes associated with WNT-signaling activation (eg, *APC* and *CTNNB1* mutations), although there was one patient with a pathogenic *MSH2* mutation that had secondary alterations in *APC*, *PTEN*, and *PIK3R1*.[9] There were three additional patients in whom WNT-pathway alterations co-occurred with PI3K-pathway alterations, including one patient with an *APC* and *PIK3CA* mutation, and two patients with *CTNNB1* and *PIK3CA* mutations. Compared with patients with CRPC, there were fewer *PTEN* alterations and more *PIK3CA* mutations in our dPC cohort, with an overall similar incidence of PI3K-pathway alterations (Table 2). Alterations in *AR* were infrequent (n = 4; 8%); however, the majority of tissue samples sequenced were primary prostate tissue that had not been exposed to hormonal therapies. *ETS* fusions were significantly less common in our dPC cohort compared with patients with both localized and CRPC (Table 2).

Pathology correlates.—We have previously reported discordance between expert genitourinary pathologists in diagnosing dPC.[24] As such, we performed a secondary pathologic review on available patients. Overall, 46 of the patients (94%) included in this analysis had slides available for central pathologic review (performed by J.I.E. at JHH). Of five ductal histologic subtypes (ie, cribriform, papillary, gland-like, prostatic intraepithelial neoplasia–like, and solid), cribriform (n = 22), and papillary (n = 23) were the most common, and 16 patients showed multiple histologic subtypes present. Although the quantity of dPC in each patient varied, there was no evidence that percentage of ductal involvement correlated with the underlying mutational profile, and a high frequency of DDR mutations was observed regardless of the overall quantity of dPC reported on secondary pathology review (Table 3).

DISCUSSION

To our knowledge, this is the largest cohort of dPC to be examined by NGS. We confirmed that dPCs are enriched for actionable mutations and, remarkably, found that almost half had at least one alteration in a DDR pathway gene. When compared with contemporary prostate

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cancer cohorts, we noted significant differences in the mutational profile of dPCs. For instance, in contrast to the Stand Up 2 Cancer–Prostate Cancer Foundation International Prostate Cancer Dream Team discovery set, which reported pathogenic DDR mutations in approximately 25% of unselected patients with metastatic CRPC, we found a significantly higher frequency of DDR alterations in dPCs, including loss-of-function mutations in MMR genes.[21] In addition, because the vast majority of patients included in this analysis had primary tissue sequenced (48 of 51 patients), it is likely that DDR alterations are early, truncal events, which can be easily identified by sequencing archival tissue, negating the need to obtain fresh metastatic tissue in men with more advanced disease. Although we did not intentionally sequence the acinar carcinoma component in patients with mixed ductal-acinar tumors, the fact that concurrent ductal and acinar carcinomas share common ERG rearrangements and other alterations suggests that the DDR alterations are likely shared between these components as well.[4,9] This study adds to the literature suggesting that aggressive histologic subtypes of localized prostate cancer (eg, primary Gleason pattern 5 acinar carcinomas, small cell carcinomas, and now dPCs) may be enriched for MMR defects.[25]

It is also notable that in addition to DDR alterations, there were a number of recurrently mutated genes, including those involved in WNT-and PI3K-signaling pathways. Interestingly, and consistent with prior work from our group, we found that PI3K-signaling alterations occurred more commonly in ductal carcinoma via *PIK3CA* mutations than by *PTEN* gene alterations, which is in contrast to unselected patients with metastatic CRPC.[6,21] These findings are also consistent with a recent report examining genomic and transcriptomic differences between dPC and acinar prostate cancer foci from the same individual.[9] However, in that report, it is worth noting that the authors did not observe enrichment for MMR alterations, and DDR alterations were relatively infrequent. Whether this is due to differences between the two series or the fact that their sample size was relatively small (10 patients) is not clear. We also confirmed that ETS gene rearrangements were significantly less common in patients with dPC compared with both primary (The Cancer Genome Atlas) and metastatic (Stand Up 2 Cancer–Prostate Cancer Foundation) patients with prostate cancer.[4] Importantly, because the NGS panel used in this study (UW-OncoPlex) provides intronic gene coverage for rearrangement hotspot areas in TMPRSS2 and other recurrently rearranged genes, it has a higher degree of sensitivity for detecting ETS fusions and other complex genomic rearrangements that could be missed by panels that only sequence exonic regions.[13,26] These findings indicate that alternative drivers may underlie dPC biology.

Another interesting observation was the apparent enrichment in patients with dPC for germline DDR gene alterations. A previous study had suggested that men with germline DDR mutations (particularly HR mutations) were more likely to harbor components of ductal or intraductal histology than those with pure acinar histology (48% *v* 12%; $P < .01$), although it is recognized that ductal and intraductal features are considered to be histologically distinct.[27] In the current analysis, the prevalence of pathogenic or likely pathogenic germline DDR lesions was 20% (10 of 51), significantly higher than that observed in primary prostate cancers (20% *v* 5%; $P < .001$) or even in unselected sporadic metastatic prostate cancers (20% *v* 12%; $P = .105$).[19,20] Taken together with the previous

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study, these findings suggest that patients with dPC should be preferentially offered germline genetic testing even in the absence of metastatic disease. Indeed, knowledge of germline status in the localized disease setting could afford opportunities for modifying management and improving outcomes before metastases develop.

There were important differences between the cohorts included in this analysis. The JHH and Calgary cohorts were assembled from archival tissue and were highly selected. In contrast, the UW cohort comprised prospectively identified men receiving care for prostate cancer in the clinic, and thus represented a real-world example of selecting patients for sequencing on the basis of histology. Another key difference is that the JHH cohort only included patients who underwent prostatectomy, and no long-term follow-up data were available. Given that all patients in the JHH cohort were considered to be prostatectomy candidates, this raises the possibility that these men had less aggressive disease, especially in light of the fact that 70% of men in the Calgary and UW cohorts either died or developed metastatic disease.

It is also notable that the UW cohort included a number of patients who were disputed in terms of whether dPC was present, and overall, 12 patients (26%) included in this series who underwent secondary pathology review were felt to not contain significant ductal features (n = 11 from UW and n = 1 from JHH). It is important to bear in mind,Ductal Prostate Cancer Genomics however, that all patients included in this analysis were believed to contain a component of ductal histology by at least one expert genitourinary pathologist. In addition, because slides from UW were not scanned before macrodissecting the ductal component, we cannot exclude the possibility that the slides sent for secondary review were not representative of the slides used for sequencing. In addition, the observed interpathologist variance is consistent with prior experience evaluating patients with dPC.[28] Importantly, there were no clear differences in mutational profiles for patients felt to not possess a clear ductal component on secondary pathology review or between patients with pure versus mixed ductal histology (Table 3). Larger studies aimed at evaluating differences between patients with pure and mixed dPC and studies evaluating differences between ductal and acinar foci from the same patient are warranted but are beyond the scope of this study.

In conclusion, despite the heterogeneity of our cohort, these results indicate that patients with any fraction of dPC should be offered NGS, given that the presence of dPC histology can serve as a rapid means to select patients enriched for actionable mutations, particularly in MMR and HR genes. On the basis of this analysis, nearly half would qualify for treatment with investigational poly (ADP-ribose) polymerase inhibitors, platinum-based chemotherapy, and/or an immune checkpoint inhibitor.[29–34]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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24. True L, Gulati R, Lange J, et al.: Histological patterns of ductal adenocarcinoma of prostate correlates with mutations in DNA repair genes and may aid in selecting the type of systemic therapy for castration-resistant prostate carcinoma. Presented at the USCAP Annual Meeting San Antonio, TX, March 4–10, 2017
25. Guedes LB, Antonarakis ES, Schweizer MT, et al.: MSH2 loss in primary prostate cancer. Clin Cancer Res 23:6863–6874, 2017 [PubMed: 28790115]
26. Pritchard CC, Morrissey C, Kumar A, et al.: Complex MSH2 and MSH6 mutations in hypermutated microsatellite unstable advanced prostate cancer. Nat Commun 5:4988, 2014 [PubMed: 25255306]
27. Isaacsson Velho P, Silberstein JL, Markowski MC, et al.: Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. Prostate 78:401–407, 2018 [PubMed: 29368341]
28. Seipel AH, Delahunt B, Samaratunga H, et al.: Diagnostic criteria for ductal adenocarcinoma of the prostate: Interobserver variability among 20 expert uropathologists. Histopathology 65:216–227, 2014 [PubMed: 24467262]
29. Cheng HH, Pritchard CC, Boyd T, et al.: Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. Eur Urol 69:992–995, 2016 [PubMed: 26724258]
30. Mateo J, Carreira S, Sandhu S, et al.: DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 373:1697–1708, 2015 [PubMed: 26510020]
31. Pennington KP, Walsh T, Harrell MI, et al.: Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res 20:764–775, 2014 [PubMed: 24240112]
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CONTEXT

Key Objective

The key objective was to provide an overview of the genomic alterations associated with ductal prostate cancers.

Knowledge Generated

Ductal prostate cancers are associated with a high incidence of mutations in DNA repair genes. Affected genes include those mediating homologous recombination and mismatch repair pathways.

Relevance

Because mutations in genes involved in DNA repair are highly actionable, sequencing all patients with ductal prostate cancer should be considered.

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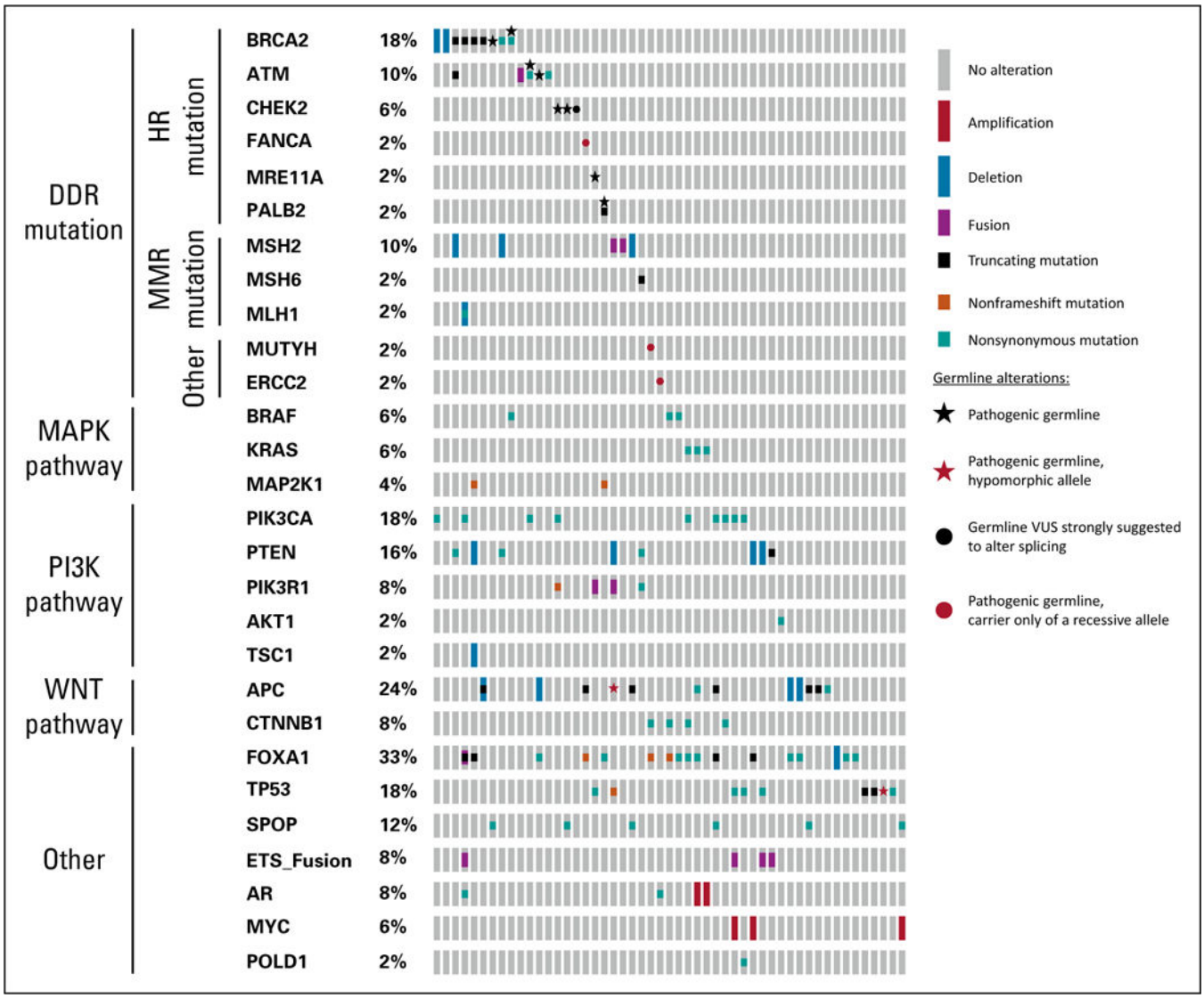


FIG 1.

Landscape of genomic alterations across 51 patients with ductal prostate cancer. Each column represents one patient. Pathogenic mutations were those predicted to either activate oncogenic signaling pathways (eg, WNT-or PI3K-signaling) or inactivate tumor suppressors (eg, DNA damage repair [DDR] genes, *TP53*). HR, homologous recombination; MMR, mismatch repair; VUS, variant of uncertain significance.

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TABLE 1.

Demographics and Characteristics

Characteristic	Value
Median age (range), years	67.5 (47–94)
Gleason *	
7	4 (13)
8	7 (23)
9	18 (60)
10	1 (3)
Metastatic disease at presentation †	11 (26)
Source of tissue for sequencing	
TURP	8 (15)
Prostatectomy	29 (56)
Prostate needle biopsy	11 (21)
Metastatic biopsy	3 (6)

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviation: TURP, transurethral resection of the prostate.

* Gleason score was only provided for patients with mixed ductalacinar histology (n = 30).

† Disease state at time of initial presentation was only available for Johns Hopkins Hospital and University of Washington (n = 43).

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TABLE 2.

Recurrent Genomic Alterations in Patients With Ductal Prostate Cancer Compared With Men With Sporadic Localized and Castration-Resistant Prostate Cancer [22,23]

	No. of Mutations (% of men)			Ductal Cohort Versus TCGA		Ductal Cohort Versus SU2C	
Gene/Pathway	**Ductal Cohort (n = 51)**	**TCGA (n = 333)***	**SU2C (n = 150)†**	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***
Any DDR	25 (49)	62 (19)	34 (23)	2.63 (1.84 to 3.77)	< .001	2.16 (1.44 to 3.25)	< .001
MMR alteration	7 (14)	11 (3)	3 (2)	4.16 (1.69 to 10.23)	.002	6.86 (1.84 to 25.55)	.004
MSH2	5 (10)	5 (2)	3 (2)	6.53 (1.96 to 21.77)	.002	4.90 (1.21 to 19.79)	.026
MLH1	1 (2)	1 (0.3)	1 (0.7)	6.53 (0.41 to 102.76)	.182	2.94 (0.18 to 46.17)	.443
MSH6	1 (2)	6 (2)	0	1.09 (0.13 to 8.85)	.937	—	.254
PMS2	0	4 (1)	0	—	1.00	—	—
High penetrance HR alterations	15 (29)	44 (13)	29 (19)	2.23 (1.34 to 3.69)	.002	1.52 (0.89 to 2.60)	.125
BRCA1	0	4 (1)	1 (0.7)	—	1.00	—	1.00
BRCA2	9 (18)	11 (3)	19 (13)	5.34 (2.33 to 12.25)	< .001	1.39 (0.67 to 2.88)	.371
ATM	5 (10)	24 (7)	7 (7.3)	1.36 (0.54 to 3.40)	.511	1.34 (0.49 to 3.66)	.572
PALB2	1 (2)	5 (2)	0	1.31 (0.16 to 10.95)	.806	—	.254
WNT pathway	16 (31)	27 (8)	19 (13)	3.87 (2.25 to 6.66)	< .001	2.48 (1.38 to 4.44)	.002
CTNNB1	4 (8)	9 (3)	6 (4)	2.90 (0.93 to 9.08)	.067	1.96 (0.58 to 6.67)	.281
APC	12 (24)	18 (5)	13 (9)	4.35 (2.23 to 8.49)	< .001	2.71 (1.32 to 5.56)	.006
PI3K pathway	19 (38)	103 (31)	73 (49)	1.20 (0.81 to 1.78)	.351	0.77 (0.52 to 1.13)	.182
PTEN	8 (16)	58 (17)	61 (41)	0.90 (0.46 to 1.77)	.762	0.39 (0.20 to 0.75)	.005
PIK3CA	9 (18)	16 (5)	8 (5)	3.67 (1.71 to 7.87)	.001	3.31 (1.35 to 8.12)	.009
PIK3R1	4 (8)	22 (7)	8 (5)	1.19 (0.43 to 3.30)	.743	1.47 (0.46 to 4.68)	.514
AKT1	1 (2)	7 (2)	2 (1)	0.93 (0.12 to 7.43)	.948	1.47 (0.14 to 15.88)	.751
TSC1	1 (2)	5 (2)	2 (1)	1.31 (0.16 to 10.95)	.806	1.47 (0.14 to 15.88)	.751
MAPK pathway	8 (16)	13 (4)	11 (7)	4.02 (1.75 to 9.21)	.001	2.14 (0.91 to 5.02)	.081
BRAF	3 (6)	12 (4)	7 (5)	1.63 (0.48 to 5.59)	.435	1.26 (0.34 to 4.69)	.73
KRAS	3 (6)	1 (0.3)	4 (3)	19.59 (2.08 to 184.72)	.009	2.21 (0.51 to 9.53)	.289
MAP2K1	2 (4)	1 (0.3)	1 (0.7)	13.06 (1.21 to 141.42)	.035	5.88 (0.54 to 63.52)	.144

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	No. of Mutations (% of men)			Ductal Cohort Versus TCGA		Ductal Cohort Versus SU2C	
Gene/Pathway	**Ductal Cohort (n = 51)**	**TCGA (n = 333)***	**SU2C (n = 150)†**	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***
Other							
ETS fusions	4 (8)	199 (60)	84 (56)	0.13 (0.05 to 0.34)	< .001	0.14 (0.05 to 0.36)	< .001
POLD1	1 (2)	2 (1)	0	3.26 (0.30 to 35.36)	.330	—	.254
CHEK2	3 (6)	10 (3)	3(2)	1.96 (0.56 to 6.88)	.294	2.94 (0.61 to 14.12)	.178

NOTE. *P* values and RRs are in comparison with the ductal cohort. Mutational frequencies for comparator data sets were derived from either the primary publications or extracted from cBioPortal.[20–23]

Abbreviations: DDR, DNA damage repair; HR, homologous recombination; MMR, mismatch repair; RR, relative risk; SU2C, Stand Up 2 Cancer; TCGA, The Cancer Genome Atlas.

*The TCGA data set comprises 333 men with localized prostate cancer.[20]

†SU2C-PCF International Prostate Cancer Dream Team discovery set comprises 150 men with metastatic castration-resistant prostate cancer. The genomic landscape of this population has been previously published.[21]

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TABLE 3.

Key Genomic Features Stratified by Ductal Involvement

Ductal Involvement	No.	Any DDR, No. (%)	*P*	MMR, No. (%)	*P*	HRD, No. (%)	*P*	Germline DDR, No. (%)*	*P*
Ductal features present	12	8 (67)	.314	3 (25)	.173	6 (50)	.37	5 (42)	.265
Ductal features absent	34	15 (44)		3 (9)		12 (35)		7 (23)	
Pure ductal	10	5 (50)	1	1 (10)	1	5 (50)	.489	1 (13)	.402
Not pure ductal	35	18 (51)		5 (14)		13 (37)		11 (32)	

NOTE. Secondary pathology review evaluated for the extent of ductal involvement, and comparative analyses assessing for correlation between key genomic features and extent of ductal histology were performed. One patient classified as positive for ductal involvement did not provide an estimate on percent involvement.

Abbreviations: DDR, DNA damage repair; HRD, homologous recombination deficiency; MMR, mismatch repair.

*Three patients were indeterminate regarding whether the DDR alteration was germline versus somatic and were therefore excluded from this analysis.

Appendix 3

Curricula vitae:

Celestia S. Higano – PI

Evan Y. Yu - co-investigator

Heather H. Cheng - sub-investigator

Michael T. Schweizer - sub-investigator

CURRICULUM VITAE

Celestia S. Higano, MD, FACP
Professor of Medicine and Urology, University of Washington School of Medicine
Member, Fred Hutchinson Cancer Research Center
Seattle Cancer Care Alliance
825 Eastlake Avenue East, G4-830
Seattle, WA 98109
Phone: (206) 606-1152
Email: thigano@u.washington.edu

EDUCATION

Undergraduate

Bryn Mawr College — 1970-1971
Bryn Mawr, Pennsylvania

Clark University — 1972-1975
Worcester, Massachusetts

Medical

University of Massachusetts — 1975-1979
Worcester, Massachusetts

Post Graduate

Internal Medicine Residency — 1979-1982
Mayo Graduate School of Medicine
Rochester, Minnesota

Hematology/Oncology Fellowship — 1982-1984
University of Washington
Seattle, Washington

AACR/ASCO Clinical Trials Graduate Workshop — 1998
Vail, Colorado

ASCO Leadership Seminar — 2011
Alexandria, Virginia

FACULTY APPOINTMENTS

Acting Instructor, Department of Medicine — 1984-1988
School of Medicine, University of Washington

Acting Assistant Professor, Department of Medicine — 1988-1989
School of Medicine, University of Washington

Associate in Clinical Research — 1988-2008
Fred Hutchinson Cancer Research Center

Assistant Professor, Department of Medicine — 1989-1997
School of Medicine, University of Washington

Associate Professor, Department of Medicine — 1997-2008
School of Medicine, University of Washington

Adjunct Associate Professor, Department of Urology — 1997-1999
School of Medicine, University of Washington

Associate Professor, Department of Urology — 1999-2008
School of Medicine, University of Washington

Professor, Department of Medicine — 2008-present
School of Medicine, University of Washington

Professor, Department of Urology School of Medicine, University of Washington	2008-present
Member, Clinical Research Division Fred Hutchinson Cancer Research Center	2008-present
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 Candidate	2017-present

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-present
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 Ccommittee	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

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
Pfizer Talazoparib Steering Committee	2017-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
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

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 Adrogen 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.

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 androgram 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) $\geq$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 PROEED Registray 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 Survivorsip 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. "Updagte 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 ofmetastatic 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 (APPCC). 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 (APPCC). Brisbane, Australia. August 2018.

79. "Hormone Sensitive Metastatic Disease: Treatment Options." Asia-Pacific Prostate Cancer Conference (APPCC). Brisbane, Australia. August 2018.

80. "New Options in MO CRPC – Who (if anybody) needs treatment." Asia-Pacific Prostate Cancer Conference (APPCC). 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.

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 infustion 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.

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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.

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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.

35. Higano CS, Chielens D, Raskind W, Bryant E, Flowers ME, Radich J, Clift R, Appelbaum FR. Use of alfa-2a-interferon to treat cytogenetic relapse of chronic myeloid leukemia after marrow transplantation. *Blood.* 1997 90(7):2549-2554.

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43. Higano CS. Side effects of androgen deprivation therapy: monitoring and minimizing toxicity. *Urology* 2003 Feb;61(2 Suppl 1):32-38 Review.

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analysis of the PROCEED registry. *J Clin Oncol* 35, 2017 (suppl 6S; abstract 216). Poster presentation, ASCO Genitourinary Cancers Symposium, Orlando, FL, February 2017.

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Eisenbergher MA, Logothetis C, Quinn DO, Fizazi K, Higano CS, George DJ, Morris MJ, Small EJ, Tannock I, Kelly WK. Overall survival between African-American (AA) and Caucasion © men with metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 36, 2018 (suppl; abstr LBA5005). Oral presentation, ASCO 2018 Annual Meeting, Chicago, IL. June 2018.

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318. Sternberg CN, Tombal B, Miller K, Saad F, Sartor O, Sade JP, Logothetis C, Bellmunt J, Dizdarevic S, Harshman LC, Logue J, Baldari S, Richardson T, Bottomley D, Schostak M, Bayh I, Kalinovsky J, Higano C. Use of bone health agents (BHAs) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with radium-223 (Ra-223) after abiraterone (Abi): An interim review of REASSURE. *Ann of Oncol* (2018) 29 (suppl 8). Poster presentation. ESMO Congress 2018, Munich Germany. October 2018.

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HIGANO SUPPORT

GRANTS - *Current*

W81XH-16-PCRP-CCRSA (Higano) 09/30/2017 – 09/29/2021
DOD Prostate Cancer Research Program $1,000,000
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

Early Phase Clinical Research Support (Higano) 01/01/2019-12/31/2019
Seattle Translational Tumor Research (NCI P30 CA015704-41) $ 44,100
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

GRANTS - *Pending*

STTR Translational Research (Liu/Higano)
Seattle Translational Tumor Research
Rachel Galbraith | 1100 Fairview Ave N | Seattle, WA 98109
Induction of prostate cancer cell differentiation by stromal factor PENK
The primary goal is to determine whether prostate cancer cells become de-differentiated to stem-like over time due to continuous absence of stromal cell inductive signaling.
Role: Co-PI

CLINICAL TRIAL CONTRACTS - *Current*

Protocol # ARN-509-002 (Higano) 02/15/2013 - 12/31/2019
Aragon Pharmaceuticals, Inc $ 209,448
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 $ 83,104
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 # D4620C00001 (Higano) 10/01/2013 - 04/30/2020
AstraZeneca AB $ 873,248

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 - 09/16/2019

Bayer Health Care $ 535,190

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 # 401 (Higano) 12/18/2014 - 12/31/2019

Emergent BioSolutions $ 353,949

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 # 16913 (Higano) 03/16/2016 - 02/29/2024

Bayer Health Care $ 24,480

Kelly Peters I Katnar Health, LLC I 11960 Westline Industrial Dr, Ste 180 I 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 - 04/30/2020

Pfizer $ 448,030

Megan Shannon I 235 East 42nd Street I 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 $207,711

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

A Phase IB, Open-Label Study of the Safety and Tolerability of Atezolizumab in Comination 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 $ 37,207
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 $ 11,670
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 $ 8,509
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 $ 26,515
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 $ 17,725
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 # MDV3800-06 (Higano)
Medivation, Inc
Rena Ullum (Quintiles) | 4820 Emperor Blvd, Q Plaza Room 895E | Durham, NC 27703
A Phase 2, Open-Label, 2-Arm, Response Rate Study of Talazoparib in Men With DNA Repair Defects and Metastatic Castration-Resistant Prostate Cancer Who Previously Received Taxane-Based Chemotherapy and Progressed on at Least 1 Novel Hormonal Agent (Enzalutamide and/or Abiraterone Acetate/Prednisone)
The primary goal of the study is to evaluate efficacy, as measured by best objective response rate (ORR).

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.

GRANTS - *Prior*

PCF Challenge Award (Febbo/Higano) 09/01/2011 – 07/31/2019
Prostate Cancer Foundation $ 450,000
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 $187,256
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 $ 755,993
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

W81XWH-BAA-11-1 (Basch) 11/06/2013 - 2/28/2017
UNC-Chapel Hill (DoD flow through) $ 118,541
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 $ 1,257,277
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 $ 90,054
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 $ 1,212,833
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) $ 491,122
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 $ 305,409
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 # 16544 (Higano) 12/03/2014 - 03/01/2019
Bayer Health Care $ 91,686
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 $ 322,640
Lynn Bui, MD | 525 Market St, 36th fl | San Francisco, CA 94105
STRIVE: A Mulitcenter 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. $ 313,075
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. $ 840,401
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 $ 98,660
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 $ 223,082
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 $ 293,715
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 $ 176,891
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 $ 157,423
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 $ 37,740
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 _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 $ 12,552
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. $ 255,068
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 $ 310,778
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 $ 75,401
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 CTC5 at baseline and cycle 2 and 4 in CRPC patients enrolled to Study Protocol OGX-O11-11, and; to demonstrate that the addition of OGX-O1 1 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. $ 238,688
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 $ 1,905
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
OncoGenex Technologies $ 30,500
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 $ 53,335
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 $ 48,497
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 Ccomparing 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. $ 81,129
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. $ 338,356
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-naive 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-naive patients with asymptomatic, metastatic AIPC.
Role: Site PI

Protocol #IMCL CP18-0601A (Higano) 12/04/2008 - 06/17/2012
ImClone Systems, Inc. $ 215,217
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 $ 127,135
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 $ 417,394
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 $ 16,125

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 $ 70,946

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 $ 440,945

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 $ 517,612

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 $ 119,297

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 $ 88,015

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

CURRICULUM VITAE

EVAN YA-WEN YU, MD
825 Eastlake Ave E, G4-830
Seattle, WA 98109
Phone: 206-606-7595
Fax: 206-606-2042
Email: evanyu@uw.edu

PERSONAL DATA

Place of birth:	Bellevue, Washington
Citizenship:	U.S.A.
Date of Birth:	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
William J. Bremner Endowed Department of Medicine Mentorship Award Nominee	2018

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 resident at Case Western Reserve	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 Medical Director at Amgen	2012
Heather H. Cheng – Now Associate Professor at University of Washington	2012-present
Jorge D. Ramos –Assistant Professor at University of Washington, now Associate 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 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 Prostate Cancer Translational Grant Study Section	2005
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
GU 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 Genitourinary Cancers Steering Committee	**2012-2014**
Steering Committee Member, PREDICT Biomarker Committee	2013-2016
Special Clinical Expert, National Cancer Institute (Served 1 year of 2nd 3-year term) Genitourinary Cancers Steering Committee	**2014-2018**
Advisory Member, Society of Urology Oncology (Clinical Trials Consortium, Inc.) Board of Directors and the Prostate Organ Site Committee	**2015-present**
Test Question Writer, American Society of Oncology and National Board of Medical Examiners ASCO University Courses, ASCO-SEP Mock Exam, In-Training Exam	**2017-2019**
Member, American Society of Oncology Annual Meeting Education Committee Genitourinary (Nonprostate) Cancer	**2017-2020**
Member, Bone Metastasis Expert Panel American Radium Society	2017-2019

GU Prostate Cancer Committee Member, SWOG 2017-present

Co-Chair (Medical Oncology), National Cancer Institute 2018-present
Prostate Cancer Task Force

Member, Education Committee 2019-present
Association of American Cancer Institutes

LOCAL RESPONSIBILITIES

4th Floor Solutions Committee, 2004–2006
Seattle Cancer Care Alliance

Genitourinary Practice Committee 2004–2005
University of Washington Department of Medicine

Recruitment and Community Outreach Core 2004–2005
University of Washington Translational Grant Committee

Multicultural Affairs Advisory Board 2006–2007
University of Washington Department of Medicine

Translational Research Task Force 2006–2008
University of Washington Translational Grant Committee

Accreditation Council for Graduate Medical Education 2006–2017
University of Washington Medicine Residency Program

Oncology and Hematology Fellowship Program Admissions Committee 2006–present
University of Washington / Fred Hutchinson Cancer Research Center

Prostate Cancer Task Force 2007–2008
Washington Comprehensive Cancer Control Partnership

Imaging Working Group 2007–2008
Prostate Specialized Programs of Research Excellence (SPORE)

Quality Improvement/Safety Steering Committee 2007–2010
Seattle Cancer Care Alliance

Medical Student Research Training Program Committee 2008-2016
University of Washington School of Medicine

Medical Student Admissions Committee 1995-1998
University of Washington School of Medicine 2009-2016

Institute for Prostate Cancer Research Committee 2009-present
University of Washington

Grant Reviewer 2010
INBRE-WSU Spokane Institute for Translational Health Sciences

Internal Medicine Residency Education Coordinator (Oncology) 2010-2017
University of Washington

Core Faculty Designation, Internal Medicine Residency 2010-present
University of Washington

Clinical Core Director 2012-present
Pacific Northwest Prostate Cancer SPORE

Reviewer for the University of Washington 2013
American Cancer Society Summer Fellowship in Clinical Cancer Research

New Faculty Search Committee Member 2013-2015
University of Washington Pediatric Oncology and Seattle Children's Hospital

Prostate Cancer Clinical Pathways 2013-2017
Seattle Cancer Care Alliance

Scientific Review Committee, Sub-Committee B Member 2014
University of Washington / Fred Hutchinson Cancer Research Center Consortium

Scientific Review Committee, Sub-Committee B Co-Chair 2015-2017

University of Washington / Fred Hutchinson Cancer Research Center Consortium

New Radiochemistry Faculty Search Committee Member 2015-2018
University of Washington Department of Radiology

New Faculty Search Committee Member 2016-2017
University of Washington Genitourinary Oncology

Genitourinary Oncology Leadership Committee 2017-present
University of Washington / Fred Hutchinson Cancer Research Center Consortium

Clinical Trials Process Improvement Oversight Committee 2017-present
Seattle Cancer Care Alliance

External Performance Site Assessment Committee 2018
Fred Hutchinson Cancer Consortium

Site Initiation Visit Escalation Policy Committee 2017-2018
Seattle Cancer Care Alliance

New Faculty Search Committee, Director of Nuclear Medicine 2018-2019
Seattle Cancer Care Alliance

Research Ethics Committee 2018-present
Fred Hutchinson Board of Trustees

Institutional Review Board Chair Liason Committee 2018-present
Fred Hutchinson Cancer Research Consortium

Compliance Sub-Committee, Clinical Research Services 2018-present
Fred Hutchinson Cancer Research Consortium

Clinical Trial Oversight Committee, Clinical Research Services 2018-present
Fred Hutchinson Cancer Research Consortium

Institutional Sponsored IND Oversight Committee, Clinical Research Services 2018-present
Fred Hutchinson Cancer Research Consortium

PEER REVIEW FUNDING

1. Prostate Cancer Research Program Clinical Consortium Award.
   W81XWH-16-PCRP-CCRSA (Higano)
   Grant amount: $1,000,000
   Source: Department of Defense
   Role: Co-site principal investigator (5% effort)
   Dates: 01/01/07 - 09/29/21 (3 successful competitive renewals)

2. Pacific Northwest Prostate Cancer SPORE – Core D (Clinical)
   P50 CA097186 (Nelson/Core D Yu and Gore)
   Grant amount: $425,000 (this funding cycle)
   Source: Pacific Northwest Prostate Cancer SPORE
   Role: Clinical Core Leader for clinical trials and biospecimen acquisition
   Dates: 9/17/13 – 08/31/23 (2 successful competitive renewals)

3. INTense Exercise foR surVivAL among men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL – MCRPC): A multicenter, randomized, controlled, phase III study
   Grant amount: $34,588
   Source: Movember GAP4
   Role: Site principal investigator
   Dates: 10/05/16 – 10/04/19

4. Cancer Consortium Support Grant
   P30 CA015704 (Gilliland) / Clinical Research Support (Yu)

Grant amount: $30,047,070
Role: Medical Director, Clinical Research Support Office
Dates: 01/01/97 – 12/31/19

PEER REVIEW FUNDING: COMPLETED

1. Pilot Project - Positron Emission Tomography Imaging of Bone in Patients with Metastatic Prostate Cancer - A Pilot Study Evaluating Treatment Response.
   5 P30 CA015704 (Hartwell) / Pilot (Yu)
   Grant amount: $40,000
   Source: NIH/NCI Cancer Center Support Grant
   Role: Concept development and overall principal investigator
   Dates: 10/01/05 – 12/31/07

2. Pilot Project - Positron Emission Tomography Imaging of Bone in Patients with Metastatic Prostate Cancer.
   P50 CA97186 (Lange) / Pilot (Yu)
   Grant amount: $50,000
   Source: Pacific Northwest Prostate Cancer SPORE
   Role: Concept development and overall principal investigator
   Dates: 01/01/07 – 12/31/07

3. A randomized phase II study of OGX-011 in combination with docetaxel and prednisone or docetaxel and prednisone alone in patients with metastatic hormone-refractory prostate cancer.
   Grant amount: $32,000
   Source: National Cancer Institute of Canada (Cooperative Group Trial)
   Role: Site Principal Investigator
   Dates: 11/01/05 – 09/30/09

4. Phase 2 randomized trial of gemcitabine and cisplatin with or without Cetuximab in patients with urothelial carcinoma.
   Grant amount: $12,260
   Source: National Comprehensive Cancer Network (Cooperative Group Trial)
   Role: Site principal investigator
   Dates: 01/15/09 - 03/04/11

5. Phase 2, multicenter evaluation of ^{18}F-fluoride PET as a pharmacodynamic biomarker for Dasatinib, a SRC kinase inhibitor, in men with castration-resistant prostate cancer and bone metastases (ACRIN 6687).
   Grant amount: $190,790
   Source: American College of Radiology Imaging Network (ACRIN) (Cooperative Group Trial)
   Role: Concept development, multicenter study chair, and overall principal investigator (20% effort)
   Dates: 07/01/09 – 06/30/12

6. Genitourinary Oncology Clinical Trials Core.
   Infrastructure Support Proposal (PI: Yu)
   Grant amount: $68,181
   Source: Institute of Prostate Cancer Research

Role: Core Director
Dates: 11/19/12 – 11/18/13

7. A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation with Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer (SWOG 0925).
   Grant amount: $177,000
   Source: Southwest Oncology Group (SWOG) (Cooperative Group Trial) and Imclone Pharmaceuticals
   Role: Concept development, multicenter study chair, and overall principal investigator
   Dates: 06/01/11 – 05/31/14

8. Advanced PET/CT imaging for improving clinical trials.
   1U01 CA148131 (Kinahan)
   Grant amount: $2,628,443
   Source: National Institute of Health
   Role: Leader of prostate cancer imaging trials (5% effort)
   Dates: 04/16/10 – 04/15/15

9. Biomarkers of response to treatment with XL184.
   Creativity Award (Co-PIs: Knudsen, Yu)
   Grant amount: $300,000
   Source: Prostate Cancer Foundation
   Role: Concept development and leader of PET imaging effort
   Dates: 05/23/12 – 08/22/16 (no cost extension)

10. A Phase II Study of MAOA Inhibitor Plus Docetaxel in Patients Currently Receiving and Progressing on Docetaxel Therapy.
    Grant amount: $16,928
    Source: Wayne D. Kuni and Joan E. Kuni Foundation (subcontract award from Oregon Health Sciences University)
    Role: Site principal investigator
    Dates: 12/01/12 – 05/31/17

11. A phase 2 study of recombinant glycosylated human interleukin-7 (CYT107) after completion of standard FDA approved therapy with sipuleucel-T for patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.
    Grant amount: $133,000
    Source: Cancer Immunotherapy Trials Network
    Role: Site principal investigator for lead site
    Dates: 02/04/15 – 02/03/18

12. A pilot study of TIL therapy generation for urothelial bladder cancer.
    Bezos family Immunotherapy Pilot Award (Yu)
    Grant amount: $150,000
    Source: Bezos family Immunotherapy Initiative
    Role: Concept development and principal investigator
    Dates: 07/01/15 – 06/30/18 (no cost extension)

PHARMACEUTICAL FUNDING: INVESTIGATOR INITIATED

1. Biologic tissue effect of sipuleucel-T on metastatic castration-resistant prostate cancer.
   Grant amount: $234,898
   Source: Dendreon
   Role: Concept development and overall principal investigator
   Dates: 01/27/15 – 04/14/22

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: $91,100
   Source: Genentech, Inc. and NCI Cancer Immunotherapy Trials Network
   Role: Concept development and overall national principal investigator
   Dates: 06/28/19 – 09/30/22

PHARMACEUTICAL FUNDING: INVESTIGATOR INITIATED: COMPLETED

1. A phase II study of BAY 43-9006 (Sorafenib) prior to prostatectomy in patients with high-risk localized prostate cancer.
   Grant amount: $102,837
   Source: Bayer Pharmaceuticals, Corp.
   Role: Concept development and overall principal investigator
   Dates: 07/01/06 – 06/31/11

2. A randomized phase II study of docetaxel + / - ZD6474 (Zactima) in metastatic transitional cell carcinoma.
   Grant amount: $65,000
   Source: Astrazeneca Pharmaceuticals, LP (subcontract award from Dana-Farber Cancer Institute)
   Role: Site principal investigator
   Dates: 05/31/07 – 03/14/12

3. A phase II trial of genomic guided therapy with dasatinib or nilutamide in metastatic castration-resistant prostate cancer.
   Grant amount: $115,000
   Source: Bristol-Myers Squibb (subcontract award from Duke University)
   Role: Site principal investigator with input into concept development
   Dates: 05/12/09 – 12/31/12

4. Phase 2, multicenter evaluation of 18F-fluoride PET as a pharmacodynamic biomarker for Dasatinib, a SRC kinase inhibitor, in men with castration-resistant prostate cancer and bone metastases.
   Grant amount: $147,143
   Source: Bristol Myers Squibb Co.
   Role: Concept development, multicenter study chair, and overall principal investigator
   Dates: 06/01/10 – 06/30/13

5. A randomized phase II study of OGX-427 (a second-generation antisense oligonucleotide to Heat Shock Protein-27) in patients with castration resistant prostate cancer who have not previously received chemotherapy for metastatic disease.
   Grant amount: $198,419

Source: OncoGeneX Techologies, Inc.
Role: Site principal investigator
Dates: 11/08/11 – 08/25/15

6. A Phase II Study of BKM120 in Men with Metastatic Castration-Resistant Prostate Cancer.
Grant amount: $97,000
Source: Novartis (subcontract award from Duke University)
Role: Site principal investigator
Dates: 07/12/13 – 09/29/15

7. Retrospective analysis of clinical benefit from radium-223 in castrate resistant prostate cancer
Grant amount: $3,600
Source: Bayer via University of Michigan
Role: Senior and site principal investigator
Dates: 05/08/15 – 05/17/17

8. PET/CT for assessment of systemic treatment response and direction of metastatic biopsy for molecular characterization of metastatic castration resistant prostate cancer
Grant amount: $315,457
Source: Bayer
Role: Concept development and overall principal investigator
Dates: 11/03/15 – 04/30/18

9. A phase 2 study of recombinant glycosylated human interleukin-7 (CYT107) after completion of standard FDA approved therapy with sipuleucel-T for patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.
Grant amount: $19,000
Sources: Dendreon
Role: Site principal investigator for lead site
Dates: 09/01/14 – 08/31/18

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: $297,128
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: $12,335,436
Source: Merck Sharp &Dohme Corp.
Role: Concept and protocol co-developed with Merck and Overall Principal Investigator for international trial
Dates: 01/13/17 – 12/31/20

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: $322,013
   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: $683,791
   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: $723,505
   Source: Taiho
   Role: Site principal investigator
   Dates: 09/12/19 – 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: $132,981
   Source: Sonus Pharmaceuticals, Inc.
   Role: Site principal investigator
   Dates: 12/15/04 – 12/15/08

2. A phase II multi-center open-label study of YM155 in subjects with hormone-refractory prostate cancer previously treated with at least one prior chemotherapy regimen.
   Grant amount: $11,000
   Source: Astellas Pharma US, Inc.
   Role: Site principal investigator
   Dates: 09/01/07 – 04/30/09

3. Phase II Study of Dasatinib for Androgen-Deprived Progressive Prostate Cancer.
   Grant amount: $213,883
   Source: Bristol Myers Squibb Co.
   Role: Overall principal investigator
   Dates: 05/01/07 – 04/01/10

4. A phase 1 study evaluating a second generation antisense oligonucleotide (OGX-427) that inhibits heat shock protein 27 (HSP27).
   Grant amount: $278,721
   Source: OncoGeneX Technologies, Inc.
   Role: Site principal investigator

Dates: 05/17/07 – 04/30/11

5. A phase III randomized placebo-controlled double blind study to assess the efficacy and safety of once-daily orally administered ZD4054 10 mg in non-metastatic hormone-resistant prostate cancer patients.
   Grant amount: $188,388
   Source: AstraZeneca Pharmaceuticals, LP
   Role: Site principal investigator
   Dates: 04/01/08 – 03/31/11

6. A phase III randomized double-blind placebo-controlled study of abiraterone acetate (CB7630) plus prednisone in patients with metastatic castration-resistant prostate cancer who have failed docetaxel-based chemotherapy.
   Grant amount: $263,350
   Source: Cougar Biotechnology
   Role: Site principal investigator
   Dates: 10/1/08 – 09/30/11

7. A randomized double-blind phase III trial comparing docetaxel combined with dasatinib to docetaxel combined with placebo in castration-resistant prostate cancer.
   Grant amount: $459,437
   Source: Bristol-Myers Squibb Co.
   Role: Steering committee member and site principal investigator
   Dates: 06/15/09 - 06/14/14

8. A phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate (CB7630) plus prednisone in asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer.
   Grant amount: $294,389
   Source: Cougar Biotechnology (changed to Janssen)
   Role: Site principal investigator
   Dates: 06/15/09 – 03/16/15

9. A phase II, open-label, single-arm trial evaluating KX2-391 in patients with bone-metastatic, castration-resistant prostate cancer who have not received prior chemotherapy.
   Grant amount: $151,070
   Source: Kinex Pharmaceuticals
   Role: Site principal investigator and assistance with protocol development
   Dates: 05/05/10 – 12/19/12

10. A randomized, open-label, phase 2 trial examining the sequencing of sipuleucel-T and androgen deprivation therapy in men with non-metastatic prostate cancer and a rising prostate specific antigen after primary therapy.
    Grant amount: $265,201
    Source: Dendreon
    Role: Site principal investigator
    Dates: 11/04/11 – 11/03/15

11. A randomized, double-blind phase 2 study comparing gemcitabine and cisplatin in combination with OGX-427 or placebo in patients with advanced transitional cell carcinoma.

Grant amount: $425,884
Source: OncoGeneX Technologies, Inc.
Role: Site principal investigator
Dates: 02/14/12 – 11/03/15

12. Open label study of the effect of GTx-758 on serum PSA and free testosterone levels in men with castration resistant prostate cancer and maintained on androgen deprivation therapy.
Grant amount: $12,347
Source: GTx, Inc.
Role: Overall principal investigator and assistance with protocol development
Dates: 02/16/12 – 02/27/12

13. An open-label, multicenter, randomized phase 2 study evaluating the safety and efficacy of docetaxel in combination with IMC-1121B or IMC-18F1 or without investigational therapy as second line therapy in patients with metastatic transitional cell carcinoma.
Grant amount: $206,595
Source: Imclone Systems, Inc.
Role: Site principal investigator
Dates: 05/08/12 – 01/14/15

14. Phase II, open label study of the effect of GTx-758 as secondary hormonal therapy on serum PSA and serum free testosterone levels in men with metastatic castration resistant prostate cancer maintained on androgen deprivation therapy.
Grant amount: $478,364
Source: GTx, Inc.
Role: Overall principal investigator
Dates: 12/20/12 – 09/30/15

15. A phase II, multicenter, single-arm study of MPDL3280A in patients with locally advanced or metastatic urothelial bladder cancer.
Grant amount: $306,248
Source: Genentech/Roche
Role: Site principal investigator
Dates: 08/21/14 – 08/20/16

16. A phase 3, randomized, double-blind, placebo-controlled study of ramucirumab plus docetaxel vs. placebo plus docetaxel in patients with locally advanced or unresectable or metastatic urothelial carcinoma who progressed on or after platinum-based therapy.
Grant amount: $414,203
Source: Eli Lilly and Company
Role: Site principal investigator
Dates: 06/21/16 – 07/31/17

17. A multicenter, single-arm, open-label, post-marketing safety study to evaluate the risk of seizure among subjects with metastatic castration-resistant prostate cancer treated with enzalutamide who are at potential increased risk of seizure.
Grant amount: $47,776
Source: Astellas, Inc.
Role: Site principal investigator
Dates: 09/12/14 – 09/11/17

18. A phase I study of the safety and pharmacokinetics of escalating doses of AGS15E given as monotherapy in subjects with metastatic urothelial cancer.
    Grant amount: $274,502
    Source: Agensys Inc.
    Role: Site principal investigator
    Dates: 03/12/14 – 12/31/17

19. A phase II clinical trial of pembrolizumab (MK-3475) in subjects with advanced/unresectable or metastatic urothelial cancer.
    Grant amount: $266,286
    Source: Merck Sharp & Dohme Corp.
    Role: Site principal investigator
    Dates: 03/22/16 – 03/21/18

REFEREED JOURNALS

1. Yu EY, Meyer GE, Brawer MK. The relation of p53 nuclear accumulation and angiogenesis in human prostatic carcinoma. *Prostate Cancer Prostatic Dis* 1997; 1(1):39-44. PMID: 12496932.

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.

3. [á]Stewart SA, [á]Dykxhoorn DM, [á]Palliser D, Mizuno H, Yu EY, An DS, Sabatini DM, Chen ISY, Hahn WC, Sharp PA, Weinberg RA, Novina CD. Lentivirus-delivered stable gene silencing by RNAi in primary cells. *RNA* 2003; 9(4):493-501. [á]*These authors contributed equally to this work.* PMID: 12649500. PMCID: 1370415.

4. Masutomi K, [á]Yu EY, [á]Khurts 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.

5. Yu EY, Hahn WC. Genetic alterations in prostate cancer. *Clin Prostate Cancer* 2005; 3(4):220-229. PMID: 15882478.

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.

7. Koreckij T, Nguyen H, Brown LG, Yu EY, Vessella RL, Corey E. Dasatinib inhibits the growth of prostate cancer in bone and provides additional protection from osteolysis. *Br J Cancer* 2009; 101(2):263-268. PMID: 19603032. PMCID: 2720213.

8. Perez FA, Fligner CL, Yu EY. Rapid clinical deterioration and leukemoid reaction following treatment of urothelial carcinoma of the bladder: possible role of granulocyte-colony stimulating factor. *J Clin Oncol* 2009; 27(34):e215-217. Epub September 28, 2009. PMID: 19786665.

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97. Bamias A, Tzannis K, Liontos M, Crabb SJ, Harshman L, De Giorgi U, Bellmunt J, Wong YN, Pal SK, Ladoire S, Sternberg CN, Powles TB, Yu EY, Niegisch G, Necchi A, Vaishampayan U, Agarwal N, Rosenberg J, RISC Investigators. Adherence to cisplatin-based regimens prescription in "fit" patients fulfilling platinum eligibility criteria. Impact on outcomes: a Retrospective International Study of Invasive/advanced Cancer of the urothelium analysis. Abstract 299P, 2016. Poster presentation at 2016 *41st ESMO European Cancer Congress*, Copenhagen, Denmark, Oct. 2016.

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103. Yu EY, Wu H, Schloss C. Phase 1b/2 KEYNOTE-365 trial: Pembrolizumab combination therapy in metastatic castration-resistant prostate cancer. *J Clin Oncol* 35, 2017 (suppl; abstr TPS5089). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2017.

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105. Brisbane WG, Holt SK, Gore JL, Wright JL, Yu EY, Ramos JD, Dash A, Porter MP, Schade GR. Severe diabetics with high grade non-muscle invasive bladder cancer are at increased risk of disease progression. *Western Section American Urological Association*, Abstract 203. Oral presentation at Western Section American Urological Association Meeting, Vancouver, BC, Canada, Aug. 2017.

106. Necchi A, Pond GR, Pal SK, Agarwal N, Bowles DW, Plimack ER, Yu EY, Ladoire S, Baniel J, Crabb S, Niegisch G, Srinivas S, Berthold RD, Rosenberg J, Powles T, Bamias A, Harshman LC, Bellmunt J, Galsky MD; RISC group. Bone metastases as the only metastatic site in patients with urothelial carcinoma: focus on a special patient population. *Ann Oncol* 28(5); 8-12 Sept. 2017. Abstract 875P. Poster presentation at 2018 *42nd ESMO European Cancer Congress*, Madrid, Spain, Oct. 2017.

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109. Lim DM, Gulati R, Aleshin-Guendel S, Cheng HH, Gawne AM, Wingate JT, Etzioni RD, Yu EY. Proportion of biochemically-recurrent prostate cancer patients with durable undetectable PSA after short-course androgen deprivation therapy. *J Clin Oncol* 36, 2018 (suppl 6S; abstr 207). Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2018.

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112. Raggi D, Pond G, Giannatempo P, Plimack ER, Niegisch G, Yu EY, Pal SK, Bamias A, Agarwal N, Alva AS, Ladoire S, Srinivas S, Crabb SJ, Baniel J, Vaishampayan UN, Bowles DW, Berthold DR, Theodore C, Sridhar SS, Powles T, Rosenberg JE, Bellmunt J, Galsky MD, Necchi A, Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC). Nomogram-based risk prediction of local and distant relapse after radical cystectomy, and role of perioperative chemotherapy, in patients with muscle-invasive bladder cancer: A multicenter study. Abstract 368, 2018. Poster presentation at *33rd Annual European Association of Urology Congress*, Copenhagen, Denmark, Mar. 2018.

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119. Yu EY, Gulati R, Aleshin-Guendel S, Cheng HH, Gawne AM, Wingate JT, Etzioni RD, Lim DM. Association of undetectable PSA with time to metastasis and survival after short-course androgen deprivation therapy for biochemically-recurrent prostate cancer patients. *J Clin Oncol* 36, 2018 (suppl; abstr e17073). ASCO Annual Meeting, Chicago, IL, Jun. 2018.

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121. Petrylak DP, Sternberg CN, Drakaki A, de Wit R, Nishiyama H, Necchi A, Castellano D, Bamias A, Chi KN, van der Heijden MS, Matsubara N, Hussain S, Flechon A, Alekseev BY, Yu EY, Walgren RA, Fusso F, Zimmermann AH, Bell-Mcguinn KM, Powles TB. RANGE, a phase III, randomized, placebo-controlled, double-blind trial of ramucirumab and docetaxel in platinum-refractory urothelial carcinoma: Overall survival results. *Ann Oncol* 29(8), 1 Oct. 2018, mdy283.071. Abstract 865PD. Oral presentation at 2018 *43rd ESMO European Cancer Congress*, Munich, Germany, Oct. 2018.

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124. Markowski MC, Eisenberger MA, Antonarakis ES, Yu EY, Barnette G, Rodriguez D, Getzenberg RH, Steiner MS. Design of phase 1b/II study of oral VERU-111, an α and β-tubulin inhibitor, for

the treatment of metastatic castration- and androgen-blocking-agent-resistant prostate cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr TPS330). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.

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126. Nyame YA, Holt SK, Winters B, Psutka SP, Dash A, Schade GR, Lin DW, Yu EY, Gore JL, Wright JL. Neoadjuvant chemotherapy utilization in muscle-invasive bladder cancer: Increasing yet inappropriate use? *J Clin Oncol* 37, 2019 (suppl 7S; abstr 441). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.

127. De Wit R, Powles T, Castellano DE, Necchi A, Lee JL, Van der Heijden MS, Matsubara N, Bamias A, Flechon A, Sternberg CN, Drakaki A, Yu EY, Hamid O, Zimmermann AH, Gao L, Long A, Walgren RA, Bell-McGuinn KM, Petrylak DP. Ramucirumab exposure-response relationship in RANGE: A randomized phase III trial of ramucirumab plust docetaxel versus placebo plus docetaxel in advanced platinum-refractory urothelial carcinoma patients. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 353). Oral presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.

128. **Yu EY, Massard C, Retz M, Tafreshi A, Galceran JC, Hammerer P, Fong PCC, Shore N, Joshua A, Linch MD, Gurney H, Romano E, Augustin M, Piulats JM, Wu H, Schloss C, Poehlein CH, De Bono JS. KEYNOTE-365 Cohort A: Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castrate-resistant prostate cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr 145). Oral presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.**

129. Sonpavde G, Maughan BL, Wei XX, McGregor BA, Kilbridge KL, Lee RJ, Yu EY, Schweizer MT, Montgomery RB, Cheng HH, Hsieh AC, Birhiray RE, Gabrail NY, Nemunaitis JJ, Rezazadeh A, Van Veldhuizen PJ, Vogelzang NJ, Heery CR, Grivas P. A phase II, multicenter, single-arm trial of CV301 plus atezolizumab in locally advanced (unresectable) or metastatic urothelial cancer. *J Clin Oncol* 37, 2019 (suppl 7S; abstr TPS494). Poster presentation at Genitourinary Cancers Symposium, San Francisco, CA, Feb. 2019.

130. Smith MR, Sandhu SK, Kelly WK, Scher HI, Efstathiou 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 metastastic 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, 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. 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, Feyerabend 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-invasice 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*

Clin Oncol 37, 2019 (suppl; abstr TPS4586). Poster presentation at ASCO Annual Meeting, Chicago, IL, Jun. 2019.

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 enzalutanmide- 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.

INVITED TALKS AND LECTURES

UNIVERSITY/LOCAL CONFERENCES

- Program in Prostate Cancer Research/SPORE: "Retroviral RNA interference: systems development, biologic discoveries with telomerase, and future applications." Fred Hutchinson Cancer Research Center, Seattle, WA. March 4, 2004.
- Jobson Education: "Hormone refractory prostate cancer: Early vs. late vs. asymptomatic" Seattle, WA. June 24, 2005.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: Clinical implications." Fred Hutchinson Cancer Research Center, Seattle, WA. October 21, 2005.
- Resident Teaching Conference: "A case-based approach to managing metastatic bone disease." University of Washington, Seattle, WA. October 25, 2005.
- Seattle Cancer Care Alliance Physician Educational Outreach Program: "Hormone-refractory prostate cancer; the medical oncologist's perspective." Mount Vernon, WA. October 25, 2005.
- Breast and Prostate Program Bone Metastases Retreat: "Response to treatment in patients with metastatic prostate cancer: using PET scans as a surrogate marker for bone-dominant disease." Fred Hutchinson Cancer Research Center, Seattle, WA. November 14, 2005.
- Puget Sound Oncology Consortium's Annual Highlights of ASCO meeting: "Genitourinary Oncology ASCO 2006: review of prostate, bladder and testicular cancer." Seattle, WA. June 29, 2006.
- 6th Annual Pacific Northwest Prostate Cancer Conference: "A rising PSA after local therapy…implications and utility of PSA kinetics." Seattle, WA. September 16, 2006.
- Nuclear Medicine Internal Advisory Board: "Metabolic Imaging in prostate cancer – the future with PET." University of Washington, Seattle, WA. September 25, 2006.
- Program in Prostate Cancer Research/SPORE: "PET measures response to therapy in prostate cancer." University of Washington, Seattle, WA. November 2, 2006.
- North Star Lodge: "New concepts in genitourinary oncology." Yakima, WA. November 9, 2006.
- Nuclear Medicine External Advisory Board: "Metabolic imaging of prostate cancer as a biomarker of treatment response." University of Washington, Seattle, WA. November 30, 2006.
- Asian Senior Concerns Foundation: "Bladder cancer – the basics." Bellevue, WA. January 20, 2007.
- Asian Senior Concerns Foundation: "Prostate cancer PSA screening, treatments, and public concerns." Bellevue, WA. January 20, 2007.
- Virginia Mason Medical Center: "Mediastinal germ cell tumors." Seattle, WA. February 1, 2007.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: the need for new knowledge." Fred Hutchinson Cancer Research Center, Seattle, WA. March 2, 2007.
- A&P Lecture: "Imaging biomarkers in prostate cancer: the potential impact of tumor metabolism on clinical trials and drug development." University of Washington, Seattle, WA. March 6, 2007.

- Pacific Northwest SPORE: "Positron emission tomography imaging of bone in patients with metastatic prostate cancer." Fred Hutchinson/University of Washington Cancer Center Support Grant, Seattle, WA. May 21, 2007.
- Patient Power Radio Show: "Prostate, bladder, and testicular cancer update: ASCO 2007." Seattle, WA. June 10, 2007.
- Puget Sound Oncology Consortium Annual Highlights of ASCO meeting: "ASCO 2007 prostate cancer review." Seattle, WA. June 28, 2007.
- Emerging Trends in Oncology: "Update in prostate cancer, ASCO review." Seattle, WA. June 30, 2007.
- Patient Power Radio Show: "Prostate cancer: who to treat and when." Seattle, WA. July 11, 2007.
- American College of Physicians, Seattle Internal Medicine Board Review Course: "Solid tumor oncology cases." Seattle, WA. July 13, 2007.
- University of Washington Internal Medicine Residents' Educational Lecture Series: "Prostate cancer – A chronic disease." University of Washington, Seattle, WA. October 31, 2007.
- Oncology Grand Rounds: "A case of urothelial carcinoma of the bladder with leukemoid reaction: was GCSF playing a negative role?" Fred Hutchinson Research Center, Seattle, WA. November 6, 2007.
- Hematology/Oncology Fellows' Lecture Series: "Germ cell tumors/testicular cancer – what you really need to know." Fred Hutchinson Cancer Research Center, Seattle, WA. November 16, 2007.
- Program in Prostate Cancer Research/SPORE: "Positron emission tomography imaging of bone in patients with metastatic prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. March 6, 2008.
- Gilda's Club: "Advanced prostate cancer: an update on hormones, chemotherapy, and clinical trials." Seattle, WA. March 29, 2008.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: An unmet need." Fred Hutchinson Cancer Research Center, Seattle, WA. May 2, 2008.
- Patient Power Radio Show: "Prostate cancer biomarkers." Seattle, WA. May 7, 2008.
- 8th Annual Pacific Northwest Prostate Cancer Conference: "When is PSA useful? Why it may not always be reliable?" Fred Hutchinson Cancer Research Center. September 27, 2008.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program - Multicare Tacoma: "Bladder cancer – an unmet need." Tacoma, WA. September 30, 2008.
- Program in Prostate Cancer Research/SPORE: "Bone health for men with prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. November 6, 2008.
- Hematology/Oncology Educational Lecture Series: "Germ cell tumors/testicular cancer - a boards exam favorite." Fred Hutchinson Cancer Research Center, Seattle, WA. April 3, 2009.
- University of Washington CME Current Concepts in Drug Therapy: "Primary care issues for patients with prostate cancer undergoing androgen deprivation therapy." Seattle, WA. May 8, 2009.
- Seattle Cancer Care Alliance Scientific Lunch: "Drug development for prostate cancer – rebounding well from tough times." Seattle Cancer Care Alliance, Seattle, WA. June 11, 2009.
- Radiation Oncology Residents' Educational Lecture Series: "PSA kinetics to drive decision making for men with prostate cancer." University of Washington, Seattle, WA. June 18, 2009.
- Pacific Northwest SPORE Retreat: "PET imaging as a prostate cancer bone biomarker." University of British Columbia, Vancouver, BC. July 10, 2009.
- American College of Physicians, Seattle Internal Medicine Board Review Course: "Solid tumor oncology cases." Seattle, WA. July 17, 2009.

- Scripps 6th Annual Oncology Update: "ASCO review of prostate cancer." Seattle, WA. July 25, 2009.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: is it our turn yet?" Fred Hutchinson Cancer Research Center, Seattle, WA. August 21, 2009.
- Virginia Mason Community Journal Review: "Androgen deprivation therapy induced estrogen deficiency side effects." Seattle, WA. October 13, 2009.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Skagit Valley and Olympic Medical Centers: "Upcoming new drugs for prostate cancer therapy." Mt. Vernon, WA. October 15, 2009.
- Center for Biomedical Continuing Education: "Bone health across the cancer continuum: Updates and insight to an evolving story." Seattle, WA. January 28, 2010.
- Oncology Grand Rounds: "Prostate cancer and broken bones? Only from sticks and stones…" Fred Hutchinson Cancer Research Center, Seattle, WA. March 9, 2010.
- Hematology/Oncology Fellow's Lecture Series: "Germ cell tumors/testicular cancer – hitting the ball out of the park." Fred Hutchinson Cancer Research Center, Seattle, WA. March 26, 2010.
- 13th Annual Advanced Prostate Brachytherapy Conference: "Managing androgen deprivation therapy associated side effects." Seattle Prostate Institute, Seattle, WA. May 14, 2010.
- American College of Physicians, Seattle Internal Medicine Board Review Course: "Solid tumor oncology cases." Seattle, WA. July 23, 2010.
- Scripps 7th Annual Oncology Update: "Prostate cancer update: New therapies for castration-resistant disease." Seattle, WA. August 14, 2010.
- Patient Power Radio Show: "New treatments for prostate cancer." Seattle, WA. August 27, 2010.
- University of Washington Comprehensive Oncology Review: "Bladder cancer – keeping in the loop." Seattle, WA. October 2, 2010.
- University of Washington Comprehensive Oncology Review: "Germ cell tumors/testicular cancer – keeping an eye on the ball." Seattle, WA. October 3, 2010.
- Sanofi-Aventis Roundtable Program: "Cabazitaxel: A new option for metastatic hormone-refractory prostate cancer following a docetaxel containing regimen." Seattle, WA. October 7, 2010.
- 10th Annual Pacific Northwest Prostate Cancer Conference: "Protecting bone for prostate cancer patients." Fred Hutchinson Cancer Research Center, Seattle, WA. October 9, 2010.
- Multicare Tacoma: "Cabazitaxel: A new option for metastatic hormone-refractory prostate cancer following a docetaxel containing regimen." Tacoma, WA. November 16, 2010.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: getting in the loop." Fred Hutchinson Cancer Research Center, Seattle, WA. November 19, 2010.
- Science over Lunch: "Rapidly changing paradigms in prostate cancer – new FDA approvals and local contributions." Fred Hutchinson Cancer Research Center, Seattle, WA. March 10, 2011.
- Hematology/Oncology Educational Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. March 11, 2011.
- Pacific Northwest Prostate Cancer SPORE: "Metabolic imaging and biomarkers to monitor treatment response of castration-resistant prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. March 28, 2011.
- Nuclear Medicine U01 Meeting: "Discerning Cabozantinib (XL184) biology with ^{11}C-acetate and ^{18}F-fluoride PET/CT imaging." Seattle Cancer Care Alliance, Seattle, WA. April 12, 2011.
- Scripps 8th Annual Oncology Update: "Genitourinary cancer update." Seattle, WA. August 13, 2011.
- University of Washington Comprehensive Oncology Review (2nd Annual): "Germ cell tumors/testicular cancer." Seattle, WA. September 18, 2011.

- University of Washington Comprehensive Oncology Review (2nd Annual): "Genitourinary Cancer Cases - Question and Answer Session." Seattle, WA. September 18, 2011.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: updates and local research endeavors." Fred Hutchinson Cancer Research Center, Seattle, WA. October 28, 2011.
- Hematology/Oncology Fellows' Solid Tumor Conference: "Prostate cancer: local research efforts." Seattle Cancer Care Alliance, Seattle, WA. October 28, 2011.
- Program in Prostate Cancer Research/SPORE: "Hormone-sensitive prostate cancer – updates on recent and ongoing clinical trials." Fred Hutchinson Cancer Research Center, Seattle, WA. November 3, 2011.
- Uganda Cancer Institute: "Cases from Kampala – prostate cancer case conference." Fred Hutchinson Cancer Research Center, Seattle, WA. June 14, 2012.
- University of Washington Comprehensive Oncology Review (3rd Annual): "Germ cell tumors/testicular cancer." Seattle, WA. September 23, 2012.
- Hematology/Oncology Fellows' Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. October 12, 2012.
- Updates in Oncology and Blood/Marrow Transplantation – A Spotlight on Seattle Cancer Care Alliance: "Research advancements for castration-resistant prostate cancer." Seattle, WA. October 15, 2012.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: the next big thing in genitourinary oncology." Fred Hutchinson Cancer Research Center, Seattle, WA. November 2, 2012.
- Program in Prostate Cancer Research/SPORE: "Prostate cancer bone biomarkers: clinical trial tool or ready for prime time in the clinic?" Fred Hutchinson Cancer Research Center, Seattle, WA. March 7, 2013.
- Institute for Prostate Cancer Research 2013 Symposium – Breakthroughs in prostate cancer research: "Imaging advanced prostate cancer – beyond finding the tumor." Fred Hutchinson Cancer Research Center, Seattle, WA. March 17, 2013.
- Uganda Cancer Institute: "Cases from Kampala – prostate cancer case conference." Fred Hutchinson Cancer Research Center, Seattle, WA. July 11, 2013.
- Pacific Northwest Cancer SPORE Retreat 2013: "Identification of molecular characteristics of prostate cancer with ^{11}C-acetate and ^{18}F-FDG PET/CT-directed rapid autopsy." Fred Hutchinson Cancer Research Center, Seattle, WA. July 12, 2013.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program - Multicare Tacoma: "Recent and future therapeutic advancements for metastatic castration-resistant prostate cancer." Tacoma, WA. July 19, 2013.
- Medical Oncology Faculty Sections Meeting: "Fellowship Updates 2013." Seattle Cancer Care Alliance, Seattle, WA. August 1, 2013.
- Hematology/Oncology Educational Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. September 13, 2013.
- University of Washington Comprehensive Oncology Review (4th Annual): "Germ cell tumors/testicular cancer." Seattle, WA. October 1, 2013.
- The Everett Clinic: "Cancer immunotherapy – fundamental concepts and emerging role." Everett, WA. October 1, 2013.
- Pacific Northwest SPORE Advocacy Meeting: "Sequencing of novel secondary hormonal therapies in metastatic castration-resistant prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. December 12, 2013.
- Program in Prostate Cancer Research/SPORE: "A review of PET imaging for prostate cancer: past, present and future." Fred Hutchinson Cancer Research Center, Seattle, WA. March 27, 2014.

- Institute for Prostate Cancer Research 2014 Symposium – Breakthroughs in prostate cancer research: "Imaging prostate cancer – present and future." Fred Hutchinson Cancer Research Center, Seattle, WA. April 12, 2014.
- Multicare Tacoma: "Overcoming cancer immunoevasion: the role of immunotherapy." Tacoma, WA. April 17, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program: "Role of immunotherapy for bladder cancer – a focus on the PDL1/PD1 axis." Bellevue, WA. June 25, 2014.
- Pacific NorthWest Prostate Cancer SPORE Retreat: "Clinical Core D." Fred Hutchinson Cancer Research Center, Seattle, WA. July 21, 2014.
- Hematology/Oncology Fellows' Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. September 5, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Skagit Valley Medical Center: "The promise of immunotherapy for bladder cancer." Mt. Vernon, WA. September 17, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Bend Memorial Clinic: "The promise of immunotherapy for bladder cancer." Bend, OR. September 25, 2014.
- University of Washington Comprehensive Oncology Review (5th Annual): "Germ cell tumors/testicular cancer." Seattle, WA. September 27, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Bozeman Deaconess Cancer Center: "Hot topics for prostate and bladder cancer." Bozeman, MT. October 14, 2014.
- Program in Prostate Cancer Research/SPORE: "Clinical experience with insulin-like growth factor receptor I (IGF-IR) inhibition in prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. October 30, 2014.
- Body Imaging Radiology Section Lecture Series: "Challenges in imaging of genitourinary malignancies." University of Washington Medical Center, Seattle, WA. November 12, 2014.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Spokane Valley Cancer Center: "The promise of immunotherapy for bladder cancer." Spokane, WA. November 13, 2014.
- Hematology/Oncology Fellows' Lecture Series: "Bladder cancer: a rapidly growing research arena." Fred Hutchinson Cancer Research Center, Seattle, WA. December 19, 2014.
- Oncology Grand Rounds: "Prostate cancer from the medical oncologist perspective…it's not all about castration-resistant disease." Fred Hutchinson Cancer Research Center, Seattle, WA. December 23, 2014.
- Us Too: "Timing and sequencing of therapeutic agents in metastatic prostate cancer." Greenwood Senior Center, Seattle, WA. March 25, 2015.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Tri Cities Cancer Center: "Metastatic prostate cancer therapeutic sequencing, combination and trials." Kennewick, WA. April 23, 2015.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – The Vancouver Clinic: "Key therapeutic questions in metastatic prostate cancer." Vancouver, WA. May 5, 2015.
- Scripps 12th Annual Oncology Update: "Genitourinary cancer update." Seattle, WA. August 15, 2015.
- Flash Rounds: "Seven tips to developing a clinical research career." Fred Hutchinson Cancer Research Center. Seattle, WA. September 4, 2015.
- Genentech Educational Presentation: "Current challenges in managing bladder cancer." Seattle, WA. October 22, 2015.

- Hematology/Oncology Fellows' Lecture Series: "Germ cell tumors/testicular cancer." Fred Hutchinson Cancer Research Center. Seattle, WA. October 23, 2015.
- Fred Hutch Clinical Oncology Grand Rounds: "PET imaging in prostate cancer: Will it ever be more than a research tool?" Fred Hutchinson Cancer Research Center. Seattle, WA. January 12, 2016.
- Seattle Cancer Care Alliance Network Physician Educational Outreach Program – Bozeman Deaconess Cancer Center: "Urothelial carcinoma – Life after platinum." Bozeman, MT. May 20, 2016.
- Pacific NorthWest Prostate Cancer SPORE Retreat: "Clinical Core D." Fred Hutchinson Cancer Research Center, Seattle, WA. July 25, 2016.
- Genitourinary Oncology Staff Education Sessions: "ASCO 2016 prostate and bladder cancer updates." Seattle Cancer Care Alliance, Seattle, WA. August 11, 2016.
- Society for Immunotherapy of Cancer's (SITC) Advances in Cancer Immunotherapy – Washington Program: "Immunotherapy for genitourinary cancers." Seattle, WA. August 19, 2016.
- Remedica Medical Education and Publishing CME – Lecture to Seattle Cancer Care Alliance Advanced Practice Providers: "P3 – Patient selection and Practice in Prostate cancer." Seattle, WA. November 21, 2016.
- Providence Regional Medical Center: "P3 – Patient selection and Practice in Prostate cancer." Everett, WA. December 8, 2016.
- Remedica Medical Education and Publishing CME – Lecture to Fred Hutchinson Cancer Research Center Hematology/Oncology Fellows: "P3 – Patient selection and Practice in Prostate cancer." Seattle, WA. December 14, 2016.
- Seattle Cancer Care Alliance Educational Lecture: "Emerging immunotherapies and systemic therapies for metastatic urothelial carcinoma." Seatac, WA. March 1, 2017.
- 2016 6th Annual Institute of Prostate Cancer Research Symposium: "PET imaging in prostate cancer: Finding local recurrences and management of oligometastatic disease." Fred Hutchinson Cancer Research Center, Seattle, WA. March 18, 2017.
- Pacific NorthWest Prostate Cancer SPORE Retreat: "Clinical Core D." Fred Hutchinson Cancer Research Center, Seattle, WA. July 24, 2017.
- Seattle Genetics Lecture Series: "The evolving urothelial carcinoma landscape." Bothell, WA. August 4, 2017.
- University of Washington Comprehensive Hematology and Oncology Review (8th Annual): "Prostate cancer board review." Seattle, WA. September 25, 2017.
- Clinical Research Division: "Informed consent elements documentation." Fred Hutchinson Cancer Research Center, Seattle, WA. November 13, 2017.
- Medical Oncology Sections Meeting: "Informed consent elements documentation." Seattle Cancer Care Alliance, Seattle, WA. December 7, 2017.
- **University of Washington Medicine Grand Rounds: "Clinical research in prostate cancer." University of Washington School of Medicine, Seattle, WA. January 11, 2018.**
- Clinical Research Services, Fred Hutchinson Cancer Research Consortium: "Prostate cancer overview and impactful clinical research." Fred Hutchinson Cancer Research Center, Seattle, WA. January 11, 2018.
- Solid Tumor Conference, Fred Hutchinson Hematology-Oncology Fellowship Program: "GU boards review for fellows – Key points to remember." Fred Hutchinson Cancer Research Center, Seattle, WA. April 27, 2018.
- Institute for Prostate Cancer Research 2018 Symposium – Breakthroughs in prostate cancer research: "Prostate Cancer Tumor Board." Fred Hutchinson Cancer Research Center, Seattle, WA. April 28, 2018.

- External Advisory Board Meeting, Fred Hutchinson/University of Washington Cancer Consortium: "Clinical Protocol and Data Management." Fred Hutchinson Cancer Research Center, Seattle, WA. June 15, 2018.
- Oncology Grand Rounds: "Treatment intensification for castration-sensitive prostate cancer and management of oligometastatic disease." Fred Hutchinson Cancer Research Center, Seattle, WA. June 19, 2018.
- University of Washington Comprehensive Hematology and Oncology Review (9th Annual): "Prostate cancer board review." Seattle, WA. September 15, 2018.
- Genitourinary Oncology Staff Education Sessions: "Prostate cancer overview – clinical and research impact." Seattle Cancer Care Alliance, Seattle, WA. February 7, 2019.
- External Advisory Board Meeting, Fred Hutchinson/University of Washington Cancer Consortium: "Clinical Protocol and Data Management." Fred Hutchinson Cancer Research Center, Seattle, WA. March 8, 2019.
- Institute for Prostate Cancer Research 2019 Symposium – Breakthroughs in prostate cancer research: "Imaging in prostate cancer – state of the field." Fred Hutchinson Cancer Research Center, Seattle, WA. May 11, 2019.
- Program in Prostate Cancer Research/SPORE: "Implications of next generation PET imaging in prostate cancer." Fred Hutchinson Cancer Research Center, Seattle, WA. May 16, 2019.
- NCI Cancer Center Support Grant Site Visit: "Clinical drotocol and data management." Fred Hutchinson Cancer Research Center, Seattle, WA. May 29, 2019.
- 7th Annual International Conferences on Advances in Hematology and Oncology: "Bladder cancer updates from ASCO 2019." Seattle, WA. June 30, 2019.
- Seattle (Bellevue) UsToo: "Prostate cancer disease states and treatments." Bellevue, WA. July 15, 2019.
- Seattle (Bellevue) UsToo: "Next generation PET imaging in prostate cancer." Bellevue, WA. July 15, 2019.
- Medical Oncology Sections Meeting: "Genitourinary Medical Oncology (GUMO) research interests and updates." Seattle Cancer Care Alliance, Seattle, WA. August 1, 2019.

INVITED SPEAKER NATIONAL/INTERNATIONAL

- Genentech, Inc.: "Retroviral RNA interference: systems development and biologic discoveries with telomerase." San Francisco, CA. April 6, 2004.
- **Stanford University Medical Center: "Retroviral RNA interference: systems development and biologic discoveries with telomerase." Stanford, CA. April 27, 2004.**
- **University of California Davis School of Medicine: "Retroviral RNA interference: systems development and biologic discoveries with telomerase." Sacramento, CA. April 30, 2004.**
- 8th Annual Western Hawaii Cancer Symposium: "Clinical implications of angiogenesis in solid tumor oncology." Kona, HI. September 10, 2005.
- Novartis Oncology: "Current issues in the treatment of bone metastases." Reno, NV. February 20, 2007.
- Novartis Oncology: "Treatment of solid tumor bone metastases with bisphosphonates." Anchorage, AK. June 13, 2007.
- Southwest Oncology Group Fall GU Committee Meeting: "Tissue inhibitor of metalloproteinase-1 (TIMP-1) as a prognostic and predictive biomarker for men receiving chemotherapy for hormone-refractory prostate cancer." Huntington Beach, CA. October 4, 2007.
- American Urologic Association Northeastern Section: "Emerging role of selective estrogen receptor modulators in prostate cancer." Santa Ana Pueblo, NM. September 20, 2008.
- American Urologic Association New England Section: "Emerging role of selective estrogen receptor modulators in prostate cancer." Rio Grande, Puerto Rico. September 26, 2008.

- **Prostate Cancer Foundation Scientific Symposium: "Prostate cancer bone metastasis biomarkers." Lake Tahoe, NV. October 16, 2008.**
- Southwest Oncology Group Spring GU Committee Meeting: "A phase 2 study of combined androgen deprivation and IMC-A12 for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. April 23, 2009.
- 12th Annual Western Hawaii Cancer Symposium: "Translational oncology in clinical practice." Kona, HI. September 4, 2009.
- **Prostate Cancer Research Institute (PCRI) 2009 Prostate Cancer Conference: "Reducing side effects of testosterone deprivation." Los Angeles, CA. September 12, 2009.**
- Southwest Oncology Group Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and IMC-A12 for patients with new hormone-sensitive metastatic prostate cancer." Chicago, IL. October 24, 2009.
- Second Annual Roche Diagnostics Bone Metastatic Cancer Advisory Board: "Prognostic markers for metastatic bone disease in prostate cancer." Arlington, VA. October 29, 2009.
- Prostate Cancer Clinical Trials Consortium Annual Review: "Using metabolic imaging to assess response to therapy in prostate cancer bone metastases." Vienna, VA. November 18, 2009.
- Prostate Cancer Educational Council: "Beyond screening and diagnosis – utility of prostate specific antigen by disease state." Content Development Working Group Moderator. Philadelphia, PA. November 20, 2009.
- 10th Annual Meeting of the Society of Urologic Oncology: "Androgen deprivation therapy induced estrogen deficiency side effects." Bethesda, MD. December 4, 2009.
- Center for Biomedical Continuing Education: "Bone health across the cancer continuum: Updates and insight to an evolving story." Chicago, IL. February 9, 2010.
- Billings Clinic Tumor Board: "Bone health across the cancer continuum: Updates and insight to an evolving story." Billings, MT. March 30, 2010.
- Center for Biomedical Continuing Education: "Bone health across the cancer continuum: Updates and insight to an evolving story." New York, NY. April 8, 2010.
- Southwest Oncology Group Spring GU Committtee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and IMC-A12 for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. April 18, 2010.
- Mercy Regional Medical Center Grand Rounds: "Bone health across the cancer continuum: Updates and insight to an evolving story." Durango, CO. April 20, 2010.
- Sparrow Professional Building Grand Rounds: "Bone health across the cancer continuum: Updates and insight to an evolving story." Lansing, MI. April 30, 2010.
- **Education Session, Evolving Standards of Care in Metastatic Castration-resistant Prostate Cancer: "Bone directed therapy for prostate cancer: present standards and potential new options." 2010 American Society of Clinical Oncology, Chicago, IL. June 7, 2010.**
- **University of Texas Southwestern Combined Modality Conference: "Boning up with prostate cancer." Dallas, TX. July 2, 2010.**
- **Wayne State University / Karmanos Cancer Institute Prostate Cancer Working Group Conference: "Bone health in prostate cancer: The basics and some propaganda." Detroit, MI. August 20, 2010.**
- 13th Annual Western Hawaii Cancer Symposium: "Emerging new therapies for metastatic castration resistant prostate cancer." Kona, HI. September 4, 2010.
- South Texas Institute of Cancer: "Clinical debates in castration-refractory prostate cancer." Corpus Christi, TX. September 7, 2010.

- Texas Hematology/Oncology: "Clinical debates in castration-refractory prostate cancer." McKinney, TX. September 9, 2010.
- **Prostate Cancer Foundation Scientific Symposium: "Imaging prostate cancer bone metastases with sodium fluoride (NaF) PET." Washington, DC. September 16, 2010.**
- **City of Hope Oncology Grand Rounds: "Clinical decision making in castration-resistant prostate cancer." Duarte, CA. October 5, 2010.**
- Mount Clemens Regional Medical Center Oncology Grand Rounds: "Clinical debates in castration-refractory prostate cancer." Mount Clemens, MI. October 13, 2010.
- Great Falls Clinic Cancer Center: "Clinical debates in castration-refractory prostate cancer." Great Falls, MT. October 14, 2010.
- Southwest Oncology Group Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." Chicago, IL. October 23, 2010.
- Mercy Hospital: "Clinical debates in castration-refractory prostate cancer." Bakersfield, CA. November 3, 2010.
- **University of California San Diego Hematology/Oncology Grand Rounds: "Prostate Cancer: Honing in on the bones." San Diego, CA. January 14, 2011.**
- Southwest Oncology Group Spring GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. April 16, 2011.
- Providence Alaska Medical Center: "Advances in castration-resistant prostate cancer." Anchorage, AK. April 27, 2011.
- Bristol-Myers Squibb ASCO Dasatinib Investigator Initiated Trial Meeting: "Determining pharmacodynamic effects of Dasatinib on bone with ^{18}F-fluoride PET imaging in men with castration resistant prostate cancer." Chicago, IL. June 4, 2011.
- Millennium Pharmaceuticals, Inc. Prostate Cancer Update Educational Program: "Hormone-sensitive prostate cancer – recent updates and ongoing trials." Cambridge, MA. October 4, 2011.
- SWOG Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Antonio, TX. October 15, 2011.
- OncoGeneX OGX-427-02 Bladder Cancer Phase 2 Investigator Meeting: "A phase 1 trial of OGX-427, a 2-methoxyethyl antisense oligonucleotide against Heat Shock Protein 27." Scottsdale, AZ. November 5, 2011.
- **Yale Cancer Center NP Conference: "Prostate cancer: It's all about the bones." New Haven, CT. November 18, 2011.**
- **2012 Genitourinary Cancers Symposium, General Session II: Castrate Resistant Prostate Cancer – Treatment Sequencing and Implementation: "Novel targets, agents, and trials." San Francisco, CA. February 2, 2012.**
- **2012 Genitourinary Cancers Symposium, General Session II: Castrate Resistant Prostate Cancer – Treatment Sequencing and Implementation: "Case study and panel discussion." San Francisco, CA. February 2, 2012.**
- Prostate Cancer Skeletal Metastasis Workshop, Combined P01 Meeting: "Imaging response to therapy in prostate cancer bone metastases – PET as a biomarker." Ann Arbor, MI. April 12, 2012.

- SWOG Spring GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. April 14, 2012.
- Astellas Pharma Medical Science Liaison Education Lecture: "The dynamic treatment landscape for castration-resistant prostate cancer." Internet lecture. May 4, 2012.
- **Vanderbilt University: "Dem bones, dem bones, dem prostate cancer bones." Nashville, TN. May 17, 2012.**
- **Genitourinary (Prostate) Cancer Poster Discussion Session: "Sex, Drugs, and Bones." 2012 American Society of Clinical Oncology, Chicago, IL. June 4, 2012.**
- Dendreon Advisory Meeting: "The oncologist's perspective of Provenge for patients with asymptomatic/minimally symptomatic metastatic castrate-resistant prostate cancer." San Diego, CA. June 15, 2012.
- Dendreon Oncology Summit Advisory Board: "Provenge and the evolving treatment landscape for advanced prostate cancer." San Francisco, CA. June 23, 2012.
- Dendreon Oncology Summit Advisory Board: "Sequencing metastatic castration-resistant prostate cancer treatments of the future." San Francisco, CA. June 23, 2012.
- **University of California Davis 13th Annual Advances in Oncology 2012: "New therapeutic options in advanced castration-resistant prostate cancer." Sacramento, CA. September 22, 2012.**
- SWOG Fall Prostate Cancer Organ Site Meeting: "A randomized phase 2-3 trial of intermittent androgen deprivation therapy using Enzalutamide with a GnRH agonist versus Bicalutamide with a GnRH agonist in patients with non-metastatic castration-sensitive prostate cancer." Chicago, IL. October 19 and 20, 2012.
- SWOG Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." Chicago, IL. October 20, 2012.
- South Texas Comprehensive Cancer Center: "Optimizing care for patients with advanced prostate cancer: evolving targets and emerging treatment paradigms." Corpus Christi, TX. December 4, 2012.
- Hoag Memorial Hospital Oncology Grand Rounds: "Optimizing care for patients with advanced prostate cancer: evolving targets and emerging treatment paradigms." Newport Beach, CA. February 28, 2013.
- Dendreon Oncology Advisory Board Meeting: "Sipuleucel-T and its use in community-based oncology practices." Washington, DC. April 18, 2013.
- SWOG Spring GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. May 2, 2013.
- Medivation Preclinical ASCO Advisory Board Meeting: "The role of SRC in prostate cancer – are there still potential clinical implications?" Chicago, IL. May 30, 2013.
- Dendreon Medical Oncologist Advisory Board: "Early detection of metastatic castration-resistant prostate cancer." Chicago, IL. May 31, 2013.
- Dendreon Medical Oncologist Advisory Board: "Metastatic castration-resistant prostate cancer, a changing landscape." Chicago, IL. May 31, 2013.
- **Genitourinary (Prostate) Cancer Poster Discussion Session: "Prognosis and predication of outcomes in castration-resistant prostate cancer." 2013 American Society of Clinical Oncology, Chicago, IL. June 1, 2013.**
- Janssen Post-ASCO Educational Update Meeting: "Updates on metastatic castration-resistant prostate cancer studies from ASCO 2013." Chicago, IL. June 4, 2013.

- Dendreon: "Cancer immunotherapy – fundamental concepts and emerging role." Las Vegas, NV. July 25, 2013.
- Challenging Cases in Oncology powered by Xcenda: "Case 6 – Advanced prostate cancer prognosis and treatment." Las Vegas, NV. July 27, 2013.
- Challenging Cases in Oncology powered by Xcenda: "Prostate cancer debrief." Las Vegas, NV. July 27, 2013.
- Compass Oncology 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Portland, OR. September 19, 2013.
- Abilene Regional Medical Center 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Abilene, TX. September 24, 2013.
- Mercy Medical Center 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Canton, OH. October 4, 2013.
- SWOG Fall Prostate Cancer Organ Site Meeting: "A randomized phase 2-3 trial of intermittent androgen deprivation therapy using Enzalutamide with a GnRH agonist versus a GnRH agonist alone in patients with non-metastatic castration-sensitive prostate cancer." Chicago, IL. October 11, 2013.
- SWOG Fall GU Committee Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." Chicago, IL. October 11, 2013.
- Myriad Genetics and Laboratories: "Prostate cancer/Prolaris medical oncology advisory board meeting." Salt Lake City, UT. October 19, 2013.
- **18th Brazilian Oncology Conference: "Post-ADT phase 3 clinical evidence: Efficacy of abiraterone acetate." Brasilia, Brazil. October 23, 2013.**
- Janssen Dinner Launch: "Metastatic castration-resistant prostate cancer cases." Brasilia, Brazil. October 24, 2013.
- **Chemotherapy Foundation Symposium: "Novel PET imaging in prostate cancer." New York City, NY. November 8, 2013.**
- St. Lukes Mountain States Tumor Institute 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Boise, ID. November 13, 2013.
- Bergan Mercy Medical Center 2013 Comprehensive Cancer Network: "Integration of novel management strategies for castrate-resistant prostate cancer." Omaha, NE. November 20, 2013.
- Medivation Incorporated: "A randomized phase 2-3 trial of intermittent androgen deprivation therapy using enzalutamide with a GnRH agonist versus a GnRH agonist alone in patients with non-metastatic castration-sensitive prostate cancer." San Francisco, CA. November 22, 2013.
- Elsevier Urology Round Table: "Measuring immune response in men with metastatic castration-resistant prostate cancer." Washington, DC. December 7, 2013.
- Dendreon: "Cancer immunotherapy – fundamental concepts and emerging role." Santa Barbara, CA. December 19, 2013.
- Hoag Memorial Hospital Oncology Grand Rounds: "Integration of novel management strategies for castrate-resistant prostate cancer." Newport Beach, CA. January 23, 2014.
- Dendreon Medical Oncologist Advisory Board: "Cancer immunotherapy – fundamental concepts and emerging role." Santa Barbara, CA. February 6, 2014.
- Dendreon: "Cancer immunotherapy – fundamental concepts and emerging role." Honolulu, HI. February 19, 2014.
- **7th Annual IntraSPORE Prostate Cancer Program Retreat: "Prostate cancer and the clinical sciences – where are we and what we need to do?" Fort Lauderdale, FL. March 17, 2014.**

- St. Lukes Mountain States Tumor Institute: "Overcoming cancer immunoevasion: the role of immunotherapy." Boise, ID. April 3, 2014.
- Dendreon: "Overcoming cancer immunoevasion: the role of immunotherapy." Billings, MT. April 22, 2014.
- SWOG Spring GU Organ Site Working Group Meeting: "A randomized phase 2 study of combined androgen deprivation versus combined androgen deprivation and Cixutumumab (IMC-A12) for patients with new hormone-sensitive metastatic prostate cancer." San Francisco, CA. May 1, 2014.
- Dendreon Junior Faculty ASCO Advisory Meeting: "A new era of immunotherapy in treating prostate cancer." Chicago, IL. May 29, 2014.
- Janssen Post-ASCO 2014 Educational Update Meeting: "Developments in initial treatment approaches for advanced prostate cancer." Chicago, IL. June 3, 2014.
- Dendreon Sales Training Workshop: "Health care provider training for clinical proficiency." Atlanta, GA. June 18, 2014.
- Enzalutamide Medical Advisory Board: "Current clinical practice landscape incorporating ASCO 2014 data and upcoming key clinical trials in prostate cancer." New York, NY. July 26, 2014.
- **Best of ASCO 2014: "Prostate cancer 2014 – Progress! Not progression." Seattle, WA. August 23, 2014.**
- Meet the Expert for Zytiga – a community forum: "The metastatic castration-resistant prostate cancer treatment paradigm: more choices, more questions." Yokohama, Japan. August 27, 2014.
- **52nd Annual Meeting of Japanese Society of Clinical Oncology: "The metastatic castration-resistant prostate cancer treatment paradigm: more choices, more questions." Yokohama, Japan. August 28, 2014.**
- Meet the Expert for Castration-Resistant Prostate Cancer – an academician forum: "The metastatic castration-resistant prostate cancer treatment paradigm: more choices, more questions." Yokohama, Japan. August 29, 2014.
- Challenging Cases in Prostate Cancer powered by Xcenda: "The metastatic castration-resistant prostate cancer smorgasbord." Las Vegas, NV. September 19, 2014.
- Regional Summit on Practical and Emerging Agents in Prostate Cancer: "Immunotherapy approaches to prostate cancer." New York, NY. October 4, 2014.
- **15th Annual Meeting of the Society of Urologic Oncology: "Prostate cancer sequencing prior to chemotherapy." Bethesda, MA. December 5, 2014.**
- **University of Chicago: "Immunotherapy for genitourinary malignancies." Chicago, IL. December 18, 2014.**
- Elmhurst Memorial Clinic: "Overcoming cancer immunoevasion: the role of immunotherapy." Elmhurst, IL. December 18, 2014.
- Tolmar Advisory Council Meeting: "Maximal castration for advanced prostate cancer? Correlations between testosterone levels and outcomes." San Diego, CA. January 9, 2015.
- Regional Summit on Practical and Emerging Agents in Prostate Cancer: "Sipuleucel-T: Current status and optimal patient selection." Dallas, TX. January 17, 2015.
- Rocky Mountain Cancer Center Boulder: "Overcoming cancer immunoevasion: the role of immunotherapy." Boulder, CO. February 5, 2015.
- Dendreon: "Overcoming cancer immunoevasion: the role of immunotherapy." Denver, CO. February 5, 2015.
- The Urology Center of Colorado: "Immunotherapy for bladder cancer." Denver, CO. February 6, 2015.

- **2015 Genitourinary Cancers Symposium, General Session II: Evolving role of multimodality treatment in low volume hormone-sensitive metastatic disease: "Selection of systemic therapy: Chemotherapy and androgen axis agents." Orlando, FL. February 26, 2015.**
- PeerView Live CME: Clinical challenges in castration-resistant prostate cancer - How to choose the right treatment for the right patient at the right time: "Current and future directions with hormone therapy in prostate cancer." Orlando, FL. February 27, 2015.
- **University of Texas Houston: "Overcoming cancer immunoevasion: the role of immunotherapy." Houston, TX. March 16, 2015.**
- **University of Arizona Oncology Grand Rounds: "Clinical research in prostate cancer – exploring the castration-sensitive disease state." Tucson, AZ. March 27, 2015.**
- Genentech Bladder Cancer Steering Committee: "Urothelial bladder cancer disease states education." Dallas, TX. April 17, 2015.
- Dendreon Advisory Meeting – Integrating Leading-Edge Data Into Prostate Cancer Treatment and Research: "Impact of recent data on treatment considerations in prostate cancer: Resistance to androgen-targeted agents." Chicago, IL. May 28, 2015.
- Dendreon Advisory Meeting – Integrating Leading-Edge Data Into Prostate Cancer Treatment and Research: "Antigen spread following sipuleucel-T treatment." Chicago, IL. May 28, 2015.
- Peerview Live CME – Applying the Latest Evidence to Treatment Decisions in CRPC: Real Cases, Difficult Choices – You Make the Call: "Management options for previously treated metastatic CRPC: Latest data and considerations." Chicago, IL. May 29, 2015.
- Urologic Oncology Summit: "Castration-resistant prostate cancer: Biology and definitions." Panama City, Panama. June 27, 2015.
- Urologic Oncology Summit: "An overview of non-metastatic (M0) castration-resistant prostate cancer." Panama City, Panama. June 27, 2015.
- Urologic Oncology Summit: "Placing the evidence together in metastatic castration-resistant prostate cancer: Sequencing, combination?" Panama City, Panama. June 27, 2015.
- Urologic Oncology Summit: "Panel discussion: Special clinical scenarios for advanced prostate cancer." Panama City, Panama. June 27, 2015.
- Urologic Oncology Summit: "Role of docetaxel in the management of castration-sensitive prostate cancer." Panama City, Panama. June 27, 2015.
- 6th International Pacrim Breast and Prostate Cancer Meeting: PET imaging in prostate cancer: Research tool of standard clinical practice?" Stevenson, WA. July 21, 2015.
- Enzalutamide Medical Advisory Board: "ASCO 2015 data review." New York, NY. July 31, 2015.
- 3rd Annual International Conferences on Advances in Hematology and Oncology: "Metastatic prostate cancer – Management in the era of novel agents." Coeur d'Alene, ID. August 29, 2015.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Portland, OR. November 10, 2015.
- Janssen West Community Oncology Advisory Board Meeting: "Data review of abiraterone and enzalutamide, clinical sequencing and future directions in prostate cancer." Los Angeles, CA. November 11, 2015.
- **16th Annual Meeting of the Society of Urologic Oncology: "Clinical implications of genomics in treating prostate cancer." Washington, DC. December 3, 2015.**
- Merck Genitourinary Oncology Global Advisory Board Meeting: "Current treatment options for metastatic castration-resistant prostate cancer and potential role for checkpoint inhibitors in the future." Barcelona, Spain. January 29, 2016.
- Merck Genitourinary Oncology Global Advisory Board Meeting: "Update on checkpoint inhibitor data in bladder cancer." Barcelona, Spain. January 29, 2016.

- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Irvine, CA. March 10, 2016.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Anchorage, AK. March 16, 2016.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Phoenix, AZ. March 24, 2016.
- Florida Society of Clinical Oncology (FLASCO) Spring Session: "Sequencing agents in metastatic prostate cancer." Kissimmee, FL. April 9, 2016.
- Seattle Cancer Care Alliance 1st Comprehensive Cancer Update: "Treatment decision making for patients with metastatic prostate cancer." Honolulu, HI. April 16, 2016.
- Seattle Cancer Care Alliance 1st Comprehensive Cancer Update: "Bladder cancer – Major advancements coming soon." Honolulu, HI. April 16, 2016.
- Seattle Cancer Care Alliance 1st Comprehensive Cancer Update: "Testicular cancer – Winning the ball game." Honolulu, HI. April 16, 2016.
- Bayer West Area Meeting: "Metastatic castration-resistant prostate cancer overview." Phoenix, AZ. April 28, 2016.
- Genentech Educational Presentation: "The PD-L1 pathway in cancer immune evasion." Oxnard, CA. May 24, 2016.
- Bayer Corporation: "Post-ASCO 2016 Point of View." Global Webex. June 23, 2016.
- 4th Annual Canadian Urological Association and Canadian Urologic Oncology Group Multidisciplinary Meeting: "The promise of checkpoint inhibitors in urothelial cancer." Vancouver, BC, Canada. June 25, 2016.
- Janssen Medical Oncology Advisory Board: "Janssen oncology clinical development program in genitourinary malignancies." Chicago, IL. July 14, 2016.
- Genentech Lung and Urothelial Cancer Advisory Board: "Atezolizumab in urothelial cancer." Seattle, WA. July 16, 2016.
- **Best of ASCO 2016: "Genitourinary (Non-prostate) Cancer." San Diego, CA. August 13, 2016.**
- 4th Annual International Conferences on Advances in Hematology and Oncology: "Choices and decisions in metastatic prostate cancer." Coeur d'Alene, ID. August 14, 2016.
- **American Urological Association Advanced Prostate Cancer: Managing the Spectrum of Disease Symposium: "Comorbidities and side effect profiles: Considerations for various castration-resistant prostate cancer therapeutic strategies." Chicago, IL. September 24, 2016.**
- Merck KEYNOTE-365 Investigator Meeting: "Metastatic castration-resistant prostate cancer overview, current treatment and future directions." Baltimore, MD. October 20, 2016.
- 3rd Annual Summit on Genitourinary Malignancies: "Identifying prostate cancer patients for immunotherapy approaches." New York, NY. October 23, 2016.
- prIME Oncology, 2nd Annual West Cancer Center Oncology Conference, Collaboration for the Future Cure – Precision Medicine and Immuno-Oncology: "Immunotherapy in genitourinary cancers: The new frontier." Memphis, TN. November 18, 2016.
- **17th Annual Meeting of the Society of Urologic Oncology: "Immunotherapy for prostate cancer: What is the way forward?" San Antonio, TX. December 2, 2016.**
- **American Urological Association Advanced Prostate Cancer: Managing the Spectrum of Disease Symposium: "Comorbidities and side effect profiles: Considerations for various castration-resistant prostate cancer therapeutic strategies." Washington, DC. December 10, 2016.**
- **Society of Government Service Urologists – 2017 Kimbrough Urological Seminar: "Considerations for the symptomatic metastatic castration resistant prostate cancer patient: Beyond Abiraterone and Enzalutamide." San Diego, CA. January 14, 2017.**

- Annenberg Center for Health Sciences CME: Experts in Residence – "Bridging the gap from knowledge to practice in castration-resistant prostate cancer." Cancer Treatment Centers of America, Zion, IL. January 27, 2017.
- St. Lukes Mountain States Tumor Institute - Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Boise, ID. February 7, 2017.
- Targeted Oncology Case-Based Peer Perspectives: "Immunotherapy in advanced bladder cancer." Orlando, FL. February 24, 2017.
- Annenberg Center for Health Sciences CME: Experts in Residence – "Bridging the gap from knowledge to practice in castration-resistant prostate cancer." Beaumont Hospital, Royal Oak, MI. March 7, 2017.
- Annenberg Center for Health Sciences CME: Experts in Residence – "Bridging the gap from knowledge to practice in castration-resistant prostate cancer." Summerlin Hospital, Las Vegas, NV. March 14, 2017.
- Bayer Pharmaceuticals - Meet the Professor: "Overview of data related to sequential use of novel hormonal therapies in metastatic castration-resistant prostate cancer." Hanover, NJ. March 24, 2017.
- Hawaii Pacific Health - Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Honolulu, HI. April 10, 2017.
- SWOG Spring GU Organ Site Working Group Meeting: "Combination immune-oncology therapeutics in metastatic castration-resistant prostate cancer." San Francisco, CA. April 28, 2017.
- **American Urological Association 2017 Castration-Resistant Prostate Cancer Live Forum for Residents & Fellows: "Role of chemotherapy for metastatic castration-resistant prostate cancer." Boston, MA. May 11, 2017.**
- **PROSPECT 2017 Symposium Keynote Presentation: "What's hot in advanced prostate cancer today?" Melbourne, Australia. May 19, 2017.**
- **PROSPECT 2017 Symposium Diagnosis, Staging and Management of Locally Advanced Prostate Cancer: "Advances in imaging and implications for treatment of oligometastatic disease." Melbourne, Australia. May 20, 2017.**
- **PROSPECT 2017 Symposium Sequencing in Advanced Prostate Cancer – Current Therapies: "Therapeutic sequencing in metastatic castration-resistant prostate cancer." Melbourne, Australia. May 20, 2017.**
- **PROSPECT 2017 Symposium Rapid Fire Multidisciplinary Cases: "Case – sequencing in metastatic castration-resistant prostate cancer." Melbourne, Australia. May 20, 2017.**
- **PROSPECT 2017 Symposium A Look to the Future – Personalised and Supportive Care in Advanced Prostate Cancer: "High-risk non-metastatic (M0) castration-resistant prostate cancer – an evolving landscape." Melbourne, Australia. May 20, 2017.**
- Denali Oncology Group's 34th Educational Program Oncology in the Last Frontier: "Comorbidities and side effects and their effect on how we use therapeutic agents for advanced prostate cancer." Barrow, AK. June 24, 2017.
- Denali Oncology Group's 34th Educational Program Oncology in the Last Frontier: "Considerations with next generation sequencing results and precision medicine in prostate cancer." Barrow, AK. June 24, 2017.
- Bozeman Health - Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Bozeman, MT. July 6, 2017.
- 5th Annual International Conferences on Advances in Hematology and Oncology: "Metastatic prostate cancer: How to sequence newer agents." Coeur d'Alene, ID. August 12, 2017.
- 18th Future Directions in Urology Symposium: "Updates on use of radiopharmaceuticals in prostate cancer clinical trials." Colorado Springs, CO. August 22, 2017.

- **American Urological Association 2017 Castration-Resistant Prostate Cancer Live Forum for Residents & Fellows: "Role of chemotherapy for metastatic prostate cancer." Dallas, TX. September 9, 2017.**
- **American Urological Association Practical Management of Metastatic Prostate Cancer: Guidelines and Beyond: "Comorbidities and side effect profiles: Considerations for various castration-resistant prostate cancer therapeutic strategies." Dallas, TX. September 10, 2017.**
- **American Urological Association Practical Management of Metastatic Prostate Cancer: Guidelines and Beyond: "Future directions in systemic therapy for prostate cancer." Dallas, TX. September 10, 2017.**
- **University of Utah/Huntsman Cancer Institute - Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Salt Lake City, UT. September 28, 2017.**
- Urological Oncology Committee of Taiwan Urological Association Preceptorship: "Novel therapies for the management of advanced prostate cancer." Taipei, Taiwan. October 14, 2017.
- Bayer Taiwan and Southeast Asia Advisory Meeting: "Real life experience with Radium-223 and new clinical evidence." Taipei, Taiwan. October 15, 2017.
- Bayer Taiwan and Southeast Asia Advisory Meeting: "Insights from evaluation criteria to treatment outcomes of Radium-223." Taipei, Taiwan. October 15, 2017.
- **American Urological Association 2017 Castration-Resistant Prostate Cancer Live Forum for Residents & Fellows: "Role of chemotherapy for metastatic prostate cancer." Los Angeles, CA. October 28, 2017.**
- **American Urological Association Practical Management of Metastatic Prostate Cancer: Guidelines and Beyond: "Comorbidities and side effect profiles: Considerations for various castration-resistant prostate cancer therapeutic strategies." Los Angeles, CA. October 29, 2017.**
- **American Urological Association Practical Management of Metastatic Prostate Cancer: Guidelines and Beyond: "Future directions in systemic therapy for prostate cancer." Los Angelese, CA. October 29, 2017.**
- Cancer Immunotherapy Trials Network Annual Meeting: "A randomized phase 2 study of atezolizumab plus recombinant human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma." National Harbor, MD. November 9, 2017.
- Remedica Medical Education and Publishing CME: "P3 – Patient selection and Practice in Prostate cancer." Summerlin Hospital, Las Vegas, NV. November 27, 2017.
- Purdue University PeerView CME: "Candid conversations in prostate cancer: State of the science and implications for improving patient care and outcomes." VA Southern Nevada Health Care System, Las Vegas, NV. December 19, 2017.
- Annenberg Center for Health Sciences CME: "Optimizing patient outcomes in castration-resistant prostate cancer: Moving urologists from knowledge to action." Holy Cross Hospital (Sinai Health System), Chicago, IL. February 28, 2018.
- Merck/MSD Prostate Cancer Global Advisory Board: "PARP inhibition and DNA repair deficiency in metastatic castration-resistant prostate cancer." San Francisco, CA. May 17, 2018.
- **Society for Basic Urology Research (SBUR)/Suociety of Urologic Oncology (SUO) Joint Meeting at the American Urological Association Annual Meeting: "Treatment of cisplatin-ineligible muscle-invasive bladder cancer patients." San Francisco, CA. May 19, 2018.**
- Onclive 2018 State of the Science: Genitourinary Cancers: "Treatment intensification for castration-sensitive prostate cancer." Salt Lake City, UT. May 24, 2018.

- **Huntsman Cancer Institute Genitourinary Oncology Symposium:** "Future of immuno-oncology in prostate cancer." Huntsman Cancer Institute/University of Utah, Salt Lake City, UT. May 25, 2018.
- Peerview Live CME – Newest Advances and Strategies in Prostate Cancer – Science and Stories on the Evolving Treatment Landscape and Implications for Patient Cancer: "DNA repair deficiency and implications for men with prostate cancer." Chicago, IL. June 1, 2018.
- **Education Session, Role of Precision Therapy in the Treatment of Advanced Urothelial Cancer: "Targeted therapies in advanced urothelial cancer." 2018 American Society of Clinical Oncology, Chicago, IL. June 4, 2018.**
- Annenberg Center for Health Sciences CME: "Optimizing patient outcomes in castration-resistant prostate cancer: Moving urologists from knowledge to action." North Side Hospital, Atlanta, GA. June 14, 2018.
- 6th Annual International Conferences on Advances in Hematology and Oncology: "Prostate cancer: Optimizing the use of newer agents." Coeur d'Alene, ID. August 5, 2018.
- 19th Future Directions in Urology Symposium: "Next generation anti-androgen therapies." Colorado Springs, CO. August 13, 2018.
- 19th Future Directions in Urology Symposium: "Next generation advanced and endocrine refractory prostate cancer." Colorado Springs, CO. August 14, 2018.
- Prostate Cancer Research Institute (PCRI) 2018 Prostate Cancer Patient Conference: "Pills, immune boosters & radiopharmaceuticals for prostate cancer treatment: Who, Where, When, How and Now?!" Los Angeles, CA. September 8, 2018.
- Singapore Urological Association: "Targeted alpha therapy in metastatic castration-resistant prostate cancer: Dawn or Dusk" Singapore. September 25, 2018.
- Asia-Pacific Metastatic Castration-Resistant Prostate Cancer Expert Exchange Summit: "Optimizing survival in metastatic castration-resistant prostate cancer: Radium-223 and its place in treatment plans: Clinician's perspective." National Cancer Center, Singapore. September 26, 2018.
- National University Hospital: "Targeted alpha therapy in metastatic castration-resistant prostate cancer: Dawn or Dusk" Singapore. September 27, 2018.
- Prostate Cancer Academy: "Role of androgen receptor blockers in advanced prostate cancer." Los Angeles, CA. October 13, 2018.
- Prostate Cancer Academy: "Role of chemotherapy and radiopharmaceuticals in the management and treatment of advanced prostate cancer." Los Angeles, CA. October 13, 2018.
- ESMO Satellite Symposium – Checkpoint inhibition in the treatment of cancer: Building the new standard of care across multiple solid tumors: "Checkpoint inhibition for the treatment of genitourinary cancers." Munich, Germany. October 19, 2018.
- Cancer Immunotherapy Trials Network Annual Meeting: "A randomized phase 2 study of atezolizumab plus recombinant human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma." Washington, DC. November 7, 2018.
- Windsor Regional Cancer Centre: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Windsor, ON, Canada. November 13, 2018.
- Ottowa Dinner Round: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Ottowa, ON, Canada. November 13, 2018.
- **Juravinski Cancer Centre Grand Rounds: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Hamilton, ON, Canada. November 14, 2018.**
- Sherbrooke Dinner Rounds: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Montreal, QC, Canada. November 14, 2018.

- **Princess Margaret Cancer Centre Grand Rounds: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Toronto, ON, Canada. November 15, 2018.**
- Greater Toronto Area Dinner Rounds: "Integrating immune-oncology within the current treatment of advanced urothelial carcinoma." Etobicoke, ON, Canada. November 15, 2018.
- Radium-223 dichloride Oncology Hospital Advisory Board: Management and unmet needs in metastatic castration-resistant prostate cancer: Radium-223 new clinical trials data. Dallas, TX. December 8, 2018.
- Peerview Live CME – Unraveling the Complexities of Prostate Cancer Management – Focus on Therapeutic Decisions for Early-Stage Disease and the Implications for Later-Stage Disease: "Androgen-targeting therapy in nonmetastatic (M0) castration-resistant prostate cancer." San Francisco, CA. February 15, 2019.
- **44th Annual UCLA State of the Art Urology Conference: "Late breaking news – treatment of oligometastatic prostate cancer." Marina Del Rey, CA. March 9, 2019.**
- **44th Annual UCLA State of the Art Urology Conference: "Pragmatic sequencing therapy for castrate resistant prostate cancer." Marina Del Rey, CA. March 9, 2019.**
- **44th Annual UCLA State of the Art Urology Conference: "Making the immune system work for the urologist." Marina Del Rey, CA. March 9, 2019.**
- Enfortumab Vedotin Community Advisory Board: "Metastatic urothelial cancer community patient profile." Dallas, TX. March 15, 2019.
- Enfortumab Vedotin Community Advisory Board: "Potential future treatment options for metastatic urothelial carcinoma." Dallas, TX. March 15, 2019.
- **Food & Drug Administration Mini-Symposium on Pathologic Complete Response in Bladder Cancer: "Clinical restaging in muscle-invasive bladder cancer – How do we do it and what does it mean?"** Silver Spring, MD. March 27, 2019.
- Annenberg Center for Health Sciences CME: "Optimizing patient outcomes in castration-resistant prostate cancer: Moving urologists from knowledge to action." Eisenhower Medical Center, Rancho Mirage, CA. March 28, 2019.
- Bayer Pharmaceuticals - Meet the Professor: "Earlier use of novel hormones for advanced prostate cancer and impact on the metastatic castration-resistant prostate cancer population." Hanover, NJ. April 4, 2019.
- Merck Pharmaceuticals – Prostate Program Phase III Studies Investigator Meeting Series: "KEYNOTE-365 Cohort A: Pembrolizumab plus olaparib in docetaxel-pretreated patients with metastatic castrate-resistant prostate cancer." Jersey City, NJ. April 12, 2019.
- **American Urological Association 2019 Evolving Role of the Urologist in Metastatic and Castration Resistant Prostate Cancer: A Guidelines and Case-Based Discussion: "Role of chemotherapy, treatment sequencing and future approaches." Chicago, IL. May 2, 2019.**
- Peerview Live CME – New Concepts in Prostate Cancer – What Oncologists Need to Know to Optimize Patient Outcomes: "Non-metastatic castration resistant prostate cancer." Chicago, IL. June 1, 2019.
- **Education Session Genitourinary (Non-prostate) Cancer – Formidable Scenarios in Urothelial and Variant Cancers of the Urinary Tract: "Cisplatin-ineligible patients with urothelial carcinoma – medical oncology perspective." 2019 American Society of Clinical Oncology Annual Meeting. Chicago, IL. June 2, 2019.**
- Washington State Urology Association Annual Conference: "Unraveling the complex treatment landscape of prostate cancer – Guidance for delivering evidence-based, patient-centered care." Leavenworth, WA. June 22, 2019.
- ASCO Direct Highlights – 2019 Official Annual Meeting Review: "Genitourinary cancers – The advances continue." New York, NY. July 19, 2019.

- FDA – Bladder Cancer Advocacy Network Workshop: "Clinical restaging in muscle-invasive bladder cancer – How do we do it and what does it mean?" Washington, DC. August 8, 2019.
- Clovis Prostate Cancer Clinical Immersion: "Biochemically-recurrent prostate cancer and implifcations of next generation PET imaging." Boulder, CO. August 27, 2019.
- Clovis Prostate Cancer Clinical Immersion: "Advanced prostate cancer and treatment sequencing." Boulder, CO. August 27, 2019.
- Clovis Prostate Cancer Clinical Immersion: "Prostate cancer biology, mechanisms of castration-resistance and drug-resistance." Boulder, CO. August 27, 2019.
- Prostate Cancer Academy: "Role of androgen receptor blockers in advanced prostate cancer." Los Angeles, CA. September 21, 2019.
- Prostate Cancer Academy: "Role of chemotherapy and radiopharmaceuticals in the management and treatment of advanced prostate cancer." Los Angeles, CA. September 21, 2019.

UNIVERSITY OF WASHINGTON **September 16, 2019**
SCHOOL OF MEDICINE

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 (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 Member, Clinical Research Division, Fred Hutchinson Cancer
Research Center, Seattle, WA

5. Hospital Positions Held:

03/2014-present Attending Physician, Genitourinary Oncology Clinics.
Seattle Cancer Care Alliance, Seattle, WA

03/2014-present Attending Physician, Bladder Multidisciplinary Clinic, 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

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 Faculty for Hematology/Oncology fellows, Internal Medicine residents and medical students in Genitourinary Oncology Outpatient and Bladder Multidisciplinary Clinics and Inpatient Solid Tumor service.

2017 Mentor for NCI Fogarty International Center Fellow Candidate, Paul Katangole, MD, MS (Uganda Cancer Institute): "Role of Prostate Cancer Antigen 3 in predicting prostate biopsy outcome in Ugandan Men"

2018-present Primary research mentor for Hematology/Oncology fellow, Alexandra Sokolova, MD

2018-2019 Research mentor for UWSOM MS1 Darren Pouv, Independent Investigative Inquiry (III).

2019-present Hematology/Oncology fellowship faculty champion for outpatient Genitourinary Oncology Block

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

Invited Local/Regional Talks:

07/15/2012 *Circulating microRNA Biomarkers in Prostate Cancer*. Oral presentation for Department of Defense/Prostate Cancer Clinical Trials Consortium. Oral presentation, teleconferenced nationally, based at Memorial Sloan Kettering Cancer Center, New York, NY

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, based at Memorial Sloan Kettering Cancer Center, New York, NY

04/12/2014 *Circulating Biomarkers in Advanced Disease***.** Institute for Prostate Cancer Research 2014 Symposium, Fred Hutchinson Cancer Research Center, Seattle, WA.

05/01/2014 *Comparison of plasma microRNAs with CTCs and PSA in patients treated on SWOG S0925.* Oral presentation at 2014 Spring SWOG Genitourinary Working Group Meeting, San Francisco, CA

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

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.

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

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

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

05/07/2015 *Prostate Cancer: Progress Made and Research in Progress.* Research Matters Series, Seattle Cancer Care Alliance, Seattle, WA

03/24/2016 *Leveraging DNA Repair Defects for Treatment of Prostate Cancer.* PPCR SPORE Seminar Series, Fred Hutchinson Cancer Research Center, Seattle, WA

06/29/2016 *Emerging Therapies in Cancer: Cancer Genetics.* Seattle Cancer Care Alliance CME lecture for Skagit Valley Hospital, Mount Vernon, WA

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

10/27/2016 *Prostate Cancer Foundation Women's Networking Forum*. Junior Investigator Panelist at the 2016 Prostate Cancer Foundation Retreat, Carlsbad, CA

11/17/2016 *Prostate Cancer Genetics: Leveraging Family Traits for Early Detection***.** Fred Hutchinson Cancer Research Center Innovators Network. Seattle, WA

12/23/2016 *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.

03/18/2017 *Inherited Risk and Prostate Cancer Behavior.* Prostate Cancer Symposium, Institute for Prostate Cancer Research; Fred Hutchinson Cancer Research Center, Seattle, WA

04/13/2017 *Metastatic Prostate Cancer*. Cases From Kampala, hosted by Uganda Cancer Institute/Hutchinson Cancer Center Alliance; WebEx between Seattle, WA, U.S.A and Kampala, Uganda

05/24/2017 *Prostate Cancer Genetics.* UsTOO Greater Seattle Area Prostate Cancer Patient Support Group; Greenwood Community Center, Seattle, WA.

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

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

11/06/2017 *Genetics and Genomics.* CCSG Prostate Program Cancer Retreat, Fred Hutchinson Cancer Research Center, Seattle, WA

01/19/2018 *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.

01/26/2018 *Expanding Clinical and Research Horizons in Prostate Cancer Genetics.* UW Medical Genetics Division Grand Rounds, Seattle, WA

02/01/2018 *Genetic Testing for Men with Metastatic Prostate Cancer: Changing Landscape and the GENTleMEN Study.* PPCR SPORE Seminar Series, Fred Hutchinson Cancer Research Center, Seattle, WA

03/08/2018 *Precision Medicine for Older Adults: Delivering on a Promise*. Plein Research Symposium in Geriatric Pharmacy, Center for Urban Horticulture, University of Washington, Seattle, WA

04/28/2018 *Inherited Risk and GENTleMEN.* Prostate Cancer Symposium, hosted by the Institute for Prostate Cancer Research; Fred Hutchinson Cancer Research Center, Seattle, WA

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

05/07/2018 *Prostate Cancer: Screening, Treatment and Genetics.* UW Internal Medicine Residents Report, University of Washington Medical Center, Seattle, WA

05/23/2018 *Prostate Cancer Genetics and the GENTleMEN Study*. CCSG Breast and Ovary Cancer Research Program Retreat, Fred Hutchinson Cancer Research Center, Seattle, WA

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

07/17/2018 *Molecular Predictors of Prostate Cancer Progression and Mortality.* PNW SPORE Symposium, Fred Hutch Cancer Research Center, Seattle, WA

08/09/2018 *Prostate Cancer Genetics and the GENTleMEN Study*. Overbaugh Lab 30th Year Symposium Retreat, Islandwood, Bainbridge Island, WA

10/05/2018 *Testicular Cancer/Germ Cell Tumors*. UW/Fred Hutch Hematology/Oncology Fellows Lecture Series, Seattle, WA.

10/12/2018 *Prostate Cancer.* Transitions in Oncology Care: Pearls for the Primary Care Provider Conference, Talaris Conference Center, Seattle, WA.

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

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 Hutchinson Cancer Research Center, Seattle, WA

09/06/2019 *Germline and Somatic DNA repair mutations in Prostate Cancer.* Genitourinary Medical Oncology Research Team Staff Education Series; Fred Hutchinson Cancer Research Center, Seattle, WA

09/06/2019 *Updates in Prostate Cancer Genetics.* Seattle Cancer Care Alliance Community Site Dinner Clinical Research Partnership Series; Seattle, WA

12. Editorial Responsibilities:

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

13. Special National Responsibilities:

June 2017 Coffey-Holden Prostate Cancer Academy*, Organizing Chair, Carlsbad, CA (*prestigious, invitation-only annual meeting for ~75 prostate cancer researchers; Prostate Cancer Foundation)

June 2017- Prostate Cancer Clinical Trials Consortium/PCF Genetics Working Group, Chair

July 2017-2018 Prostate Cancer Foundation DNA Repair Working Group, Co-Leader

October 2017 Prostate Cancer Foundation 24th Scientific Retreat, Session Chair, DNA Repair, Washington D.C.

February 2018 Prostate Cancer Foundation Delegation on Prostate Cancer Genetics, Tel Aviv, Israel.

June 2018 American Society for Clinical Oncology, 2018 Annual Meeting Education Session Chair, Practical Methods for Integrating Genetic Testing into Clinical Practice for Advanced Prostate Cancer, Chicago, IL

August 2019- National Comprehensive Cancer Network (NCCN) Prostate Cancer Guidelines Panel, Member

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

15. Research Funding

Current Research Support

Title: Genitourinary Cancer Clinical Research Database Support
Supporting Agency: Institute for Prostate Cancer Research (IPCR)
Performance Period: 09/01/14 – 12/30/19
Level of Funding: $470,000
Project Goals: The GU Cancer Clinical Research Database (GUCCRD) is designed to inventory, display, aggregate, and integrate comprehensive clinical information derived from patients with prostate cancer (and potentially other GU malignancies).

Title: 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 – 11/30/19
Level of Funding: $58,000
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
Performance Period: 12/28/16 – 12/27/20
Level of Funding: $50,000
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: Pharmacogenetic dissection of protein synthesis control across the spectrum of PI3K pathway mutations in prostate cancer
Supporting Agency: Movember Foundation & Prostate Cancer Foundation (2016CHAL1523)
Performance Period: 10/01/16 – 09/30/18
Level of Funding: $500,000
Project Goals: The major goal of this project is to delineate the biology of various PI3K pathway mutations that occur in CRPC and develop strategies to effectively target tumors harboring these mutations.

Title: A phase 1b study of enzalutamide plus CC-115 in men with castration-resistant prostate cancer
Supporting Agency: PCCTC, LLC (Celgene)
Performance Period: 10/01/17 – 10/31/2020
Level of Funding: $120,000
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: 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: 11/01/17 – 10/31/20
Level of Funding: $250,000
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: 10/01/18 – 09/30/21
Role: Co-Investigator
Level of Funding: $701,735 Direct Costs, 0.24 Calendar Months
Project Goals: 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, then implement the assay in 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: 08/15/18 – 08/14/21
Role: Co-Investigator
Level of Funding: $650,818 Direct Costs, 0.60 Calendar Months
Project Goals: To determine if germline and somatic aberrations in homologous recombination DNA repair pathways associate with responses to FDA-approved therapeutics in men with mCRPC.

Title: *Telehealth to Reduce Prostate Cancer Burden in Rural Underserved Communities*
Supporting Agency: Cancer Center Support Grant
Performance Period: 7/1/2018 – 6/30/2019
Level of Funding: $80,000 Direct Costs
Role: Co-Investigator

Title: *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: $720,000 Direct Costs
Role: Co-Investigator

Pending Research Support

Title: *PROMISE Registry: A Prostate Cancer Registry of Outcomes and Germline Mutations for Improved Survival and Treatment Effectiveness*
Supporting Agency: ACT/Brown
Role: Co-Primary Investigator

Title: *Enhanced Genetic Awareness and Genetic Evaluation for Men Through Technology - The ENGAGEMENT Study*
Supporting Agency: DOD
Role: Co-Investigator

Title: *Enhanced Genetic Awareness and Genetic Evaluation for Men Through Technology - The ENGAGEMENT Study*
Supporting Agency: PCF
Role: Co-Investigator

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); **$48,022**. 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); **$92,000**. 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); **$30,000.** Goal: to identify the underlying genetic cause in some hereditary prostate cancer families
2014-2017	CCSG: New Investigator Award; NIH/NCI (P30 CA015704); **$60,000.** 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; **$40,000.** 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; **$720,000**. 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; **$250,000**. 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**: $100,000**. 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.

16. Bibliography:

h-index: 17
i10-index: 23
Cumulative citations: 4,289 *(as of 9/07/2019)*

a) Publications in Refereed Journals

1. Pöpperl H, Rikhof H, **Cheng H**, Haffter P, Kimmel CB, Moens CB. lazarus is a novel pbx gene that globally mediates hox gene function in zebrafish. Molecular Cell. 2000 Aug; 6(2): 255-267. [**original work**]

2. Lauring, A.S., **Cheng, H.H.**, Eiden, M.V., and Overbaugh, J. Genetic and biochemical analyses of receptor and cofactor determinants for T-cell-tropic feline leukemia virus infection. Journal of Virology. 2002 Aug; 76(16): 8069-8078. [**original work**]

3. **Cheng, H.H**., Anderson, M.M., Hankenson, F.C., Johnston, L., Kotwaliwale, C.V., Overbaugh, J. Envelope determinants for dual-receptor specificity in feline leukemia virus subgroup A and T variants. Journal of Virology. 2006 Feb; 80(4): 1619-1628. [**original work**]

4. **Cheng, H.H.**, Anderson, M.M., Overbaugh, J. Feline Leukemia Virus T entry is dependent on both expression levels and specific interactions between cofactor and receptor. Virology. 2007 Mar; 359(1): 170-178. [**original work**]

5. Pritchard, C.C., **Cheng, H.H.**, Tewari, M. MicroRNA Profiling: approaches and considerations. Nature Reviews Genetics. 2012 Apr 18; 13(5): 358-69. **[review]**

6. **Cheng, H.H.,** Lin, D., Yu, E.Y. Advanced Clinical States in Prostate Cancer. Urologic Clinics of North America. 2012 Nov;39 (4):561-71. **[review]**

7. ****Cheng, H.H.,** Yi, H.S., Kim, Y., Kroh, E., Goodman, M., Chien, J., Tait, J.F., Tewari, M., Pritchard, C.C. Plasma processing conditions substantially influence circulating microRNA biomarker levels, PLoS ONE 2013 Jun 7;8(6). [**original work**] ***One of the top 1% of most highly cited articles in PLoS ONE.***

8. **Cheng, H.H.,** Mitchell, P.S., Kroh, E., Dowell, A.E., Chéry, L., Siddique J., Nelson, P.S., Vessella, R., Knudsen, B.S., Chinnaiyan, A.M., Pienta, K.J., Morrissey, C., Tewari, M. Circulating microRNA Profiling Identifies a Subset of Metastatic Prostate Cancer Patients with Evidence of Cancer-Associated Hypoxia, PLoS ONE, 2013 Jul 30;8(7). [**original work**]

9. Lee, F., Harris, W.P., **Cheng, H.H.**, Shenoi, J., Zhao, S., Wang, J., Champion, T., Izard, J., Gore, J.L., Porter, M.P., Yu, E.Y., Wright, J.L. Pathologic Response Rates of Gemcitabine/Cisplatin VS. Methotrexate/Vinblastine/Adriamycin/Cisplatin Neoadjuvant Chemotherapy for Muscle Invasive Urothelial Bladder Cancer. Advances in Urology, 2013; 2013:317190. [**original work**]

10. Mossanen, M., Lee, F., **Cheng, H.H.**, Harris, W., Shenoi, J., Zhao, S., Wang, J., Champion, T., Izard, J., Gore, J.L., Porter, M.P., Yu, E.Y., Wright, J.L. Non-Response to Neoadjuvant Chemotherapy for Muscle Invasive Urothelial Cell Carcinoma of the Bladder. Clinical Genitourinary Cancer, 2013 Nov 12. [**original work**]

11. James, A.C., Lee, F.C., Izard, J.P., Harris, W.P., **Cheng, H.H.,** Zhao, S., Gore, J.L., Lin, D.W., Porter, M.P., Yu, E.Y., Wright, J.L. Role of maximal endoscopic resection prior to cystectomy for invasive urothelial bladder cancer. Clinical Genitourinary Cancer, 2014 Jan 23. [**original work**]

12. Montgomery, R.B., **Cheng, H.H.,** Drechsler, J., Mostaghel, E.A. Glucocorticoids and prostate cancer treatment: Friend or foe? Asian Journal of Andrology, 2014 Mar 7. **[review]**

13. **Cheng, H.H.** and Higano. C.S. Targeting the AR signaling axis: how low to go? Oncology, 2014 Aug 15. **[editorial]**

14. Ramos, J.D., **Cheng, H.H.,** Yu, E.Y. Long-term survival in bone-predominant metastatic urothelial carcinoma. Clinical Genitourinary Cancer, 2014 Jul 23. **[case report]**

15. Chevillet, J.R., Kang, Q., Ruf, I.K., Briggs, H.A., Vojtech, L.N., Hughes, S.M., **Cheng, H.H.**, Arroyo, J.D., Knouf, E.C., Gallichotte, E.N., Pogosova-Agadjanyan, E.L., Vessella, R.L., Stirewalt, D.L., Hladik, F., Yu, E.Y., Higano, C.S., Tewari, M. Quantitative and stoichiometric analysis of the microRNA content of exosomes, PNAS, 2014 Oct 14. **[original work]**

16. **Cheng, H.H.,** 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.***

21. **Cheng, H.H.*,** Klemfuss, N., Montgomery, B., Higano, C.S., Schweizer, M.T., Mostaghel, E.H., McFerrin, L.G.,Yu, E.Y., Nelson, P.S., Pritchard, C.C. Pilot study of clinical targeted next generation sequencing for prostate cancer: consequences for treatment and genetic counseling. The Prostate, 2016 Jun 21. [**original work]** *(*HHC corresponding author*)

22. Schweizer, M.T., Gulati, R., Mostaghel, E.M., Nelson, P.S., Montgomery,B., Yu, E.Y., **Cheng, H.H.** Docetaxel-Related Toxicity in Metastatic Hormone-Sensitive Versus Castration-Resistant Prostate Cancer; Medical Oncology, 2016 Jul. **[original work]**

23. **Pritchard, C.C., Mateo, J., Walsh, M.F., De Sarkar, N., Abida, W., Beltran, H., Garofalo, A., Gulati, R., Carreira, S., Eeles, R., Elemento, O., Rubin, M.A., Robinson, D., Lonigro, R., Hussain, M., Chinnaiyan, A.M., Vinson, J., Filipenko, J., Garraway, L.A., Taplin, M-E, AlDubayan, S., Celine Han, G., Beightol, M., Morrissey, C., Ngheim, B., **Cheng, H.H**., Montgomery, B., Walsh, T., Casadei, S., Berger, M., Zhang, L., Zehir, A., Vijai, J., Scher, H.I., Sawyers, C., Schultz, N., Kantoff, P., Solit, D., Robson, M., Van Allen, E.M., Offitt, K., De Bono, J.S., Nelson, P.S. Inherited DNA Repair Gene Mutations in Men with Metastatic Prostate Cancer; New England Journal of Medicine, 2016 Jul 6*.* **[original work]**

24. Schweizer, M.T.*, **Cheng, H.H**.*, Tretiakova, M.S., Vakar-Lopez, F., Klemfuss, N., Mostaghel, E.A., Morrissey, C., Nelson, P.S., Yu, E.Y., Montgomery, R.B., True, L.D., Pritchard, C.C., Mismatch Repair Deficiency is Common in Ductal Prostatic Adenocarcinoma. Oncotarget, 2016, Oct. **[original work]** *(*co-first authorship*)

25. Gulati, R., **Cheng, H.H.**, Lange, P.H., Nelson, P.S., Etzioni, R. Screening men at increased risk for prostate cancer diagnosis: Model estimates of benefits and harms. Cancer Epidemiology Biomarkers and Prevention, 2016, Oct. **[original work]**

26. **Cheng, H.H.*,** Pritchard, C.C., Montgomery, B., Lin, D.W., Nelson, P.S. Prostate Cancer Screening in a New Era of Genetics. Clinical Genitourinary Cancer, 2017, May 31. **[editorial]** *(*HHC corresponding author*)

27. Miyahira, A.K., **Cheng, H.H.,** Abida, W., Ellis, L., Harshman, L., Spratt, D., Simons, J.W., Pienta, K.J., and Soule, H.R. Beyond the Androgen Receptor II: New Approaches to Understanding and Treating Metastatic Prostate Cancer; Report from the 2017 Coffey-Holden Prostate Cancer Academy Meeting. The Prostate, 2017, Sept 18. [**review**]

28. Ly, A., **Cheng, H.H.**, Alwan, L. Hepatitis C infection and chemotherapy toxicity. Journal of Oncology Pharmacy Practice, 2018, Jan 1. [**case series**]

29. **Cheng, H.H.,** Plets, M., Li, H., Higano, C.S., Agarwal, N., Vogelzang, N.J., Hussain, M., Thompson, I.M., Tewari, M., Yu, E.Y. Circulating microRNAs and treatment response in the Phase II SWOG S0925 study for patients with new metastatic hormone-sensitive prostate cancer. The Prostate, 2018, Feb. **[original work]**

30. **Cheng, H.H.**, Salipante, S., Nelson, P.S., Montgomery, B., Pritchard, C.C. Polyclonal *BRCA2* reversion mutations detected in circulating tumor DNA after platinum chemotherapy in a patient with metastatic prostate cancer. JCO Precision Oncology, 2018 Feb 14. **[case report]**

31. **Mateo, J.*, **Cheng, H.H.*,** Beltran, H.*, Dolling, D., Xu, W., Pritchard, C.C., Mossop, H., Rescigno, P., Perez-Lopez, R., Kolinsky, M., Balasapoulou, A., Carreira, S., Thorne, H., Montgomery, B., Sandhu, S., Rubin, M.A., Nelson, P., de Bono, J.S. Clinical Outcomes of Prostate Cancer Patients with Germline DNA Repair Mutations: Follow-up From an International Study, European Urology, 2018 Jan 29. *(*co-first authorship)* **[original work]**

32. **Cheng, H.H.,** The Resounding Impact of DNA Repair Deficiency in Prostate Cancer. Urologic Oncology, 2018 Mar 16 **[editorial]**

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]**

36. Carlo, M.I., Giri, V.N., Paller, C.S., Abida, W., Alumkal, J.J., Beer, T.M., Beltran, H., George, D.J., Heath, E.I., Higano, C.S., McKay, R.R., Morgans, A.K., Patnaik, A., Ryan, C.J., Schaeffer, E.M., Stadler, W.M., Kauff, N.D., Vinson, J., Antonarakis, E.S., **Cheng, H.H.*** Evolving Intersection Between Inherited Cancer Genetics and Therapeutic Clinical Trials in Prostate Cancer: A White Paper from the Germline Genetics Working Group of the Prostate Cancer Clinical Trials Consortium. JCO Precision Oncology, 2018 Aug 16. *(*HHC corresponding author*) **[original work]**

37. Hahn, A.W. Stenehjem, D.D., Alex, A.B., Esther, J. Gill, D.M., **Cheng, H.H.,** Kessler, E.R., Chittoria, N., Twardowski, P., Vaishampayan, U., Agarwal, N. Time from definitive therapy to onset of metastatic disease predicts outcomes in men with metastatic hormone sensitive prostate cancer. Urologic Oncology, 2019 Feb 13. **[original work]**

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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44. Labrecque, M.P., Coleman, I.M., Brown L.G., True, L.D., Kollath, L., Lakely, B., Holly M. Nguyen., H.M., Yang,Y.C., Kaipainen, A.H., Coleman, R.T., Higano, C.S., Yu, E.Y**., Cheng, H.H.,** Mostaghel, E.A., Montgomery, B., Schweizer, M.T., Hsieh, A.C., Lin, D.W., Corey, E., Nelson, P.S., Morrissey, C. The phenotypic diversity of treatment-refractory metastatic castration-resistant prostate cancer (*in press, Journal of Clinical Investigation)* **[original work]**

45. Kwon D.H., Borno H.T., **Cheng H.H.,** Small E.J. A registry study characterizing germline variants in prostate cancer among men of diverse ethnic backgrounds (*in press, Urologic Oncology: Seminars and Original Investigations)* **[original work]**

46. **Cheng, H.H.** Germline Contributions to Metastatic Prostate Cancer *(in press, Canadian Journal of Urology)* **[review]**

47. Mohler, J.L., Higano, C.S., Schaeffer, E.M., **Cheng, H.H.,** Current Recommendations for Prostate Cancer Genetic Testing: NCCN Prostate Guideline *(in press, Canadian Journal of Urology)* **[review]**

b) Book Chapters:

1. **Cheng, H.H.** and Montgomery, R.B., (2015) Androgen Receptor Biology In Castration Resistant Prostate Cancer. Management of Castration Resistant Prostate Cancer, Current Clinical Urology, Springer Science and Business Media, NY.

2. **Cheng, H.H**. and Nelson, P.S. Genetic Risk Factors in Prostate Cancer. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on April 14, 2017.)

c) Published Books, Videos, Software:

1. Dahut, W., **Cheng, H.H.** and Fadich, A. *The Future of Prostate Cancer Research and Treatment***.** National Cancer Institute YouTube Live, January 12, 2017. https://www.youtube.com/watch?cid=eb_govdel&v=2UTHKQuo2Ng

2. **Cheng, H.H.** *New Discoveries in Prostate Cancer*. Morning CME Webinar, January 17, 2017. MorningCME.com

d) Other Publications:

1. **Cheng, H.H.** and Linenberger, M. Into Thin Air: New Insights to the Role of Hypoxia-Inducible Factor in Cancer Biology and as a Target to Optimize Cell-Based Therapies. The Hematologist, Sept/Oct 2011.

2. **Cheng, H.H.** University of Washington Hematology/Oncology Fellows' Handbook. Author and editor of first edition, 2011.

3. **Cheng, H.H**. Expert contributor to patient educational website, 2015. (http://talkabouthealth.com/HeatherChengMDPhD)

4. **Cheng, H.H.,** Morgan, T.M., Dahut, W. Clinical Implications of Genetics: Expanding the Reach from Precision Therapy Opportunities for Prostate Cancer Patients to Prostate Cancer Screening for Genetically At-Risk Previvors. ASCO Genitourinary Symposium Expert Editorial, 2019.

e) Manuscripts Submitted:

1. Narayan V, Harrison M, **Cheng H.H.,** Kenfield S, Aggarwal R, Kwon D, McKay R, Hauger R, Hart N, Conzen S, Borno H, Jim H, Dicker A, Dorff T, Moslehi J, Mucci L, Parsons JK, Saad F, Soule H, Morgans AK, Ryan CJ. Improving Research for Prostate Cancer Survivorship: A Consensus Statement from the SuRECaP (Survivorship Research in Prostate Cancer) Working Group. (*submitted)* **[review]**

2. Shore, N.D., Morrow, M.P., McMullan, T., Kraynyak, K.A., Bhatt, K., Cheung, J., Boyer, J.D., Liu, L., Sacchetta, B., Rosencranz, S., Heath, E.I., Nordquist, L., **Cheng, H.H**., Tagawa, S.T., Appleman, L.J., Tutrone, R., Garcia, J., Whang, Y., Kelly, W.K., Bagarazzi, M., Skolnik, J.M. DNA-based immunotherapy targeting prostate specific antigen and prostate specific membrane antigen activates T cells and impacts rising PSA levels in biochemically relapsed prostate cancer patients: A Phase 1/2 clinical trial. (*submitted)* **[original work]**

3. 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 (*submitted)* **[original work]**

4. Sokolova, A.O., Shirts, B.H., Konnick, E.Q., Tykodi, S., Goulart, B.H.L., Montgomery, B., Pritchard, C.C., Yu, E.Y., **Cheng, H.H.** Complexities of Next Generation Sequencing for Solid Tumors: Case Studies in Interference from Clonal Hematopoiesis and Germline Variant Reclassification (*submitted) (*HHC corresponding author*) **[original work]**

5. Vaklavas, C., Chae, Y.K., **Cheng, H.H.,** Hong, F., Harris, L., Mitchell, E., Zwiebel, J., Rubinstein, L., McShane, L., Gray, R., Li, S., Ivy, P., Ansher, S., Hamilton, S., Williams, M., Patton, D., Tricoli, J., Arteaga, C., Conley. B., O'Dwyer, P., Chen, A., Flaherty, K. A Phase II Study of AZD4547 in Patients with Tumors harboring Aberrations in the FGFR Pathway: Results from the NCI-MATCH Trial (EAY131) Sub-protocol W (*submitted)* **[original work]**

6. 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 (*in preparation)* **[original work]**

7. 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 (*in preparation)* **[original work]**

f) Abstracts

1. **Cheng, H.H.**, Anderson, M.M., Hankenson, F.C., Johnston, L., Kotwaliwale, C.V., Overbaugh, J. *Identifying the Requirements and Mechanisms of FeLV-T Entry*. 2002 International Workshop of Retroviral Pathogenesis, Indian Wells, CA [Oral presentation]

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

3. **Cheng, H.H.,** Yi, H.S., Tewari M., Pritchard, C.C. Candidate Circulating MicroRNA Cancer Biomarkers Are Altered By Blood Sample Processing. American Society of Clinical Oncology 2012 Markers in Cancer, Abstract #8, Poster discussion session. **(Recipient of Merit Award)**

4. Wright, J.L., Lee, F., Harris, W.P., **Cheng, H.H.,** Zhao, S., Champion, T., Gore, J.L., Dean, J., Porter, M.P., Yu, E.Y. Pathologic response rates between gemcitabine-cisplatin (GC) and methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) neoadjuvant chemotherapy in muscle invasive urothelial cell carcinoma of the bladder. American Society of Clinical Oncology 2012 Genitourinary Cancer Symposium. Abstract #107130 [Poster].

5. Yu, E.Y., Kuo, K.F., Hunter-Merrill, R., Gulati, R., **Cheng, H.H.,** Flamiatos, J.F., Gambol, T.E., Hall, S.P., Higano, C.S. A pilot study of high-dose exisulind in men with biochemical relapse (BCR) of prostate cancer after definitive local therapy treated with intermittent androgen deprivation (IAD). American Society of Clinical Oncology 2012 Genitourinary Cancer Symposium. Abstract #107188. [poster].

6. Chevillet, J.R., Gallichotte, E., **Cheng, H.H.,** Vojtech, L.N., Arroyo, J.D., Briggs, H., Vessella, R.L., Higano, C.S., Yu, E.Y., Pogosova-Agadjanyan, E.L., Stirewalt, D.L., Hladik, F., Tewari, M. Circulating microRNA biomarkers for cancer exist in multiple biophysical states. 2013 American Association for Cancer Research Annual Meeting. Abstract #1118 [Poster].

7. Aparicio, A., Gallichotte, E., **Cheng, H.,** Maity, S., Logothetis, Yoo, S.-Y., Baggerly, K., Tewari, M. *Circulating miRNAs as Clinically Meaningful Classifiers of Castration-Resistant Prostate Cancers*. 2013 American Association for Cancer Research Annual Meeting. Abstract #1205 [Poster].

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9. Yu, E.Y., Tangen, C.M., 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*. 2014 American Society of Clinical Oncology Annual Meeting. Abstract, Oral presentation

10. **Cheng, H.H.,** Tangen, C.M., Higano, C.S., Li, H., Agarwal, N., Yan, J., Vogelzang, N.J., Hussain, M., Thompson, I.M., Tewari, M., Yu, E.Y. *Comparison of plasma microRNAs with CTCs and PSA in patients treated on SWOG S0925, a randomized phase II study of androgen deprivation combined with cixutumumab versus androgen deprivation alone for patients with new metastatic hormone-sensitive prostate cancer.* 2014 American Society of Clinical Oncology Annual Meeting. Abstract #5017, Poster highlights session **(Recipient of Merit Award)**

11. Nguyen, H., Gawne, A., Taub, J., Soleau, C., Teller, S., So, M., and **Cheng, H.** *Improving Efficiency and Accuracy in Medical Records Review for Clinical Care, Clinical Trials and Clinical Database in Genitourinary Medical Oncology (GUMO) Through Better Communication Tools.* 2014 Solid Tumor Translational Research Process Improvement Project, Oncology Recognition Day, Poster Finalist. Poster

12. Winters, B., Holt, S., Lin, D., Porter, M., **Cheng, H.,** Wright, J. *Treatment and survival in young men under age 55 years diagnosed with Gleason 8-10 Prostate Cancer: Implications for PSA screening.* 2015 American Urological Association; Abstract

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16. Alex, A., Stenehejem, D., Twardowski, P., **Cheng, H.**, Buckley, T., Gill, D., Patel, S., Vaishampayan, U., Agarwal, N. *Impact of prior definitive therapy on survival outcomes in men with new hormone sensitive metastatic prostate cancer (mHSPC).* January 2015, Genitourinary Oncology Symposium, San Francisco, CA. Abstract #269. Poster

17. Nelson, P.S., Mateo, J., Beltran, H., De Sarkar, N., Elemento, O., Rubin, M.A., Vinson, J.N., Filipenko, J., Robinson, D.R., Chinnaiyan, A.M., Van Allen, E.M., Garofalo, A., Taplin, M-E, Garraway, L.A., Carreira, S., Montgomery, R.B., Morrissey, C., **Cheng, H.H**., De Bono, J.S., Pritchard, C.C. *Inherited*

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29. Lam, H., Vakar-Lopez, F., Hsieh, A.C., Winters, B., **Cheng, H.**, Schweizer, M., Yu, E.Y., Montgomery, B., Corey, E., Wright, J.L. *Bladder Cancer Rapid Autopsy: A mechanism for collecting metastatic tumor tissue and establishing xenograft models of metastatic disease,* Genitourinary Cancers Symposium, San Francisco, CA (2018). [Abstract]

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45. Winters, B., Ngo, S., Vakar-Lopez, F., Tretriakova, M., True, L., Dighe, M., Lee, J., Russell, K., Zeng, J., Liao, J.J., **Cheng, H.,** Montgomery, B., Schweizer, M., Hsieh, A., Yu, E., Schade, G., Gore, J., Lin, D., Wright, J. *Multi-specialty bladder cancer clinics can be associated with significant radiologic and pathologic diagnostic changes resulting in updated treatment recommendations: Results from a tertiary referral center*. American Urological Association Annual Meeting, Chicago, IL (2019). [Abstract]

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)

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)

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)

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 oral presentation]

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 faculty speaker]

19. 11/06/2019 *(anticipated) Molecular-Driven Therapy in GU Cancers.* 37th Annual CFS®: Innovative Cancer Therapy for Tomorrow, New York, NY [invited faculty speaker]

January 24, 2019

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	*Temple University School of Medicine*, Philadelphia, PA Doctor of Medicine, May 2008
1999 – 2004	*University of Delaware*, Newark, DE Bachelor of Chemical Engineering, May 2004

3. Postgraduate Training:

2011 – 2014	Medical Oncology Fellowship, *The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University*, Baltimore, MD
2008 – 2011	Internal Medicine Residency, *The University of Chicago*, Chicago, IL

4. Faculty Positions Held:

2014 – Present	Assistant Professor Internal Medicine, Division of Medical Oncology, *The University of Washington*, Seattle, WA
2014 – 2019	Assistant Member, Clinical Research Division, *Fred Hutchinson Cancer Research Center*, Seattle, WA
2019 – Present	Associate Member, Clinical Research Division, *Fred Hutchinson Cancer Research Center*, Seattle, WA

5. Hospital Positions Held:

2014 – Present	Attending Physician, *University of Washington Medical Center*, Seattle, WA
2014 – Present	Attending Physician, *Seattle Cancer Care Alliance*, Seattle, WA

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

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 – present	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

12. Special National Responsibilities:

2014 – 2019	Grant and Funding Organization Reviews: Department of Defense Prostate Cancer Research Program

13. Special Local Responsibilities: University and hospital committees.

2015 – 2019	SPORE Pilot Grant Review
2017 – present	Member, UW/FHCRC Cancer Consortium Scientific Review Committee
2017 – present	Leader, Genitourinary Oncology Advanced Disease Meeting
2017 – present	Leader, Seattle Cancer Care Alliance, Prostate Cancer Clinical Pathway Team

14. Research Support

Ongoing Research Support:

W81XWH-14-2-0189 Denmeade (PI) 01/01/15 – 03/29/19
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

W81XWH-16-1-0484 Schweizer (PI) 09/30/16 – 09/29/20
Pharmacologic Dose Testosterone to Treat Castration-Resistant Prostate Cancer: Mechanisms of Action and Drivers of Response
The major goal of this project is to determining 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 – 06/30/19
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) 11/01/16 – 10/31/20
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 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 tests antibody drug conjugates targeting these antigens in preclinical models of androgen receptor-null prostate cancer.
Role: Co-Investigator

Industry Sponsored Trial Schweizer (PI) 07/27/18 – 04/30/23
A Phase 1b 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

Recently Completed Research:

2015 PCF Young Investigator Award Schweizer (PI) 10/12/15 – 12/31/18
Bipolar Androgen Therapy (BAT): Molecular Drivers of Response and Resistance
The major goals of this project are to determine the drivers of response/resistance to supraphysiologic testosterone in men with castration-resistant prostate cancer. This will be accomplished by conducting molecular assessments on circulating tumor cells and metastatic biopsies obtained from men enrolled to a Phase II trial testing this therapy.
Role: PI

P30 CA015704 Gilliland (PI) 01/01/16 – 12/31/18
A Neoadjuvant Clinical Trial to Assess the Effectiveness of Intense Combinatorial Targeting of AR-Signaling to Eradicate Prostate Carcinoma
The major goal of this study is to test a neoadjuvant AR-signaling ablative regimen that includes the AKR1C3 inhibitor indomethacin. The primary objective will be to determine the pathologic complete response rate following 3-months of therapy in men with high-risk prostate cancer.
Role: Project PI

15. Bibliography:

Manuscripts in referred journals:

1. Graham, L.S., Schade, G. & **Schweizer, M.T.** Multimodality Treatment of Bilateral Wilms Tumor in a Pregnant Female. Urology (2019). [case report]

2. Labrecque, M.P., Coleman, I.M., Brown, L.G., True, L.D., Kollath, L., Lakely, B., Nguyen, H.M., Yang, Y.C., Gil da Costa, R.M., Kaipainen, A., Coleman, R., Higano, C.S., Yu, E.Y., Cheng, H.H., Mostaghel, E.A., Montgomery, B., **Schweizer, M.T.**, Hsieh, A.C., Lin, D.W., Corey, E., Nelson, P.S. & Morrissey, C. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. The Journal of clinical investigation 130(2019). [original work]

3. *Chatterjee, P., †**Schweizer, M.T.**, Lucas, J.M., Coleman, I., Nyquist, M.D., Frank, S.B., Tharakan, R., Mostaghel, E., Luo, J., Pritchard, C.C., Lam, H.M., Corey, E., Antonarakis, E.S., Denmeade, S.R. & Nelson, P.S. Supraphysiological androgens suppress prostate cancer growth through androgen receptor-mediated DNA damage. The Journal of clinical investigation 130(2019).
†Co-first author

4. Lam, H.M., Nguyen, H.M., Labrecque, M.P., Brown, L.G., Coleman, I.M., Gulati, R., Lakely, B., Sondheim, D., Chatterjee, P., Marck, B.T., Matsumoto, A.M., Mostaghel, E.A., **Schweizer, M.T.**, Nelson, P.S. & Corey, E. Durable Response of Enzalutamide-resistant Prostate Cancer to Supraphysiological Testosterone Is Associated with a Multifaceted Growth Suppression and Impaired DNA Damage Response Transcriptomic Program in Patient-derived Xenografts. European urology (2019).

5. Winters, B.R., De Sarkar, N., Arora, S., Bolouri, H., Jana, S., Vakar-Lopez, F., Cheng, H.H., **Schweizer, M.T.**, Yu, E.Y., Grivas, P., Lee, J.K., Kollath, L., Holt, S.K., McFerrin, L., Ha, G., Nelson, P.S., Montgomery, R.B., Wright, J.L., Lam, H.M. & Hsieh, A.C. Genomic distinctions between metastatic lower and upper tract urothelial carcinoma revealed through rapid autopsy. JCI insight 5(2019).

6. **Schweizer MT**, Antonarakis ES, Bismar TA, Guedes LB, Cheng HH, Tretiakova MS, Vakar-Lopez F, Klemfuss N, Konnick EQ, Mostaghel EA, Hsieh AC, Nelson PS, Yu EY, Montgomery RB, True LD, Epstein JI, Lotan TL, Pritchard CC. Genomic characterization of prostatic ductal adenocarcinoma identifies a high prevalence of DNA repair gene mutations. JCO Precision Oncology (In Press). [original work]

7. Brennen, W.N., **Schweizer, M.T.**, Wang, H., Bivalacqua, T.J., Partin, A.W., Lim, S.J., Chapman, C., Abdallah, R., Levy, O., Bhowmick, N.A., Karp, J.M., De Marzo, A., Isaacs, J.T. & Denmeade, S.R. In Reply to the Letter to the Editor from Raj et al.: Clinical Evidence Indicates Allogeneic Mesenchymal Stem Cells Do Not Pose a Significant Risk for Cancer Progression in the Context of Cell-Based Drug Delivery. Stem cells translational medicine (2019). [response letter]

8. ***Schweizer, M.T.**, Gulati, R., Beightol, M., Konnick, E.Q., Cheng, H.H., Klemfuss, N., 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). [original work]

9. 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 Treatment Among Men with Metastatic Castration-resistant Prostate Cancer Harboring BRCA1 or BRCA2 Versus ATM Mutations. European urology (2019). [original work]

10. ***Schweizer, M.T.**, Wang, H., Bivalacqua, T.J., Partin, A.W., Lim, S.J., Chapman, C., Abdallah, R., Levy, O., Bhowmick, N.A., Karp, J.M., De Marzo, A., Isaacs, J.T., Brennen, W.N. & Denmeade, S.R. A Phase I Study to Assess the Safety and Cancer-Homing Ability of Allogeneic Bone Marrow-Derived Mesenchymal Stem Cells in Men with Localized Prostate Cancer. Stem cells translational medicine (2019). [original work]

11. Nava Rodrigues, D., Rescigno, P., Liu, D., Yuan, W., Carreira, S., Lambros, M.B., Seed, G., Mateo, J., Riisnaes, R., Mullane, S., Margolis, C., Miao, D., Miranda, S., Dolling, D., Clarke, M., Bertan, C., Crespo, M., Boysen, G., Ferreira, A., Sharp, A., Figueiredo, I., Keliher, D.,

Aldubayan, S., Burke, K.P., Sumanasuriya, S., Fontes, M.S., Bianchini, D., Zafeiriou, Z., Teixeira Mendes, L.S., Mouw, K., **Schweizer, M.T.**, Pritchard, C.C., Salipante, S., Taplin, M.E., Beltran, H., Rubin, M.A., Cieslik, M., Robinson, D., Heath, E., Schultz, N., Armenia, J., Abida, W., Scher, H., Lord, C., D'Andrea, A., Sawyers, C.L., Chinnaiyan, A.M., Alimonti, A., Nelson, P.S., Drake, C.G., Van Allen, E.M. & de Bono, J.S. Immunogenomic analyses associate immunological alterations with mismatch repair defects in prostate cancer. The Journal of clinical investigation 128, 4441-4453 (2018). [original work]

12. **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. Correction: A phase I study of niclosamide in combination with enzalutamide in men with castration-resistant prostate cancer. PloS one 13, e0202709 (2018). [corrigendum]

13. ***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 13, e0198389 (2018). [original work]

14. Hempelmann, J.A., Lockwood, C.M., Konnick, E.Q., **Schweizer, M.T.**, Antonarakis, E.S., Lotan, T.L., Montgomery, B., Nelson, P.S., Klemfuss, N., Salipante, S.J. & Pritchard, C.C. Microsatellite instability in prostate cancer by PCR or next-generation sequencing. Journal for immunotherapy of cancer 6, 29 (2018). [original work]

15. Teply, B.A., Wang, H., Luber, B., Sullivan, R., Rifkind, I., Bruns, A., Spitz, A., DeCarli, M., Sinibaldi, V., Pratz, C.F., Lu, C., Silberstein, J.L., Luo, J., **Schweizer, M.T.**, Drake, C.G., Carducci, M.A., Paller, C.J., Antonarakis, E.S., Eisenberger, M.A. & Denmeade, S.R. Bipolar androgen therapy in men with metastatic castration-resistant prostate cancer after progression on enzalutamide: an open-label, phase 2, multicohort study. The Lancet. Oncology 19, 76-86 (2018). [original work]

16. Mohammad, O.S., Nyquist, M.D., **Schweizer, M.T.**, Balk, S.P., Corey, E., Plymate, S., Nelson, P.S. & Mostaghel, E.A. Supraphysiologic Testosterone Therapy in the Treatment of Prostate Cancer: Models, Mechanisms and Questions. Cancers 9(2017). [review]

17. **Schweizer, M.T.**, Hancock, M.L., Getzenberg, R.H. & Yu, E.Y. Hormone levels following surgical and medical castration: defining optimal androgen suppression. Asian journal of andrology 20, 405-406 (2018). [original work]

18. Graham, L., True, L.D. & **Schweizer, M.T.** Metastatic Adenocarcinoma of the Epididymis: A Case Report and Brief Literature Review. Clinical genitourinary cancer 16, e335-e338 (2018). [case report]

19. **Schweizer, M.T.** & Antonarakis, E.S. Prognostic and therapeutic implications of DNA repair gene mutations in advanced prostate cancer. Clinical advances in hematology & oncology : H&O 15, 785-795 (2017). [review]

20. Bluemn, E.G., Coleman, I.M., Lucas, J.M., Coleman, R.T., Hernandez-Lopez, S., Tharakan, R., Bianchi-Frias, D., Dumpit, R.F., Kaipainen, A., Corella, A.N., Yang, Y.C., Nyquist, M.D., Mostaghel, E., Hsieh, A.C., Zhang, X., Corey, E., Brown, L.G., Nguyen, H.M., Pienta, K., Ittmann, M., **Schweizer, M.**, True, L.D., Wise, D., Rennie, P.S., Vessella, R.L., Morrissey, C. & Nelson, P.S. Androgen Receptor Pathway-Independent Prostate Cancer Is Sustained through FGF Signaling. Cancer cell 32, 474-489.e476 (2017). [original work]

21. Guedes, L.B., Antonarakis, E.S., **Schweizer, M.T.**, Mirkheshti, N., Almutairi, F., Park, J.C., Glavaris, S., Hicks, J., Eisenberger, M.A., De Marzo, A.M., Epstein, J.I., Isaacs, W.B., Eshleman, J.R., Pritchard, C.C. & Lotan, T.L. MSH2 Loss in Primary Prostate Cancer. Clinical cancer research : an official journal of the American Association for Cancer Research 23, 6863-6874 (2017). [original work]

22. Chi, E.A. & **Schweizer, M.T.** Durable Response to Immune Checkpoint Blockade in a Platinum-Refractory Patient With Nonseminomatous Germ Cell Tumor. Clinical genitourinary cancer 15, e855-e857 (2017). [case report]

23. **Schweizer, M.T.**, Antonarakis, E.S. & Denmeade, S.R. Bipolar Androgen Therapy: A Paradoxical Approach for the Treatment of Castration-resistant Prostate Cancer. European urology 72, 323-325 (2017). [review]

24. **Schweizer, M.T.** & Yu, E.Y. AR-Signaling in Human Malignancies: Prostate Cancer and Beyond. Cancers 9(2017). [review]

25. **Schweizer, M.T.**, Cheng, H.H., Tretiakova, M.S., Vakar-Lopez, F., Klemfuss, N., Konnick, E.Q., Mostaghel, E.A., Nelson, P.S., Yu, E.Y., Montgomery, B., True, L.D. & Pritchard, C.C. Mismatch repair deficiency may be common in ductal adenocarcinoma of the prostate. Oncotarget 7, 82504-82510 (2016). [original work]

26. **Schweizer, M.T.** & Yu, E.Y. Targeting intratumoral androgens: statins and beyond. Therapeutic advances in medical oncology 8, 388-395 (2016). [review]

27. **Schweizer, M.T.** & Plymate, S.R. Response: letter to the editor. Expert opinion on therapeutic targets 21, 229 (2017). [response letter]

28. **Schweizer, M.T.**, Wang, H., Luber, B., Nadal, R., Spitz, A., Rosen, D.M., Cao, H., Antonarakis, E.S., Eisenberger, M.A., Carducci, M.A., Paller, C. & Denmeade, S.R. Bipolar Androgen Therapy for Men With Androgen Ablation Naive Prostate Cancer: Results From the Phase II BATMAN Study. The Prostate 76, 1218-1226 (2016). [original work]

29. Cheng, H.H., Klemfuss, N., Montgomery, B., Higano, C.S., **Schweizer, M.T.**, Mostaghel, E.A., McFerrin, L.G., Yu, E.Y., Nelson, P.S. & Pritchard, C.C. A Pilot Study of Clinical Targeted Next Generation Sequencing for Prostate Cancer: Consequences for Treatment and Genetic Counseling. The Prostate 76, 1303-1311 (2016). [original work]

30. **Schweizer, M.T.**, Gulati, R., Mostaghel, E.A., Nelson, P.S., Montgomery, R.B., Yu, E.Y. & Cheng, H.H. Docetaxel-related toxicity in metastatic hormone-sensitive and metastatic castration-resistant prostate cancer. Medical oncology (Northwood, London, England) 33, 77 (2016). [original work]

31. Graham, L. & **Schweizer, M.T.** Targeting persistent androgen receptor signaling in castration-resistant prostate cancer. Medical oncology (Northwood, London, England) 33, 44 (2016). [review]

32. **Schweizer, M.T.** & Plymate, S.R. Targeting constitutively active androgen receptor splice variants in castration resistant prostate cancer. Expert opinion on therapeutic targets 20, 903-906 (2016). [review]

33. **Schweizer, M.T.** & Yu, E.Y. Persistent androgen receptor addiction in castration-resistant prostate cancer. Journal of hematology & oncology 8, 128 (2015). [review]

34. **Schweizer, M.T.** & Antonarakis, E.S. Liquid biopsy: Clues on prostate cancer drug resistance. Science translational medicine 7, 312fs345 (2015). [review]

35. 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]

36. ***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]

37. 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]

38. Suzman, D.L., Luber, 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]

39. 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]

40. **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]

41. **Schweizer, M.T.** & Drake, C.G. Immunotherapy for prostate cancer: recent developments and future challenges. Cancer metastasis reviews 33, 641-655 (2014). [review]

42. **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]

43. **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]

44. **Schweizer, M.T.**, Zhou, X.C., Wang, H., Yang, T., Shaukat, 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]

45. **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]

46. **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]

47. **Schweizer, M.T.** & Antonarakis, E.S. Abiraterone acetate: a hat trick of clinical benefits. The Lancet. Oncology 13, 1173-1174 (2012). [review]

48. **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]

49. **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, Shaukat F, Eisenberger MA, Antonarakis ES. Metastasis-Free Survival (MFS) is Associated with Overall Survival (OS) in Men with PSA-Recurrent Prostate Cancer Treated with Deferred Androgen Deprivation Therapy. J Clin Oncol 31, 2013 (suppl 6; abstr 109). Poster presented at: 2013 ASCO Genitourinary Cancers Symposium, Orlando, FL.

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, 5th Annual Men's Health Update. *Prostate Cancer: A Lifelong Disease,* Seattle, WA. August 23, 2019
2019	Speaker, Gordon's Research Conference: Hormone-dependent Cancers. *Targeting Prostate Cancer Drug Resistance*, Newry, ME. August 7, 2019
2019	Keynote Speaker, Brotman Baty Institute for Precision Medicine: Cell-free DNA Symposium, *Applications of cfDNA in Prostate Cancer*, Seattle, WA. April 17, 2019.
2019	Speaker, UWMC Chief of Medicine Conference, *Germ Cell Tumors/Testicular Cancer,* Seattle, WA. March 19, 2019
2019	Speaker, Selected Topics in Hematology / Oncology Fellow's Lecture Series, *Bladder Cancer,* Seattle, WA. March 15, 2019
2019	Speaker, Nuclear Medicine Topical Conference, *Prostate Cancer 101*, Seattle, WA. March 12, 2019.
2019	Speaker, Prostate Cancer SPORE Seminar, *Targeting Backdoor Androgen Synthesis vis AKR1C3 Inhibition,* Seattle, WA. February 28, 2019
2019	Speaker, Skagit Valley Hospital, *Emerging Therapies in Cancer: New Treatments for Prostate Cancer*, Mt Vernon, WA. February 27, 2019
2019	Speaker, VA Puget Sound Health Care System, *Oncologic Emergencies*, Seattle, WA. February 26, 2019.
2018	Speaker, Cancer Immunotherapy Trial Network Meeting, *CDK12 Mutation as a Biomarker for Response to Immune Checkpoint Blockade*, Washington, D.C. November 7, 2018.

2018 Speaker, Society for Immunotherapy of Cancer: Advances in Cancer Immunotherapy, *Immunotherapy for the Treatment of Genitourinary Malignancies*, Seattle, WA. November 3, 2018.

2018 Speaker, Fred Hutchinson Cancer Research Center Grand Rounds, *Targeting Prostate Cancer Drug Resistance*, Seattle, WA. October 2, 2018.

2018 Speaker, Society of Utah Medical Oncologists, *Urothelial Carcinoma: Updates and Future Directions*, Park City, UT. September 22, 2018.

2018 Speaker, Prostate Cancer SPORE Seminar, *PNW Prostate Cancer Clinical Trials Overview: UW/SCCA*, Seattle, WA. September 6, 2018

2018 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Systemic Therapy In The Treatment of Bladder Cancer*, Seattle, WA. September 15, 2018.

2018 Speaker, Fellow Research Flash Rounds, *Translational Prostate Cancer Research*, Seattle, WA. July 31, 2018.

2018 Speaker, University of Utah: Huntsman Cancer Institute Genitourinary Oncology Symposium, *MSI-high Prostate Cancer: Finding the Needle in the Haystack*, Salt Lake City UT. May 25, 2018

2018 Speaker, University of Utah: Huntsman Cancer Institute Translational Oncology Seminar, *High-dose Testosterone Therapy for Prostate Cancer: Biomarkers and Combination Strategies*, Salt Lake City UT. May 24, 2018.

2018 Speaker, Institute for Prostate Cancer Research Symposium, *Improving Survival with Combination Therapy*, Seattle, WA. April 28, 2018.

2018 Speaker, City of Hope: Special Lecture, *Prostate Cancer: Histologic Subtypes and Molecular Correlates*, Duarte, CA. January 18, 2018.

2017 Speaker, CCSG Retreat, *State of Research: Clinical Trials*, Seattle, WA. November 9, 2017.

2017 Speaker, Everett Clinic, *Evolving Options for GU Cancer*s, Everett, WA. November 6, 2017

2017 Speaker, Selected Topics in Hematology / Oncology Fellow's Lecture Series, *Systemic Therapy in the Treatment of Bladder Cancer*, Seattle, WA. October 20, 2017.

2017 Speaker, Prostate Cancer Clinical Trials Consortium, *High-dose Testosterone Plus PARP Inhibition in mCRPC*, teleconferenced nationally. August 29, 2017.

2017 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Systemic Therapy in The Treatment of Bladder Cancer*, Seattle, WA. September 25, 2017.

2017 Speaker, SWOG GU Organ Site Meeting: Prostate Organ Site, *Bipolar Androgen Therapy for Metastatic Castration-Resistant Prostate Cancer,* San Francisco, CA. April 28, 2017.

2017 Speaker, Prostate Cancer Clinical Trials Consortium, *Durvalumab in MSI-high CRPC,* teleconferenced nationally. April 20, 2017.

2017 Speaker, Institute for Prostate Cancer Research Symposium, *Liquid Tumor Biopsies to Guide Precision Medicine*. Seattle, WA. March 18, 2017.

2017 Speaker, Fred Hutchinson Cancer Research Center Grand Rounds, *High-dose Testosterone to Treat Prostate Cancer*, Seattle, WA. January 31, 2017.

2016 Speaker, Selected Topics in Hematology / Oncology Fellow's Lecture Series, *Systemic Therapy in the Treatment of Bladder Cancer,* Seattle, WA. December 30, 2016.

2016 Speaker, Department of Medicine Core Teaching Conference, *Prostate Cancer: Screening and Beyond,* Seattle, WA. October 17, 2016.

2016 Speaker, Prostate Cancer SPORE Seminar, *Immunotherapy in Hypermutated Prostate Cancers*, Seattle, WA. September 29, 2016.

2016 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Systemic Therapy in The Treatment of Bladder Cancer,* Seattle, WA. September 24, 2016.

2016 Speaker, Prostate Cancer SPORE Seminar, *A Phase I Study of Niclosamide in Combination with Enzalutamide in Men with Androgen Receptor Splice Variant Positive Castration- Resistant Prostate Cancer,* Seattle, WA. July 28, 2016.

2016 Speaker, Institute for Prostate Cancer Research Symposium, *Cancer Immunology 101,* Seattle, WA. April 30, 2016.

2015 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Systemic Therapy in The Treatment of Bladder Cancer,* Seattle, WA. September 27, 2015

2015 Speaker, Comprehensive UW Medicine Hematology & Oncology Review Course, *Germ Cell Tumors/Testicular Cancer,* Seattle, WA. September 27, 2015

2015 Speaker, Coffey-Holden Prostate Cancer Academy Meeting, *Moving Chemotherapy Earlier in the Disease Process*, La Jolla, CA. June 26, 2015.

2015 Speaker, Institute for Prostate Cancer Research Symposium**,** *Testosterone Therapy: Science, Rationale and Caution*, Seattle, WA. April 11, 2015.

2015 Speaker, Prostate Cancer SPORE Seminar, *Old Drugs, New Tricks: Repurposing Approved Drugs to Treat Prostate Cancer,* Seattle, WA. February 5, 2015.

2014 Speaker, Annual Multi-Institutional Prostate Cancer Program Retreat, *A Pilot Study of Supraphysiologic Testosterone and Oral Etoposide in Men with Castrate-Resistant Prostate Cancer,* Fort Lauderdale, FL. March 17, 2014.

1. Graham, L.S., Schade, G. & Schweizer, M.T. Multimodality Treatment of Bilateral Wilms Tumor in a Pregnant Female. *Urology* (2019).
2. Labrecque, M.P., Coleman, I.M., Brown, L.G., True, L.D., Kollath, L., Lakely, B., Nguyen, H.M., Yang, Y.C., Gil da Costa, R.M., Kaipainen, A., Coleman, R., Higano, C.S., Yu, E.Y., Cheng, H.H., Mostaghel, E.A., Montgomery, B., Schweizer, M.T., Hsieh, A.C., Lin, D.W., Corey, E., Nelson, P.S. & Morrissey, C. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. *The Journal of clinical investigation* **130**(2019).
3. Chatterjee, P., Schweizer, M.T., Lucas, J.M., Coleman, I., Nyquist, M.D., Frank, S.B., Tharakan, R., Mostaghel, E., Luo, J., Pritchard, C.C., Lam, H.M., Corey, E., Antonarakis, E.S., Denmeade, S.R. & Nelson, P.S. Supraphysiological androgens suppress prostate cancer growth through androgen receptor-mediated DNA damage. *The Journal of clinical investigation* **130**(2019).
4. Lam, H.M., Nguyen, H.M., Labrecque, M.P., Brown, L.G., Coleman, I.M., Gulati, R., Lakely, B., Sondheim, D., Chatterjee, P., Marck, B.T., Matsumoto, A.M., Mostaghel, E.A., Schweizer, M.T., Nelson, P.S. & Corey, E. Durable Response of Enzalutamide-resistant Prostate Cancer to Supraphysiological Testosterone Is Associated with a Multifaceted Growth Suppression and Impaired DNA Damage Response Transcriptomic Program in Patient-derived Xenografts. *European urology* (2019).
5. Winters, B.R., De Sarkar, N., Arora, S., Bolouri, H., Jana, S., Vakar-Lopez, F., Cheng, H.H., Schweizer, M.T., Yu, E.Y., Grivas, P., Lee, J.K., Kollath, L., Holt, S.K., McFerrin, L., Ha, G., Nelson, P.S., Montgomery, R.B., Wright, J.L., Lam, H.M. & Hsieh, A.C. Genomic distinctions between metastatic lower and upper tract urothelial carcinoma revealed through rapid autopsy. *JCI insight* **5**(2019).