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Introduction

The 26th Annual Prostate Cancer Foundation (PCF) Scientific Retreat was held from October 24-26, 2019, at the Omni La Costa Resort in Carlsbad, California. The PCF Retreat is the foremost scientific conference in the world focusing on research advances in prostate cancer biology and treatment. Attendees comprise the world’s leaders in basic, translational, and clinical research in prostate cancer and other biomedical fields, as well as world leaders in industry, technology, government, and business.

The Retreat is PCF’s primary prostate cancer global knowledge exchange event, held to bring together the brightest minds in science to discuss the most significant and promising advancements and new areas of research that may lead to new treatments for prostate cancer. The Retreat has had an immeasurable historical impact on the prostate cancer research field and community. Attendance at the Retreat has directly led to the establishment of a strongly networked and highly collaborative research community, unparalleled by any other biomedical research field. Retreat attendees have been involved in the development of almost every treatment advancement for prostate cancer since the Foundation’s inception, and many of them trace critical origins of their work to attendance at a PCF Retreat.

The 26th Annual Scientific Retreat featured the following:

- 42 presentations in the Plenary Session including a “Precision Policy” panel discussion on the evidence for a biological basis, access to health care, and other contributors to racial disparities in prostate cancer
- 133 poster presentations
- 26 different scientific disciplines related to prostate cancer research presented and discussed
- 51% of speakers presented first-in-field, unpublished data at a PCF Scientific Retreat for the first time
- Attendance by 665 participants from 18 countries, including 263 PhDs, 199 MDs, 105 MD PhDs, 16 PharmDs, 1 DDS, 1 DMD, 1 DO, 1 DBA and 1 RN.
- 118 academic institutions, 57 biopharmaceutical companies, and 13 medical research foundations
- NIH, NCI, Dept. of Defense, and Veterans Affairs research leaders
- Attendance by 175 PCF Young Investigators
- Attendance by 25 PCF Board of Director members, major donors and special guests
- The 4th Annual PCF Women in Science Forum was held with 154 attendees

PCF is the world’s leading philanthropic organization funding and accelerating prostate cancer research. The PCF “Global Research Enterprise” currently extends to 22 countries and funds a robust research portfolio. Founded in 1993, PCF has raised more than $831 million
and provided funding to more than 2,040 research programs at more than 213 cancer centers and universities. This includes $59 million awarded to 287 PCF Young Investigators since 2007 and more than $210 million to PCF Challenge Award teams since 2008.

We thank the sponsors of the Retreat for their generous support: Sanofi Genzyme, Janssen Oncology, Amgen, Bayer, Bristol-Myers Squibb, Clovis Oncology, Pfizer Oncology, Advanced Accelerator Applications, Astellas, Daiichi-Sankyo, AstraZeneca, Celgene, Genentech, EcoR1 Capital, Constellation Pharmaceuticals, Ezra, Harpoon Therapeutics, Merck, Dendreon, and Sun Pharma.

The 2019 State of Science Report was prepared by the Prostate Cancer Foundation to summarize the scientific presentations from the Retreat in order to globally disseminate this knowledge to researchers, clinicians, patients, the public, philanthropists, industry, and other interested stakeholders. We hope that this Report advances understanding of the current state of prostate cancer research, encourages discourse and the exchange of new ideas and information, inspires new research, and stimulates increased support for scientific research. Please contact Dr. Andrea Miyahira at amiyahira@pcf.org if you have any questions about this Report.

Yours sincerely,

Jonathan W. Simons, MD
President & CEO

Howard R. Soule, PhD
Executive Vice President
Chief Science Officer

Andrea K. Miyahira, PhD
Director, Global Research &
Scientific Communications
Neighborhood Factors and Prostate Cancer Outcomes

Mindy C. DeRouen, PhD, MPH
University of California, San Francisco

• African American men are at significantly higher risk for diagnosis and death from prostate cancer compared with non-Hispanic White men. Understanding the factors that contribute to these disparities is critical in order to reduce this racial disparity.

• Prostate cancer disparities may result from multiple factors, including biologic, socioeconomic, health behaviors, environmental, and other factors. These factors may impact disparities at any point (and at multiple points) along the cancer continuum, including prevention, risk, diagnosis, treatment, survivorship, and mortality. In addition, it is critical to study how multiple factors may interact to result in disparities.

• To better understand the factors that contribute to health disparities, Dr. Mindy DeRouen is investigating the impact of neighborhood factors, which are the features that make up the physical and social environment of a person’s neighborhood, usually approximated as their census tract of residence.

• Features of the physical “built” environment include housing, street connectivity, food environment, commuting patterns, parks/green space, and population density.

• Features of the social environment include social capital, neighborhood socioeconomic status, demographic composition, crime, segregation, and displacement (gentrification). Neighborhood socioeconomic status is measured using census measures that aggregate the income, education, and occupation of residents.

• Within the Neighborhoods and Prostate Cancer Study, led by Dr. Scarlett L. Gomez (University of California, San Francisco), Dr. DeRouen and team conducted a study to evaluate the impact of 13 neighborhood built and social environment factors as well as individual sociodemographics, medical history, family history of prostate cancer, behavioral factors, and hospital factors, on racial disparities in prostate cancer survival. In this study, the team found that neighborhood socioeconomic status, but not individual education levels, partially accounted for shorter survival among African American men compared to White men.

• While some built and social environment factors contributed to survival, none of them accounted for the dramatic impact of neighborhood socioeconomic status on survival. Among other things, this study illustrated that more work is needed to better understand how interactions between different neighborhood built and social environment factors impact prostate cancer outcomes.

• In another study led by Dr. Salma Shariff-Marco (University of California, San Francisco), Dr. DeRouen and team used a large number of measures related to the built and social environment to classify neighborhoods into 5-9 distinct types and evaluate their associations with prostate cancer mortality.

• The nine types of neighborhoods were: upper middle-class suburb, high status, new urban/pedestrian, mixed socioeconomic status class suburb, suburban pioneer, rural/micropolitan, city pioneer, Hispanic small towns, and inner city (Figure). These categorizations were based on prominent features such as urbanicity, demographics,
socioeconomic status, age and household types, land use, food, commuting and street properties.

- The team examined the impact of neighborhood types and survival for different racial/ethnic groups using data on 185,000 California prostate cancer cases in the California Cancer Registry from 1996-2005. Disparities in overall and prostate cancer-specific mortality were observed by neighborhood archetypes, but the patterns of these disparities differed for groups defined by race/ethnicity. Survival disparities were highly linked to lower socioeconomic status, but were also affected by neighborhood factors including rural/urban status, age of residents, commuting and traffic patterns, residential mobility, and food environment.

- RESPOND is an ongoing national study led by Dr. Christopher Haiman (University of Southern California) that seeks to recruit 10,000 African American men to study the full range of factors that impact disparities in prostate cancer aggressiveness and survival, including neighborhood factors and individual-level biologic factors. As a part of this study, Dr. DeRouen and team are evaluating how social stressors at both the individual and neighborhood level impact prostate cancer biology and outcomes.

- Overall, this research aims to identify neighborhood environment factors that play a key role in disparities in prostate cancer outcomes in order to drive structural changes in healthcare, research, and society that will alleviate disparities and improve outcomes.
Exercise and Weight Management in the Supportive Care of Prostate Cancer Patients Undergoing Androgen Deprivation Therapy

Brian C. Focht, PhD, FACSM, CSCS
The Ohio State University

- Androgen deprivation therapy (ADT) is a standard of care treatment for advanced prostate cancer and works by blocking the production or activity of male hormones. While ADT is highly effective in slowing prostate cancer progression, its negative side effects can include changing body composition by promoting gain of fat and loss of muscle. The changes in body composition caused by ADT can lead to poorer mobility and ultimately to disability in daily living.

- Previous studies have found that diet, obesity, and exercise may impact prostate cancer outcomes. However, few studies have evaluated the impact of interventions combining exercise and dietary changes in prostate cancer patients.

- Dr. Brian Focht and team are studying the efficacy of combining diet and exercise as a synergistic approach to lifestyle weight management and reducing mobility impairment and disabilities in men with prostate cancer who are undergoing ADT.

- Several clinical studies have tested the impact of exercise in prostate cancer patients on ADT. In a review of those studies, Dr. Focht and team noted that the amount of exercise prescribed was enough to prevent further changes in body composition caused by ADT, but not enough to consistently improve or reverse its effects, and only had a limited impact on reducing disability.

- To test the hypothesis that combining exercise and dietary intervention would improve outcomes in prostate cancer patients, Dr. Focht and team conducted the Individualized Diet and Exercise Adherence-Pilot Trial (IDEA-P) trial. This randomized trial compared the effect of an exercise + dietary lifestyle intervention vs. standard of care disease management education in 32 prostate cancer patients undergoing ADT.

- The exercise + dietary intervention consisted of a progressive 12-week program which included exercise sessions (resistance and aerobic exercises), group dietary and behavioral counseling sessions (Figure), and a personalized dietary prescription which emphasized increasing intake of fruits, vegetables, and whole grains, while limiting intake of red/processed meats, sugar, salt, high caloric and low nutrient dense foods. The exercise program progressed from twice-per week supervised and personalized sessions to independent sessions over the 12 week course.

- A major challenge for exercise and dietary interventions has been patient adherence, especially how to keep people on the intervention once the trial is over. The type of group counseling session used in IDEA-P was designed to maximize self-regulatory behaviors such as self-monitoring and goal-setting, as a method to improve short and long-term patient adherence to the exercise and dietary changes.

- After three months, patients were evaluated for mobility performance, body composition, and muscular strength, as well as adherence to the exercise and dietary changes.

- The trial found significant improvements in mobility performance, self-regulatory behaviors, muscular strength (both upper and lower body), weight, body fat, and lean body mass in the exercise + dietary intervention group compared to the standard education group. Increased self-regulatory behaviors were associated with more favorable mobility performance and exercise participation.
• Overall, the IDEA-P trial demonstrated that an intervention consisting of exercise + dietary changes combined with group counseling could achieve a healthier body weight, improve health outcomes, and can attenuate or reverse the negative body composition changes caused by ADT. Patients also achieved short-term independence in maintaining the exercise and dietary changes.

• In future research, Dr. Focht and team plan on conducting the CLIP-PC trial, which will test the exercise + dietary + group counseling intervention versus a community-based exercise program (the Livestrong program) in prostate cancer patients undergoing ADT.

• Together, these studies demonstrate the importance of lifestyle changes as a key addition to the future of standard care. Also, IDEA-P indicates that integrating a group counseling component may be a successful method to potentially increase adherence and maintenance of diet and exercise changes in individuals.

![Integrating a Group Counseling Component to Improve Adherence](image)

**Figure:** "Group-Mediated Cognitive Behavioral Lifestyle Intervention" is a type of group counseling session designed to maximize self-regulatory behaviors such as self-monitoring and goal-setting, as a method to improve short and long-term patient adherence to the exercise and dietary changes.
The Biology and Therapeutic Impact of Targeting IL-23 in Prostate Cancer

Andrea Alimonti, MD
Institute of Oncology Research, Switzerland

- Studies have found that tumors of many cancer types, including prostate cancer, are composed not only of cancer cells, but also are infiltrated by many types of non-cancer cells, including blood vessel cells and various types of immune cells that modulate tumor growth.

- While some types of tumor-infiltrating immune cells can directly kill tumor cells and limit tumor growth, tumors also recruit and corrupt other types of immune cells to support and drive tumor growth. Understanding how some types of immune cells drive tumor growth will lead to the discovery of promising new therapeutic strategies.

- Myeloid-derived suppressor cells (MDSCs) are a class of immune cells that infiltrate tumors in large numbers and promote cancer growth by suppressing the activities of anti-tumor immune cells and supplying tumor-growth factors. Their role in driving prostate cancer and as treatment targets is an important area in need of study.

- Dr. Andrea Alimonti and team have found that MDSCs are significantly increased in mouse models of castration-resistant prostate cancer (CRPC) and promote the development of resistance to androgen deprivation therapy (ADT). ADT is part of the standard of care for advanced prostate cancer, and stops testosterone from being produced or directly blocks it from acting on prostate cancer cells.

- MDSCs are also found within metastatic tumors from patients with CRPC at much higher numbers, compared with metastatic tumors from patients with hormone-sensitive prostate cancer (HSPC).

- These studies suggest that MDSCs that develop in bone marrow can be recruited to prostate tumors and play a role in the development of resistance to ADT and progression to CRPC.

- The team discovered that MDSCs secrete factors that promote the development of resistance to ADT in prostate cancer models. The critical factor was found to be the protein IL-23. The team further found that both IL-23 and its receptor, IL-23R, were upregulated in patients with CRPC compared with HSPC (Figure).

- Treatment of prostate cancer models with an anti-IL-23 antibody enhanced the efficacy of ADT.

- Based on these findings, in collaboration with the team of Dr. Johann de Bono of the Institute of Cancer Research and Royal Marsden NHS Foundation Trust (UK), a Phase I/II clinical trial is being initiated in mCRPC patients assessing the safety and efficacy of anti-IL-23 combined with ADT. This drug, tildrakizumab is FDA-approved for treatment of psoriasis and represents a novel drug repurposing approach.

- Altogether, Dr. Alimonti and team have identified MDSCs and IL-23 as novel drivers and therapeutic targets in CRPC and will initiate a clinical trial to test an IL-23-targeting therapy for the treatment of CRPC. This may lead to an effective new treatment for patients with CRPC.
Figure: IL-23 and its receptor, IL-23R, are upregulated in patients with castration-resistant prostate cancer (CRPC) compared with hormone-sensitive prostate cancer (HSPC).

**Precision Immunotherapy for CDK12-Biallelic Loss**

**Ajjai Alva, MBBS**
University of Michigan

- The immune system has the powerful potential to detect and kill cancer cells, yet anti-tumor immune responses are often suppressed in patients with progressive cancer.
- Immunotherapy are a wide class of treatments that aim to activate a patient’s own immune system to fight their cancer.
- Checkpoint immunotherapy is an effective type of immunotherapy that may lead to cures in some patients with certain types of cancer such as melanoma and lung cancer. Checkpoint immunotherapy works by blocking immune-suppressive signals to allow activation of an anti-tumor immune response.
- In prostate cancer however, checkpoint immunotherapy has limited activity. A significant research goal is to identify subsets of prostate cancer patients who may benefit from checkpoint immunotherapy.
- Dr. Ajjai Alva discussed a unique and distinct subtype of prostate cancer characterized by loss of both copies (alleles) of the \( CDK12 \) gene, first identified by Dr. Arul Chinnaiyan and team.
- \( CDK12 \) is an enzyme that plays a role in several cellular processes, including repair of damaged DNA and the maintenance of chromosome stability.
- Prostate cancer with \( CDK12 \) mutation or loss exhibited distinct genomic alterations including genomic instability and internal focal tandem deletions, which resulted in high levels of gene fusions and neoantigens. Neoantigens are protein mutations that can be recognized by the
immune system as foreign, and may generate immune responses. In CDK12-loss tumors, the neoantigens were generated by the gene fusion mutations.

- The genomic alterations seen in CDK12-loss tumors were distinct from those seen in prostate tumors that had lost other DNA repair genes including BRCA1/2, ATM, mismatch repair (MMR), and SPOP genes.
- MMR-deficient prostate cancers exhibit very low levels of gene fusions, but have the highest level of neoantigens of any prostate cancer subtype. BRCA1/2-deficient prostate cancer expresses some neoantigens, but a far lower number than CDK12-deficient tumors.
- Prostate cancer with CDK12-loss also exhibited high levels of infiltration by T cells and high levels of T cells clones (T cells which recognize different antigens). MMR-deficient tumors also exhibit high levels of T cell infiltration.
- Importantly, MMR-deficiency is a biomarker for tumors that are more likely to respond to checkpoint immunotherapy, due to the high level of neoantigens, which can be recognized by the immune system. In 2016, the FDA approved pembrolizumab checkpoint immunotherapy for the treatment of all solid tumor types, including prostate cancer, that exhibit MMR-deficiency, in patients who have no other standard of care treatment options.
- Together, these results suggest that CDK12-loss may identify another subset of prostate cancers that may respond to treatment with checkpoint immunotherapy due to expression of a large number of neoantigens.
- The team identified 4 patients with CDK12-mutant advanced prostate cancer that had received off-label treatment with checkpoint immunotherapy at the University of Michigan. Two of the four patients exhibited exceptional PSA and radiographic responses (Figure).
- In a separate retrospective study, 34 of 317 mCRPC patients consecutively treated at 3 academic medical centers were found to have loss of both CDK12 alleles (bi-allelic loss). At a median follow-up of 66.6 months, patients with CDK12-loss were found to have significantly worse outcomes compared to patients with TP53 mutations or BRCA1/2 mutations. These included more rapid time to metastasis, more rapid time to castration-resistance, and more rapid time to PSA progression on first line anti-androgen therapy.
- Of the 34 patients with bi-allelic CDK12-loss, 5 had received anti-PD1 checkpoint immunotherapy, of whom 2 had >50% PSA responses.
- In contrast, 3 patients with CDK12-loss received treatment with PARP-inhibitors, none of whom responded.
- Similarly, in a separate clinical trial (TRITON-2), 0 of 12 patients with CDK12-loss had PSA responses after treatment with the PARP-inhibitor rucaparib.
- A third retrospective study also saw no responses to PARP-inhibitors among 11 patients with CDK12-loss, but observed responses in 3 of 8 patients with CDK12-loss who were treated with anti-PD1 checkpoint immunotherapy.
- Altogether, these studies demonstrate that loss of CDK12 through mutation or deletion identifies a molecularly distinct subset of prostate cancer patients who may benefit from checkpoint immunotherapy but not PARP-inhibitors.
- Based on these findings, Dr. Alva and team have opened a clinical trial (IMPACT) to test nivolumab + ipilimumab checkpoint immunotherapy in mCRPC patients with CDK12-loss.
- Other similar trials are being opened, including the CHOMP trial in the VA, which is testing pembrolizumab in US Veterans with mCRPC who have MMR deficiency or bi-allelic CDK12-loss.
- These studies may result in the identification of a distinct subgroup of prostate cancer patients who may benefit from checkpoint immunotherapy.
Testosterone Effects on Innate Immunity; Implications for Combination Therapies

Samuel Denmeade, MD
Johns Hopkins University

Sushant Kachhap, PhD
Johns Hopkins University

- Prostate cancer growth and survival is in part driven by and dependent on signals received from male hormones (androgens such as testosterone) transmitted by the androgen receptor (AR).
- Treatments that block the production and actions of androgens and/or AR have been the backbone of treatment for advanced prostate cancer for decades. However, prostate cancer cells nearly always develop resistance to androgen deprivation therapy (ADT) within months to years, and the disease then progresses to castration-resistant prostate cancer (CRPC). New treatment strategies to prevent or treat CRPC are urgently needed.
- Tumor cells can develop resistance to ADT by gaining mutations that increase the levels or activity of AR, which allow adaption to low levels of androgens.
- However, because extremely high AR activity can stall cell replication, Dr. Samuel Denmeade and others hypothesized that prostate cancer cells that have increased AR levels/activity in order to adapt to the low levels of androgens during ADT may now be sensitive to extremely high levels of androgens.

Anecdotal Responses to Immunotherapy in mCRPC Patients with CDK12-loss

Figure: Left: PSA responses were observed in two of four patients with CDK12-loss advanced prostate cancer that received treatment with checkpoint immunotherapy. Right: T cell infiltration into tumors (top, T cells indicated by red staining) and radiographic responses (bottom) in the two patients who responded.
- Bipolar androgen therapy (BAT) is an experimental treatment in which men are rapidly cycled between extremely high ("supra-physiologic") and extremely low (castrate) levels of testosterone.

- This strategy is hypothesized to cause killing of both AR-expressing cells (vulnerable at supra-physiologic levels of testosterone) and AR-low cells (vulnerable at castrate levels of testosterone). Cells that adapt to either polar extreme by upregulating or downregulating AR levels will die during the next cycling between polar extremes.

- The BAT strategy consists of monthly injections of a supra-physiologic level of testosterone (400mg) while co-administering continuous androgen deprivation therapy (ADT). ADT will cause testosterone levels to drop to near-castrate levels over a 4 week cycle.

- Drs. Samuel Denmeade and Sushant Kachhap performed a randomized phase 2 clinical trial (TRANSFORMER) to test whether BAT therapy would be effective in patients with CRPC. The patients on this trial must have progressed on ADT and abiraterone. Patients enrolled were randomized to receive BAT therapy vs. enzalutamide. At the time of disease progression (tumor growth on scans), patients would be crossed over to receive the other treatment (or a standard of care). This trial will also inform if BAT therapy can re-sensitize CRPC patients to enzalutamide, as enzalutamide typically has little to no benefit in patients who are resistant to abiraterone. 195 patients were enrolled on this trial.

- The results from the TRANSFORMER trial were promising. Compared with enzalutamide, more patients treated with BAT therapy exhibited an objective response, and PSA progression-free survival was improved. Additionally, after crossing over, more patients who went from BAT therapy to receiving enzalutamide responded, compared with the alternate treatment sequence, suggesting that BAT therapy can re-sensitize men with mCRPC to enzalutamide.

- Sequencing of BAT followed by enzalutamide also resulted in a longer overall time until PSA progression on the second treatment, compared with the alternate sequence.

- These data suggest that men with mCRPC who have progressed on abiraterone may benefit more from receiving BAT therapy followed by enzalutamide, rather than enzalutamide followed by BAT.

- Interestingly, Drs. Denmeade and Kachap observed exceptional responses in some patients who were treated with checkpoint immunotherapy after BAT therapy (Figure).

- Of three patients presented, none had tumor mutations in mismatch repair genes (MMR) or microsatellite instability (MSI), which are genomic alterations known to sensitize tumors to checkpoint immunotherapy.

- These results have led to a clinical trial (“COMBAT-CRPC”) testing BAT therapy in combination with vs. followed by nivolumab.

- The mechanisms which cause BAT to sensitize prostate cancer to checkpoint immunotherapy are being explored.

- Preliminary studies indicate that extremely high testosterone levels activate the STING pathway, which activates immune responses and tumor infiltration by tumor-killing Natural Killer (NK) cells.

- Altogether, these studies demonstrate that BAT may be a promising treatment option for men with CRPC. Drs. Denmeade and Kachap have observed that some patients treated with BAT therapy and who progress have exceptional responses when treated subsequently with checkpoint immunotherapy. This treatment approach is now being formally tested in clinical trials and the mechanisms which drive this are being studied.
Extreme Responder to Immune Checkpoint Blockade after BAT-Enzalutamide

Figure: Example of a patient who exhibited complete PSA (left) and radiographic (right) responses to treatment with immunotherapy (nivolumab + anti-CD73) after receiving BAT therapy (doses indicated by “testosterone”).
Session 3: Novel Insights from Prostate Cancer Genomics

Near-Mendelian Prostate Cancer Risk Variants of 8q24 and the HOXB Cluster

Jeffrey Smith, MD, PhD
Vanderbilt University Medical Center

- Prostate cancer is one of the most heritable forms of cancer. Based on studies in twins, ~58% of cases are thought to have a heritable component that drove the development of the disease. In addition, the relative risk a man has for developing prostate cancer roughly doubles for each affected first degree relative in his family, and is further increased if these family members were diagnosed at a younger age.
- Understanding the genes involved in hereditary prostate cancer will have a significant impact on screening, genetic testing and counseling, hereditary cancer care, and precision medicine.
- Dr. Jeffrey Smith discussed studies to identify inherited prostate cancer risk genes.
- Because the human genome is so large and thus costly to sequence in mass, studies to identify disease risk genes often start with genome-wide association studies (GWAS) to identify single nucleotide polymorphisms (SNPs) that are associated with a disease.
- SNPs are small, strategically selected genetic variations that can easily be tested. Tests have been developed to look at up to several million SNPs across a person’s genome at once.
- If certain SNPs are found to be significantly more frequent in individuals with a particular disease compared with the rest of the population, this indicates that an affected gene nearby may play a role in the disease.
- To identify genes that drive the development of inherited prostate cancer, Dr. Smith performed a GWAS SNP study comparing prostate cancer patients who have a strong family history of prostate cancer to prostate cancer-free, screened controls with no family history of prostate cancer. 28 million SNPs were evaluated in two different cohorts of patients and controls, totaling 3,640 patients and 2,208 controls.
- A cluster of highly significant prostate cancer-associated SNPs were identified in both cohorts on chromosome 8, at locus 8q24. Numerous additional cancer types (bladder, breast, colon, CLL, Hodgkin’s lymphoma, ovarian, and pancreatic) are also associated with genetic variants of the 8q24 region.
- The 8q24 region does not harbor typical protein-coding genes, but instead includes regulatory elements and several non-coding genes, as well as POU5F1B, a retrogene of the master embryonic stem cell gene OCT4. At least eight independent risk signals are present in the region, each detected by a set of variants that reside on a distinct corresponding inherited ancestral DNA segment.
- DNA sequencing identified candidate causal mutations in gene enhancer regions (regions that control the degree to which a gene is expressed, including POUF51B), and mutation candidates in two non-coding genes with unknown functions, CASC19 and PRNCR1. The strongest 8q24 mutation conveyed an 11.5-fold increased risk of prostate cancer and was carried by 2.3% of men with hereditary prostate cancer. A separate 8q24 mutation is more common, and when inherited from both parents carries similarly strong risk.
- A second genomic region found to be associated with increased prostate cancer risk was 17q21. The HOXB13 G84E mutation of this region has previously been found to be associated with increased prostate cancer risk. Dr. Smith’s team observed two additional independent risk signals in this region, often though not always inherited together with the G84E mutation. Together they convey 13.6-fold increased risk, and are carried by 1.4% of men with hereditary prostate cancer.

- Collectively, the team identified a set of 11 risk variants of the two genomic loci that are predictive of the development of prostate cancer and that explain ~5% of hereditary prostate cancer.

- Current NCCN Guidelines include testing the HOXB13 G84E mutation in familial prostate cancer. However, the additional risk variants identified in this study at the 8q24 and 17q21 regions also hold predictive power. Whether these also should be integrated into guidelines is now an important question.

- Overall, Dr. Smith’s studies have identified genetic variation carrying strong risks for prostate cancer, building a foundation for understanding its origins. The work contributes to care of cancer-prone families, but can also lead to a better understanding of the pathways that drive the development of prostate cancer.

**Mendelian Prostate Cancer**

3-5% of cases: 3 or more affected in pedigree  
“Hereditary Prostate Cancer” (HPC)

*Figure:* Example of a hereditary prostate cancer family pedigree that appears to be autosomal dominant.
Circular RNA in Prostate Cancer

Housheng Hansen He, PhD
Princess Margaret Cancer Centre, Canada

- Circular RNAs are a recently discovered class of RNA that consist of covalently closed circular strands of RNA which are generated by specialized RNA-processing factors. Circular RNAs are made from the mRNA of protein-coding and non-coding genes, as a general form of alternative RNA splicing (via “backsplicing”).
- Circular RNAs are highly stable in blood due to their structure which prevents degradation by enzymes that chop up linear RNA.
- Some functions of circular RNA that have been described include acting as scaffolds in protein complexes, regulating interactions of proteins with one another, acting as “sponges” to bind other types of RNA and remove them from the system, and aiding in protein synthesis. The role of circular RNA in cancer is yet unclear.
- Studies by Drs. Housheng Hansen He, Paul Boutros and others have characterized the landscape of circular RNA in prostate cancer and have begun to determine their role in tumor biology. Approximately 25,000 different circular RNAs have been identified as expressed in prostate cancer.
- Circular RNA abundance (either very high or very low amounts, relatively) was associated with worse clinical outcomes in prostate cancer patients. This suggests that altered biogenesis of circular RNA may be related to prostate cancer progression.
- To determine the role of circular RNAs in prostate cancer, Dr. He and team performed a study to knock out the expression of circular RNA vs. their linear RNA counterparts in prostate cancer cell lines. Out of 1,336 circular RNAs screened, 171 were essential for prostate cancer cell growth. For 90% of the 171 circular RNAs, the linear RNA counterpart was not important for prostate cancer cell growth.
- SchLAP1 is a long non-coding RNA that has previously been found to be highly prognostic for prostate cancer outcomes including metastasis-free survival (Figure).
- SchLAP1 can be expressed as both circular and linear RNA forms. Dr. He found that both circular and linear forms of SchLAP1 were important for prostate cancer cell growth, but that the genes that they regulated were almost entirely unique, suggesting unique biological roles for circular vs linear SchLAP1.
- Because of the stability of circular RNA in blood and other body fluids, Dr. He is evaluating their potential as non-invasive biomarkers. Circular RNAs from tumors were highly represented in exosomes, compared with linear RNA. Exosomes are small vesicles secreted from tumor and other cells into the blood.
- Most of the SchLAP1 RNA found in patient serum and urine was the circular form compared with the linear form (Figure). These studies suggest that circular SchLAP1 may serve as a prognostic biomarker in liquid biopsies.
- Together, these studies warrant further research into the role of circular RNAs in prostate cancer biology and their potential as biomarkers and therapeutic targets.
**Detection of SChLAP1 in liquid biopsy samples**

![Graph](image.jpg)

*Prensner et al. 2014. The Lancet Oncology.*

**Figure:** Left: SChLAP1 is prognostic for metastasis-free survival in prostate cancer patients and is associated with prostate cancer but not with other types of cancer. Right: Most of the SChLAP1 RNA found in patient serum and urine was the circular form compared with the linear form.

**SPECIAL LECTURE: Cell Types of the Proximal Prostate are Enriched in Tumors, but are they Progenitors?**

**Douglas Strand, PhD**
**The University of Texas Southwestern Medical Center**

- Identification of prostate stem cells may improve our understanding of the biology of normal prostate and prostate cancer cells.
- Studies have long sought to identify the population of prostate stem cells, including where they are located and what features can be used to identify them from other cells.
- The prostate gland consists of a tree-like structure of glands that start at the urethra and branch out to distal structures.
- Studies have found that cells from both the urethra and prostate gland areas proximal to the urethra contain cells with stem-like properties that can regenerate prostate tissues in culture. These stem-like prostate cells may be identified by high expression levels of Ska1 and intermediate expression levels of CD49f, and can grow without the need for androgens.
- Dr. Douglas Strand created a “cellular atlas” of the normal human prostate using RNA sequencing profiles from single cells taken from different regions of the prostate and urethra (Figure). These studies found basal and luminal prostate epithelial cells which are known to compose the prostate glands. In addition, two previously undescribed epithelial cell types were identified in the urethra, which were similar to “club” and “hillock” cell types that have recently been identified in the lung bronchus and were found to be lung stem cells.
- Dr. Strand found that urethra club cells were increased in primary prostate cancer as compared to normal prostate tissues (14% vs. 3%).

- The anatomy of mouse and human prostate are quite different. To identify the corresponding cell type in mice, single cell RNA sequencing was performed on mouse prostate and urethra tissues. These studies identified hillock cells in mouse urethra and extending into proximal prostate regions. Mice did not possess prostate club cells.

- Urethral hillock cells in mice expressed stem cell markers as well as prostate markers, and can be uniquely identified as Krt4+/Sca1+/Trop2+/NKX3.1- cells.

- Overall, these studies suggest that club and hillock cells may be stem cells that generate the prostate gland but primarily exist in the urethra. These cell types appear to increase in prostate cancer and may be resistant to hormone deprivation therapies. Further studies into the role of these cells in normal prostate and prostate cancer are warranted.

**Figure:** Single cell RNA sequencing was performed on cells taken from different regions of the prostate (left), in order to construct an atlas of the different populations of cells in the prostate gland (right).
PANEL DISCUSSION:

Point-Counter Point: Is there a Biological Basis for Racial Disparities in Prostate Cancer?

Precision Policy

Moderator:
Lorelei Mucci, ScD
Harvard T.H. Chan School of Public Health

Panelists:
Daniel George, MD (Duke University)
Susan Halabi, PhD (Duke University)
Brandon Mahal, MD (Harvard: Dana-Farber Cancer Institute)
Elizabeth Platz, MPH, ScD (Johns Hopkins Bloomberg School of Public Health and the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins)
Westley Sholes, MPA (Member, California Prostate Cancer Coalition)
Kosj Yamoah, MD, PhD (Moffitt Cancer Center)

This Panel Discussion can be viewed in full at PCF.org:
https://www.pcf.org/scientific-retreat/video/
VA-PCF Precision Oncology Program for Cancer of the Prostate: POPCAP

Bruce Montgomery, MD
University of Washington; VA Puget Sound

Matthew Rettig, MD
University of California, Los Angeles; VA Greater Los Angeles Healthcare System

- The United States Department of Veterans Affairs (VA) is the largest integrated healthcare system in the U.S., comprising 1,243 facilities, with over 9 million veterans enrolled.
- Approximately 50,000 U.S. veterans are diagnosed and treated for cancer each year, making up 3.5% of all cancer cases in the U.S. Of cancer patients in the VA, 78% are White, 19% are Black, and 3% are of other racial or ethnic backgrounds. 97% of VA cancer patients are male.
- Prostate cancer is the most frequently diagnosed cancer among veterans, representing 32% of cancer cases seen in the VA. There were 11,376 cases of prostate cancer diagnosed in the VA in 2014.
- Veterans who receive their medical care from the VA usually remain in the VA healthcare system for their lifetimes. Thus the VA health care system represents a place where investments in prostate cancer care have significant potential for wide implementation and great impact.
- In 2016, the Prostate Cancer Foundation (PCF) and the VA announced a partnership to advance precision medicine for U.S. veterans. As part of this announcement, PCF pledged $50 million to support the PCF Veterans Health Initiative to expand prostate cancer precision oncology research among veterans to speed the development of new precision treatment options and cures for prostate cancer patients.
- This initiative includes funding for investigators conducting studies involving veteran prostate cancer patients and the VA, establishing PCF-VA Centers of Excellence, and the establishment of prostate cancer precision medicine clinical trials within the VA.
- Drs. Bruce Montgomery and Matthew Rettig have led the implementation of the VA/PCF Precision Oncology Program for Cancer of the Prostate (POPCAP) program, which has opened several prostate cancer precision medicine clinical trials within the VA.
- The goal of the POPCAP program is to implement precision medicine for US Veterans with prostate cancer across a network of VA centers that have the capacity to facilitate genomic sequencing and clinical trials. Treatments for patients would be selected based on results from genomic sequencing for germline (inherited) and somatic (tumor) mutations, including standard of care treatment, enrollment onto precision medicine clinical trials, or off-label use of FDA-approved drugs for patients found to have targetable mutations.
- In 2018, PCF funded the establishment of ten VA hospitals as “PCF-VA Centers of Excellence” to advance best-in-class precision oncology treatment and care for prostate cancer patients. PCF-VA Centers of Excellence include VA Medical Centers in Chicago, Los Angeles, Tampa, Bay Pines, Seattle, Ann Arbor, Manhattan, the Bronx, Washington DC, Durham, and Philadelphia.
• The POPCAP network includes these 10 PCF-VA Centers of Excellence, plus additional VA Medical Centers in Minneapolis, MN, Portland, OR, San Francisco, CA, Dallas, TX, Houston, TX, and Orlando, FL.

• A Data Core has been implemented to support the goals of the POPCAP program. The VA has its own electronic medical record system, VINCI, which houses all clinical patient data including clinic notes and reports from imaging scans, lab tests, and pathology.

• A PCF-funded team is developing artificial intelligence algorithms to study patient data from the VINCI system.

• The team trained a natural language processing algorithm to identify all veterans with metastatic prostate cancer from the notes on their clinical charts (Figure). The algorithm was found to be ~98% accurate at identifying patients with metastatic prostate cancer.

• At the time of this presentation, using this program, the team had identified 1,081,137 prostate cancer patients within the VA, 488,984 of whom are living, 63,222 of whom had metastatic prostate cancer, and 16,618 who are living with metastatic prostate cancer. The ages and race of these veterans could also be determined.

• The team is now building a biorepository of archival biopsy and/or prostatectomy samples from VA prostate cancer patients. These samples will be studied to understand tumor pathology, mutations, gene expression, and other biological features.

• The Million Veteran Program (MVP) is a program within the VA that aims to study germline genomic variations in 1 million veterans. Thus far, data for ~750,000 veterans has been collected, including ~70,000 prostate cancer patients.

• This study enables identification of individuals who carry inherited mutations in genes that increase cancer risk, and have implications for precision medicine treatment selection (BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, and PALB2). Of the ~70,000 prostate cancer patients evaluated thus far, 2,833 were found to have mutations in one of these genes. A program is currently being set up to return the results from the MVP study to patients, along with any treatment recommendations based on mutations identified.

• The POPCAP program has opened several prostate cancer precision medicine clinical trials in the VA.

• These include the phase 2 BRACeD trial, which is comparing the efficacy of carboplatin followed by docetaxel versus docetaxel followed by carboplatin in mCRPC patients with a germline or somatic inactivation in BRCA1/2 or PALB2.

• The phase 2 CHOMP trial is testing checkpoint immunotherapy in mCRPC patients with a mismatch repair (MMR) gene deficiency or loss/inactivation of both alleles of the CDK12 gene.

• To date, PCF has provided an estimated $40 million in funding commitments to advance our Veterans Health Initiative. This includes $25 million to support our 10 Centers of Excellence, $11.5 million to 12 team science “Valor” Challenge Awards, and $3.8 million to 18 PCF-VA Young Investigators.
**SPECIAL LECTURE: Becoming a Great Partner in the Fight Against Prostate Cancer**

Rachel Ramoni, DMD, ScD  
Veterans Health Administration

- The United States Department of Veterans Affairs (VA) is the largest integrated healthcare system in the U.S., with 170 medical centers and over 1,000 community-based outpatient clinics. Approximately 9 Million veterans seek care at the VA every year.

- The VA has a 2020 research budget of $800 million per year, which is used to fund intramural research and infrastructure.

- Currently there are over 16,000 veterans living with metastatic prostate cancer who are receiving care within the VA.

- The VA serves as an important site for national clinical trials. The first multi-site clinical trial in the VA was conducted in the 1940s. Prostate cancer clinical trials conducted at VA sites include PIVOT, a trial which compared radical prostatectomy vs. observation for localized prostate cancer.

- An ongoing VA program is the Million Veteran Program, which aims to determine relationships between genetics, lifestyle, and military exposures with disease risk and health outcomes in 1 Million veterans. Thus far, ~800,000 men have been enrolled in this program.

- Dr. Rachel Ramoni, chief research and development officer (CRADO) at the VA, discussed ongoing VA programs to increase access to high quality clinical trials in the VA and the real world impact of VA research.
• In 2016, the Prostate Cancer Foundation (PCF) and the VA announced a partnership to advance translational prostate cancer care and research. (Further details on this program and its achievements were discussed in the previous talk by Drs. Bruce Montgomery and Matthew Rettig.)

• In 2018, the VA Access to Clinical Trials for Veterans Initiative (actforveterans.org) was initiated. This initiative outlined infrastructure changes that will speed and remove barriers to clinical trials in the VA. These include increasing IRB review capacity, creating a single point-of-contact for industry-sponsored trials, implementing a single VA-wide electronic IRB platform, reducing the time to sign non-disclosure agreements, and developing tools to help with site selection.

• The VA is also working to increase the real-world impact of VA research. This includes implementing post-trial surveillance into trials, working with clinical partners to help select the most impactful research for funding, and using findings from the Million Veteran Program to direct impactful new clinical research and trials.

• As a part of the PCF-VA partnership, a Data Core is being established that can be used for operations and research. The Data Core has identified all Veterans diagnosed with prostate cancer. It contains curated patient demographics, clinical data, treatments, and outcomes, including results from clinical genetic and genomic sequencing tests. Natural language processing algorithms have been developed to identify all veterans diagnosed with metastatic prostate cancer, both living and deceased. This initiative will enable deployment of artificial intelligence based systems to make new discoveries and will facilitate rapid identification of patients eligible for clinical trials.

• Next generation sequencing (NGS) of patient tumor tissues or blood is used in precision oncology to identify clinically actionable gene alterations that may inform treatment selection. Since 2012, 975 patients have undergone NGS testing for their prostate cancer diagnosis under the VA National Precision Oncology Program (Figure). The genomic test results from these patients is being merged into the Prostate Cancer Data Core.

• This demonstrates that Veterans with prostate cancer have access to cancer genomic testing, which may be better than most prostate cancer patients in the U.S. Furthermore, it may be possible to conduct and fulfill enrollment for metastatic prostate cancer precision oncology clinical trials for less common mutations like CDK12-loss (present in ~5-10% of metastatic prostate cancer cases) entirely within the VA.

**Figure:** The most commonly identified gene alterations among 975 VA prostate cancer patients who underwent next generation sequencing (NGS) tests.
Immunotherapy Associated Cardiotoxicities: Of Mice and Men

Javid Moslehi, MD
Vanderbilt University Medical Center

- Immune checkpoint inhibitors (ICI) are highly effective treatment options that can produce long-term remissions and even cures in some patients with cancer, although this treatment type is still being optimized for prostate cancer.
- Dr. Javid Moslehi has found that about 1% of cancer patients treated with combination checkpoint immunotherapy develop myocarditis, with a 50% mortality rate in affected patients. This new clinical syndrome has been termed “Immune Checkpoint-Inhibitor (ICI) Associated Myocarditis” (Figure).
- This syndrome occurs early, is unpredictable, and is defined by T cell and macrophage infiltration into heart tissue, leading to various heart problems, including arrhythmias.
- The main risk factor for ICI-myocarditis is ICI-combination treatment (for example, CTLA4 + PD1 inhibition).
- Dr. Moslehi’s laboratory has created pharmacological mouse models of ICI-myocarditis. In collaboration with Dr. James Allison’s group, he has additionally made genetic knockout models. In both mouse models, CTLA4 signaling appears to be critical for the development of myocarditis. Early data from both mouse models and patients with ICI-myocarditis suggest that treatment with the CTLA4-ligand abatacept could ameliorate the phenotype and even prevent mortality.
- Dr. Moslehi’s group is now utilizing a web-based platform (www.cardioonc.org) which he has used to collect ICI-myocarditis cases to start an international trial with abatacept for ICI-myocarditis treatment.
- In summary, Dr. Moslehi identified a new syndrome of “Immune Checkpoint Inhibitor (ICI)-Associated Myocarditis” that affects about 1% of cancer patients treated with combination checkpoint immunotherapy and has a 50% mortality rate. Treatment with the CTLA4-ligand abatacept may prevent myocarditis in these patients. Investigations into novel treatment-associated syndromes and therapeutic approaches to overcome these morbidities and mortalities is critical for advancing cancer patient care.
- Dr. Moslehi’s work exemplifies the unique power of multi-disciplinary collaborations for this type of research. He emphasized the close collaborations with Drs. Doug Johnson (melanoma specialist, Vanderbilt University Medical Center), Justin Balko (cancer biologist, Vanderbilt University Medical Center), Jeff Sosman (oncologist, Northwestern University) and Joe-Elie Salem (cardiologist/pharmacologist, Sorbonne University, France).
ICI-Associated Myocarditis: Defining a New Clinical Syndrome

Figure: Histopathology and clinical features of the new clinical syndrome "Immune Checkpoint-Inhibitor (ICI) Associated Myocarditis."

ICI-Associated Myocarditis:
- T cell and macrophage infiltration in striated muscle
- ECG abnormalities,
- Arrhythmia
- 1% incidence with combination therapy

Who and when:
- Early and unpredictable
- 50% mortality
- Combination ICI- main RF
- Concomitant myositis, MG

Mosleh...Johnson, Lancet, 2018

Bigger problem:
- Other heart and vessel Problems (Pericarditis, Vasculitis, Arrhythmias)
- High mortality

Salem...Johnson, Mosleh, Lancet Oncology 2018

Johnson...Sosman, Mosleh. New England Journal of Medicine, 2016
Clinical trials are necessary to determine whether a new treatment is superior to the current standard of care for improving the length and/or quality of patients' lives. To receive FDA-approval, a new treatment must typically proceed through three phases of clinical trials. Phase 1 trials test safety and determine an optimal and tolerable dose in a small number (up to a few dozen) of patients. Phase 2 trials are used to indicate if a treatment has promising anti-cancer activity (typically a few dozen to a few hundred patients). If treatments “pass” a phase 2 trial, they may be taken into a phase 3 trial, which typically randomizes patients to the new treatment compared to the standard of care in several hundred to several thousand patients, often in a blinded fashion (the patient and physician do not know which treatment the patient received). Phase 3 trials can be complex, time consuming, and very costly, but are typically required for regulatory approval of a new treatment.

In an effort to streamline and reduce the cost and number of patients needed to test multiple treatments in phase 3 trials, investigators in the UK and Switzerland devised the STAMPEDE trial. STAMPEDE is a multi-arm, multi-stage randomized phase 3 clinical trial that is comparing several different treatment regimens in prostate cancer patients who are starting long-term ADT (men with node-positive or metastatic disease, who are newly diagnosed or relapsing after previous primary treatment with surgery or radiation).

The unique multi-arm multi-stage design of the STAMPEDE trial allows test arms to be added over time and compared to men treated with a contemporary standard-of-care from a single ongoing control arm. Because of the trial design, only a single “control” arm is needed for many comparison arms, significantly reducing the number of patients that would have been needed if each treatment had been tested in an independent trial requiring its own control arm (Figure).

The primary outcome measure for the STAMPEDE trial is overall survival.

Secondary outcome measures include failure-free survival (FFS; time to death from prostate cancer, distant metastasis, lymph node failure, local failure, or PSA failure (rise to >4ng/ml & 50% above nadir in first 24 weeks), whichever comes first), progression-free survival (PFS; time to death from prostate cancer, distant metastasis, lymph node failure, or local failure, whichever comes first), metastatic progression-free survival (MPFS; time to death from any cause, new distant metastases, or metastatic progression, whichever comes first), skeletal-related events (SRE), toxicity, quality of life, and health economics.

Since 2005, the trial has enrolled over 11,000 men into the equivalent of 11 randomized control trials and made several practice-changing findings.

Dr. Nicholas James, a leader of STAMPEDE, discussed the practice-changing findings of the trial.

Importantly, the trial demonstrated that adding new arms to the trial is fast and feasible. When the trial initiated in 2005, there was one control arm and 5 comparator arms. Between 2011 and 2019, 5 additional comparator arms have been added. While the control arm is ongoing, the first 7 comparator arms have been completed.

Activating new clinical trials can be time consuming, as much paperwork and institutional and governmental reviews and approvals are needed, which must be performed for all clinical sites involved. The design of STAMPEDE significantly reduces the time to open new treatment arms at all of the study centers (currently over 120).
• The trial demonstrated that the addition of docetaxel in men with hormone-naïve prostate cancer who are starting ADT improves overall survival, with a reduction in risk of death representing 22%. Docetaxel also improved failure-free survival by 39% and reduced the risk of skeletal events by 40%.

• While the phase 3 CHAARTED trial found that the addition of docetaxel in this setting only benefitted men with high-burden metastatic disease, STAMPEDE found that adding docetaxel to the standard of care (ADT +/- radiotherapy) improves overall and failure free survival in newly diagnosed metastatic hormone-naïve prostate cancer regardless of metastatic burden. In STAMPEDE, docetaxel reduced the risk of death by 34% in patients with low-burden metastatic disease and by 19% in patients with high-burden metastatic disease (Figure).

• These results demonstrate that docetaxel be considered as a first-line option alongside second generation anti-androgens for all patients newly diagnosed with metastatic hormone-naïve prostate cancer, regardless of disease burden.

• The STAMPEDE trial found that the addition of Zoledronic acid alone or with docetaxel had no benefit.

• The STAMPEDE trial found that the addition of abiraterone in men with hormone-naïve prostate cancer who are starting ADT improves overall survival, with a reduction in risk of death representing 37% (Figure). Abiraterone was beneficial in patients with both high risk and low risk disease (reduction in risk of death representing 46% and 34%). Abiraterone also improved failure-free survival by 71% and reduced the risk of skeletal events in patients with metastatic disease by 64%.

• A head-to-head comparison performed using 566 patients who were treated contemporaneously on the abiraterone and docetaxel arms found no significant difference in overall survival between the two regimens. However, slightly more men on the abiraterone arm died from non-prostate cancer causes such as cardiovascular disease and fractures, suggesting that overtreatment with abiraterone may have increased the risk of death in some men.

• The STAMPEDE trial found that addition of radiotherapy to the primary tumor improves survival in men with newly-diagnosed low burden metastatic prostate cancer who are starting ADT +/- docetaxel (reduction in risk of death representing 32%; reduction in failure-free survival of 41%). No statistical benefit was seen for the addition of radiotherapy in patients with high-burden metastatic disease.

• Health economic analyses are being conducted for the different treatments. Thus far, data has demonstrated that patients treated with docetaxel experience a quality-of-life gain, due to delaying metastatic disease progression.

• Approximately 4,000 men have already experienced a gain in survival on the completed arms in this trial.

• Correlative studies are being conducted using samples from patients on the trial to evaluate questions such as whether patients with certain hereditary cancer risk genes or tumor mutations have different treatment responses, and to evaluate the relationships between tumor biology, pathology, and molecular imaging.

• New trial designs and data evaluation methods are being employed to efficiently add new trial arms in new international centers.

• Thus far, over 3,000 investigators in the UK and Switzerland have contributed to this trial. New sites for some trial arms are being activated in the U.S., Germany, Australia and New Zealand.
Altogether, STAMPEDE has demonstrated that a trial of this design can rapidly test numerous treatment regimens in a multi-center phase 3 randomized setting, and has resulted in several new standard-of-care regimens for men with advanced prostate cancer.

**Multi-arm multi-stage (MAMS) approach**

- **Multi-arm**
  - Test many relevant approaches

- **Use fewer resources**
- **Cost per comparison is much less**
- **Less bureaucracy**

**Figure:** The unique multi-arm multi-stage design of the STAMPEDE trial allows test arms to be added over time and compared to men treated with a contemporary standard-of-care from a single ongoing control arm. Because of the trial design, only a single "control" arm is needed for many comparison arms, significantly reducing the number of patients that would have been needed if each treatment had been tested in an independent trial requiring its own control arm.

![Multi-arm multi-stage (MAMS) approach diagram](image)

**Overall Survival: All Patients**

**Docetaxel + SOC vs. SOC**

- **Low Burden**
  - HR: 0.76
  - 95% CI: 0.54 - 1.07
  - P = 0.107
  - Survival: A = 57%, C = 72%
  - Time to randomization: 0-10 weeks

- **High Burden**
  - HR: 0.81
  - 95% CI: 0.64 - 1.02
  - P = 0.064
  - Survival: A = 24%, C = 34%
  - Time to randomization: 10+ weeks

**Figure:** STAMPEDE found that adding docetaxel to the standard of care (SOC; ADT +/- radiotherapy) reduced the risk of death by 34% in patients with low-burden metastatic disease (left) and by 19% in patients with high-burden metastatic disease (right).
Figure: The STAMPEDE trial found that the addition of abiraterone in men with hormone-naive prostate cancer who are starting ADT improves overall survival, with a reduction in risk of death representing 37%.

**SPECIAL LECTURE: Molecular Stratification: PARP Inhibitors and Beyond**

Johann de Bono, MD, PhD  
Institute of Cancer Research; Royal Marsden NHS Foundation Trust, UK

- PARP-inhibitors, including olaparib, are a new class of therapies that are FDA-approved for the treatment of breast and ovarian cancers with mutations in the \( BRCA1 \) and \( BRCA2 \) genes.
- The use of PARP-inhibitors in \( BRCA1/2 \)-deficient tumors represents an example of “synthetic lethality.” Synthetic lethality is a concept in which tumor cells that have lost activity of one molecular pathway (typically via mutations) become highly dependent on a second related pathway for survival. Therapeutically targeting the second pathway achieves selective killing of the cancer cells while sparing normal cells in which the first pathway is still intact.
- The PCF International Dream Team found that alterations in \( BRCA2 \) and related DNA damage repair (DDR) genes are present in 20-30% of metastatic castration-resistant prostate cancer (mCRPC) cases, suggesting that these patients may exhibit sensitivity to PARP-inhibitors.
Dr. Johann de Bono and team initiated the phase 2 TOPARP trial to evaluate the anti-tumor efficacy of the PARP-inhibitor olaparib in prostate cancer and to clinically qualify predictive biomarkers of response to olaparib. This trial consisted of a two-part schema, TOPARP-A and TOPARP-B.

In TOPARP-A, patients were not molecularly selected for enrollment onto the trial, but were evaluated retrospectively for tumor mutations that associated with responses. Results from TOPARP-A demonstrated that 14 of 16 patients who responded to olaparib had tumor mutations in BRCA1/2 or other DDR genes. Only two patients who had mutations in BRCA1/2 or other DDR genes did not exhibit a response to olaparib. These results thus suggested that olaparib may be effective in mCRPC patients with certain DDR gene alterations, particularly BRCA2.

In TOPARP-B, mCRPC patients were prescreened for tumor mutations in BRCA1/2 or other DDR genes for enrollment onto the trial. Patients enrolled were randomized to receive 300mgs vs 400mgs twice daily (BID) tablets of olaparib. This is because the dose of olaparib used in TOPARP-A was 400mgs twice daily, while the dose approved in breast and ovarian cancer is 300mgs twice daily.

The primary endpoint in TOPARP-B was a composite response rate, defined as any of the following: a confirmed radiological response; a PSA decline of ≥50%; or conversion of circulating tumor cell count (CTC) count from ≥5 cells/7.5ml blood at baseline to <5 cells/7.5ml. PSA and CTC responses had to be confirmed by a second consecutive value ≥4 weeks later.

Secondary endpoints included radiologic progression free survival, progression free survival, overall survival, safety and tolerability.

Of 711 patients screened for the trial, 161 had DDR gene mutations (27.2%), 431 had no DDR gene mutations (72.8%), and 119 were unsuccessfully screened. 98 patients with DDR mutations were enrolled onto the trial (49 in each arm), 92 of whom were evaluable for the primary endpoint analysis. Of the 98 patients treated, 31 had BRCA1 or BRCA2 mutations, 21 had ATM mutations, 20 had CDK12 mutations, 5 had PALB2 mutations, 18 had mutations in other DDR genes, and 3 had mutations in more than one DDR gene.

Overall, of 92 evaluable patients, composite responses were observed in 43 patients (46.7%), including 39.1% of patients in the 300mg dose arm and 54.3% of patients in the 400mg dose arm. The higher dose was slightly more active, however more patients on this arm had dose reductions, and some gene mutations were unbalanced between the two arms.

Composite responses were observed in 25 of 30 (83.3%) patients with BRCA1/2 mutations, 7 of 19 (36.8%) patients with ATM mutations, 5 of 20 (25%) patients with CDK12 mutations, 4 of 7 (57.1%) patients with PALB2 mutations, and 4 of 20 (20%) patients with other DDR gene (BRCA2+CDK12+CHEK2; FANCA; WRN; and CHEK2) mutations. (These are non-mutually exclusive subgroups, as one patient with BRCA1/2+CDK12+other mutations and two patients with PALB2+other mutations were included in the analysis for each subgroup separately.)

Patients with BRCA1/2 mutations tended to have the most consistent, deep, and longest responses.

Dr. de Bono also presented results from the phase 3 PROfound trial, which tested olaparib versus physician’s choice of enzalutamide or abiraterone men with mCRPC who failed prior treatment with enzalutamide or abiraterone, and who had a tumor mutation in a DDR gene.

PROfound enrolled two cohorts: patients with mutations in BRCA1, BRCA2, or ATM (cohort A), and patients with mutations in any of 12 other predetermined DDR genes (cohort B; BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD51E, and XRCC5).
Patients in each cohort were randomized 2:1 to receive olaparib vs. physician’s choice of enzalutamide or abiraterone.

- The primary endpoint in this trial was radiographic progression free survival (growth of tumors on scans or death, whichever came first).

- Of 4,425 patients prescreened internationally for this trial, 4,047 patients were tested for tumor mutations, testing was successful in 2,792 (69%) patients, and 387 patients were enrolled into the trial. Most of the tumor samples tested were archival tissues including primary and metastatic tumor specimens.

- Overall, 17.1% of successfully tested patients had a Cohort A mutation (BRCA2, BRCA1, ATM), and 28% had a mutation in any one of the 15 DDR genes being tested for (Cohort A+B). The most commonly mutated DDR gene was BRCA2 (8.7%).

- The patients on this trial had been heavily pretreated: all had been treated with either abiraterone (40%), enzalutamide (41%) or both (19%), and 66% had previously been treated with taxane chemotherapy (docetaxel, cabazitaxel, or both).

- In PROfound, olaparib significantly delayed the time to radiographic disease progression (tumors growing on scans) or death (whichever came first) compared with abiraterone or enzalutamide, by an average of 3.84 months (7.39 months vs. 3.55 months) in Cohort A (BRCA1, BRCA2, or ATM mutations), and by an average of 2.3 months (5.82 months vs. 3.52 months) in Cohorts A+B combined (mutations in any qualifying DDR gene) (Figure). This represents a reduction in risk of metastatic disease progression or death by 66% in Cohort A, and by 51% in Cohorts A+B.

- In a subgroup analysis in cohort A for radiographic disease progression, olaparib was superior to physician’s choice for all subgroups analyzed, including whether patients were previously treated with taxane chemotherapy, the presence vs absence of measurable disease at baseline, sites of distant metastasis, ECOG scores, age, baseline PSA levels below or above the median, and the continent where patients received treatment.

- At 12-months post-enrollment, 40% of men in Cohort A who received olaparib had no radiographic disease progression vs 11% of men who had received abiraterone or enzalutamide.

- Response rates, a measure of tumor shrinkage on scans, could be determined for men who had metastatic sites considered measurable at the start of treatment. Overall, in men with measurable disease in Cohort A, 33.3% who received olaparib responded, while only 2.3% who received abiraterone or enzalutamide responded. In men with measurable disease in Cohorts A+B, 21.7% who received olaparib responded and 4.5% who received abiraterone or enzalutamide responded.

- Olaparib prolonged overall survival by an average of 3.39 months (18.5 vs 15.11 months) in Cohort A (36% reduction in risk of death), and by 3.25 months (17.51 vs 14.26 months) in Cohorts A+B (33% reduction in risk of death), despite 80% of the men in the control arm crossing over to receive olaparib as soon as they progressed on abiraterone or enzalutamide. However, the data from the trial is still not mature enough to definitively conclude whether olaparib prolongs overall survival.

- Olaparib also significantly delayed the average time to pain progression by 56% in Cohort A, and by 36% in Cohorts A+B.

- Patients with mutations in BRCA2 were the most likely to benefit from olaparib, although some responses were seen in patients with other, rarer DDR gene mutations. In patients with BRCA2 mutations, olaparib delayed the time to radiographic disease progression by an average of 7.36 months, compared with abiraterone or enzalutamide (10.84 months vs. 3.48 months).
Across both cohorts A and B, adverse events were more common in patients receiving olaparib vs abiraterone or enzalutamide (95.3% vs. 87.7% for adverse events of any grade; 50.8% vs 37.7% for grade 3 adverse events). However, patients on olaparib received treatment for a longer time (an average of 7.4 vs. 3.9 months), which may have contributed to higher rates of side effects.

Grade 3 adverse events occurring in patients who received olaparib included anemia (21.5%), fatigue and physical weakness (2.7%), vomiting (2.3%), difficult or labored breathing (2.3%), urinary tract infection (1.6%), nausea (1.2%), and decreased appetite (1.2%). 4.3% of patients who received olaparib experienced a non-fatal pulmonary embolism (vs. 0.8% who received abiraterone or enzalutamide). Overall, physicians considered olaparib to be well-tolerated.

Overall, the PROfound trial was the first biomarker-preselected “precision medicine” phase 3 study that demonstrated a clinical benefit for a targeted therapy in men with mCRPC. These results demonstrate the potential for precision medicine and synthetic lethal approaches to cancer treatment.

These results may soon lead to an FDA-approval for olaparib that may benefit many of the 20-30% of men with advanced prostate cancer that harbor a single DNA alteration in their tumor, particularly patients with BRCA2 gene alterations.

**Figure:** In the phase 3 PROfound trial, olaparib significantly delayed the time to radiographic disease progression (tumors growing on scans) or death (whichever came first) compared with abiraterone or enzalutamide, by an average of 3.84 months (7.39 months vs. 3.55 months) in Cohort A (BRCA1, BRCA2, or ATM mutations). This represents a reduction in risk of metastatic disease progression or death by 66% in Cohort A.
SPECIAL LECTURE:
STATE OF THE SCIENCE 2019

Jonathan Simons, MD
President and CEO
Prostate Cancer Foundation

This talk can be viewed in full at PCF.org:
https://www.pcf.org/scientific-retreat/video/

KEYNOTE ADDRESS

Michael Milken
Founder and Chairman
Prostate Cancer Foundation

This talk can be viewed in full at PCF.org:
https://www.pcf.org/scientific-retreat/video/
Merkel cell carcinoma (MCC) is a rare but highly aggressive form of skin cancer. MCC is more lethal than melanoma with ~40% mortality rate, compared with a ~8% mortality rate for melanoma.

MCC is characterized by its neuroendocrine features.

Study of MCC may provide important insights into the biology and possible treatment approaches for the aggressive subtype of neuroendocrine prostate cancer (NEPC) as these two cancer types share many clinical and biological features.

MCC is caused by either a ubiquitous skin virus, the Merkel cell polyomavirus (~80% of cases), or by mutations caused by sunlight exposure (~20% of cases). While the Merkel cell polyomavirus is present on the skin of nearly everyone, the steps required for it to transform skin cells into cancer are extremely rare, and include breakage of the viral genome and integration of certain segments of the viral sequences into the genome of the skin cell.

MCC driven by the virus will express viral proteins. MCC driven by sunlight exposure have very high levels of mutations and will express many mutated proteins. Thus, MCC driven by either etiology are "immunogenic." Cells that express viral or mutated proteins appear foreign to the patient and can be targeted by the immune system.

While MCC are often able to evade the immune system through various mechanisms, studies have found that patients with MCC tumors that are infiltrated by T cells do not die from this disease. These data suggested that MCC may be responsive to treatment with checkpoint immunotherapy, which is a type of treatment that activates a patient's immune system to fight their cancer.

Until recently, the standard of care for MCC was chemotherapy, however this treatment delivers only a slight and temporary benefit and nearly all patients eventually succumbed to their disease.

Dr. Nghiem and team led several clinical trials testing the efficacy of immune checkpoint therapy in MCC, which ultimately demonstrated that many MCC patients are highly responsive and can achieve durable responses with this treatment.

In a trial testing second line therapy in MCC patients, overall survival of patients treated with the anti-PDL1 immune checkpoint therapy avelumab was 50% at 1 year and 36% at 2 years. In comparison, based on historical data, 0% of patients treated with chemotherapy as second line therapy were alive after 1 year.

In a trial testing pembrolizumab as first-line therapy in MCC patients, overall survival was 72% at 1 year and 64% at 3 years (Figure). In comparison, in historical data, only 10% of patients treated with chemotherapy as first-line therapy were alive after 3 years.

These studies resulted in recent FDA approvals for avelumab (2017) and pembrolizumab (2018) for the treatment of MCC. Checkpoint immunotherapy is now first-line treatment for MCC.

Despite these advances, only approximately half of MCC patients experience long-term benefit from immune checkpoint therapy. More research is needed to identify which patients will benefit from checkpoint immunotherapy and to develop new treatments for MCC.
Like MCC, NEPC is characterized by the expression of neuroendocrine proteins. NEPC is currently incurable.

NEPC is often characterized by mutations in the tumor suppressor genes RB1 and TP53. RB1 and TP53 are also commonly mutated in MCC.

Ongoing studies by Dr. Nghiem’s lab are comparing the molecular features and biology of MCC and NEPC in order to identify new treatments for both types of cancer. These studies may also benefit patients with other types of cancer that develop neuroendocrine features, such as small cell lung cancer.

**Figure:** Overall survival of MCC patients treated with pembrolizumab as first-line therapy was 72% at 1 year and 64% at 3 years. In comparison, in historical data, 10% of MCC patients treated with chemotherapy as first-line therapy remained alive after 3 years.
Treatment-Associated Small Cell/Neuroendocrine Prostate Cancer: Defining the Syndrome

Eric Small, MD
University of California, San Francisco

- The Androgen receptor (AR) is the primary driver of prostate cancer. Androgen deprivation therapy (ADT) has long been the primary treatment for advanced prostate cancer. Unfortunately, most prostate cancer cases eventually develop resistance to ADT and progress to become castration resistant prostate cancer (CRPC). A primary treatment option for men with metastatic CRPC are the more potent AR-targeted therapies, abiraterone and enzalutamide. However, nearly all cases of CRPC eventually develop resistance to these treatments as well.

- Dr. Eric Small led the PCF West Coast Prostate Cancer Dream Team which conducted a clinical study to understand the mechanisms of treatment resistance in metastatic CRPC. Patients enrolled in this study had metastatic CRPC. The majority had developed progressive disease following treatment with abiraterone or enzalutamide, and underwent metastatic tumor biopsies before starting their next line of therapy and, whenever possible, following treatment failure. These biopsies were studied to determine mechanisms of AR-targeted therapy resistance.

- Overall, biopsy success rate was greater than 70%, and over 300 evaluable biopsy samples were obtained from various metastatic sites including bone, liver, lymph node, and other soft tissues.

- One mechanism of resistance to AR-targeted therapy is the transformation of CRPC into treatment associated small cell/neuroendocrine (t-SCNC) prostate cancer. t-SCNC prostate cancer is highly aggressive and can be defined both histologically as well as genomically.

- Although SCNC can be found in prostate cancer patients at initial diagnosis (de novo), it is extremely rare, occurring in less than 1% of patients. De novo SCNC has similar histology to treatment induced-SCNC and is also associated with a poorer prognosis.

- A surprising finding of this study was the high frequency at which t-SCNC was found to be present. Of the patients with evaluable biopsies in this study, 17% could be classified as having either pure (12%) or mixed (5%) t-SCNC prostate cancer. Pure t-SCNC tumors had no areas with typical adenocarcinoma CRPC cells. Tumors from patients with “mixed SCNC” had areas with both typical adenocarcinoma CRPC and t-SCNC cells. The presence of t-SCNC on biopsy, whether pure or mixed, was associated with shorter overall survival times (Figure). Median overall survival was 44.5 months for patients with typical adenocarcinoma CRPC vs. 36.6 months for patients with t-SCNC.

- t-SCNC appears to be a distinct entity from de novo SCNC, in that patients with t-SCNC may sometimes have elevated PSA levels.

- Many clinical features were similar between adenocarcinoma CRPC and t-SCNC including serum PSA levels, AR expression, and the anatomic location of metastases.

- It was previously thought that t-SCNC metastases are more prevalent in soft tissue sites such as lung and liver and less prevalent in bone. However, in this study, both
adenocarcinoma CRPC and t-SCNC metastases were found at similar frequencies in bone, liver, and lymph nodes.

- It was also previously thought that t-SCNC tends not to express PSA and AR. However, in this study, median PSA levels were 64.8 in patients with t-SCNC and 46.2 in patients with adenocarcinoma CRPC. 75% of t-SCNC samples expressed medium to high levels of AR (compared with 87% of adenocarcinoma CRPC).

- Amplification of the AR gene or mutations that increase AR pathway activity are common resistance mechanisms observed in CRPC. AR amplification or AR-activating mutations were observed in 67% of t-SCNC samples and 51% of adenocarcinoma CRPC.

- Despite high levels of AR, its activity was lower in t-SCNC. AR activity, as measured by the expression of genes regulated by AR, was lower specifically in patients who had developed t-SCNC in biopsies taken after the development of treatment resistance.

- A gene-expression based signature was developed that could identify t-SCNC tumors with high accuracy. Patients with a t-SCNC gene expression signature had significantly shorter overall survival than patients with an adenocarcinoma CRPC gene expression signature.

- Genomic sequencing analyses found that 83% of t-SCNC tumors had loss of the tumor suppressor genes, TP53 and/or RB1, while only 34% of non-SCNC tumors had these mutations.

- Overall, these studies demonstrate that t-SCNC is prevalent among CRPC patients, and is associated with poorer outcomes and certain distinct molecular features. Clinical features such as location of metastases and serum PSA levels are not able to distinguish t-SCNC, suggesting that tumor and/or liquid biopsies are likely necessary to diagnose t-SCNC. New therapeutic approaches remain urgently needed for this aggressive subtype of CRPC.

**Figure:** The presence of treatment induced-SCNC (t-SCNC) on biopsy was associated with shorter overall survival times than for patients with typical adenocarcinoma CRPC.
Lineage Plasticity in Advanced Prostate Cancer: How Many Lineages? And How Plastic Are They?

Peter Nelson, MD
Fred Hutchinson Cancer Research Center

- The androgen receptor (AR) is the primary driver of growth and survival of both normal prostate cells and prostate cancer cells. Because prostate cancer cells are so highly dependent on signals from AR to survive, androgen deprivation therapy (ADT) has been the cornerstone of treatment for advanced prostate cancer for decades.

- However, most cases of prostate cancer eventually develop resistance to ADT and progress to “castration-resistant prostate cancer” (CRPC). CRPC is commonly still driven by AR due to mutations that amplify the activity of the AR pathway, a finding which led to the development of an even stronger class of AR-targeted therapies (abiraterone, enzalutamide, apalutamide and darolutamide).

- Unfortunately, nearly all cases of CRPC will eventually develop resistance to these stronger AR-targeted therapies. This increasingly occurs through mechanisms which allow the prostate cancer cells to lose dependence on AR and/or to convert into other cell types that do not use AR to grow or survive. The ability of cancer cells to convert into other cells types is referred to as “plasticity” or “trans-differentiation.”

- Alternate prostate cancer cell states that have now been observed in patients with CRPC include neuroendocrine, amphicrine (the same cells having both prostate (AR) and neuroendocrine features), adult stem cell, neuronal stem cell, mesenchymal, basal, gastrointestinal, squamous, and other cell types. The tumor and tumor environment features which drive the development of these different prostate cancer states remain unclear.

- Dr. Peter Nelson and team have evaluated new technologies to investigate the complexity and plasticity of prostate cancer cells and the prostate tumor microenvironment, including other cell types present in prostate tumors, such as immune cells.

- Digital spatial profiling allows simultaneous quantification of over 2,000 genes and 60 proteins expressed in selected microscopic regions of prostate tumor tissues.

- Dr. Nelson presented an example of a gradient of cellular plasticity within a single metastatic tumor, in which different regions across the tumor progressively lost AR expression and gained expression of an alternate program stimulating prostate cancer growth driven by the FGF-MAPK pathway (Figure).

- Loss/mutation of the tumor suppressor genes TP53 and RB1 have been observed in aggressive variants of CRPC including neuroendocrine prostate cancer (NEPC).

- In an autopsy case series evaluated by Dr. Nelson, ~6% of CRPC cases had lost both TP53 and RB1. While many were NEPC, a large subset retained AR expression.

- Dr. Nelson further investigated the biology and clinical features of CRPC tumors that had lost RB1 and TP53, but were not NEPC. These tumors expressed AR and responded to enzalutamide. However, patients with CRPC with loss of TP53 and RB1 had poorer outcomes, including shorter overall survival and shorter time on enzalutamide and abiraterone treatment.

- Dr. Nelson sought to determine if any treatments could be identified that were more effective against CRPC cells with loss of TP53 and RB1 compared with TP53/RB1-positive CRPC. No single treatment was found to be more effective in this subtype of CRPC, including platinum chemotherapy, AURKA-inhibitors, topoisomerase inhibitors, CDK4/6-inhibitors,
bromodomain-inhibitors, and EZH2-inhibitors. However, several drug combinations were promising, including the combination of a PARP-inhibitor with an ATR-inhibitor.

- Overall, these studies demonstrate that loss of $TP53+RB1$ does not universally lead to the development of NEPC, but can result in various prostate cancer states with different biology and clinical features.
- Overall, these studies highlight the ability of prostate cancer to differentiate into many different cell types (at least 6) in the presence of more potent and longer-term use of AR-targeting therapies.
- Future studies are needed to better understand the mechanisms of prostate cancer lineage plasticity and to identify new treatments that are effective at preventing the development and/or growth of these various aggressive and currently untreatable subtypes of CRPC.

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**Emerging Therapeutic Strategies for Aggressive Variant Prostate Cancers**

Ana Aparicio, MD
University of Texas MD Anderson Cancer Center

- Androgen deprivation therapy (ADT) is a standard of care treatment for advanced prostate cancer. Prostate cancer that has progressed on ADT is referred to as castration-resistant prostate cancer (CRPC).
- While early CRPC often remains responsive to more potent androgen-targeted therapies and/or taxane chemotherapy, such responses are often transient, and the disease typically progresses to more treatment-resistant forms of CRPC.
• Aggressive Variant Prostate Cancer (AVPC) are a subset of highly advanced and aggressive CRPC that are resistant to all standard prostate cancer treatments. AVPC can be defined by certain atypical clinical and pathological features, many of which are shared with small cell prostate cancer.

• AVPC clinical-pathologic features include at least one of the following: visceral metastases only (metastases in soft tissues outside of bone and lymph nodes such as lung and liver); lytic bone metastases; bulky nodes or prostate mass; low PSA levels relative to tumor volume; elevated serum CEA or LDH; primary castration-resistance; and/or small cell carcinoma morphology.

• Dr. Ana Aparicio and others have found that AVPC is characterized molecularly by combined defects (≥ 2) in the TP53, RB1 and PTEN tumor suppressor genes (Figure).

• Prior reports have demonstrated that AVPC may respond to treatment with platinum chemotherapy agents such as carboplatin, which are commonly used to treat other cancer types, but are not standard treatments for prostate cancer.

• Dr. Aparicio and team performed a phase 2 clinical trial in 160 men with metastatic CRPC to test whether patients may benefit with the addition of platinum chemotherapy (carboplatin) to standard taxane chemotherapy (cabazitaxel). Patients on this trial were randomized to receive either cabazitaxel alone or cabazitaxel plus carboplatin.

• This trial demonstrated that the addition of carboplatin extended overall survival of CRPC patients with molecular features of AVPC (defined as defects in ≥ 2 of TP53, RB1 and PTEN). CRPC patients without AVPC did not benefit from the addition of carboplatin.

• Studies have found that defects in the TP53, RB1 and PTEN tumor suppressor genes can result in DNA damage. Also, defects in DNA damage response genes have been shown to predict benefit with platinum chemotherapy and PARP-inhibitors. In addition, studies have found increased expression of DNA damage response genes in neuroendocrine prostate cancer (NEPC), a prostate cancer subtype that overlaps with AVPC, suggesting AVPC patients may benefit from treatment with PARP-inhibitors.

• Based on these studies, Dr. Aparicio initiated a randomized phase 2 clinical trial to test the efficacy of maintenance therapy with the PARP-inhibitor olaparib vs. observation in men with AVPC, after treatment with cabazitaxel plus carboplatin. Early promising results have been seen in this ongoing study.

• AVPC represents a very advanced disease state, where treatments are less likely to be effective. Dr. Aparicio is evaluating whether AVPC can be predicted earlier in the course of disease, and whether distinct subsets of mCRPC can be identified that will respond to specific therapies.

• Dr. Aparicio found that immune response genes were highly expressed in early mCRPC tumors with an androgen-indifferent signature and therefore might represent pre-existing AVPC. These data suggest that AVPC tumors may be immune-suppressive, and that treatments that can overcome this immunosuppression will be needed to treat them effectively. However, treatment with checkpoint immunotherapy alone has not been very effective in patients with advanced prostate cancer. Combinations therapeutic approaches are likely necessary.

• Previous studies have suggested that checkpoint immunotherapy may be synergistic with chemotherapy in various cancers including small cell lung cancer and triple-negative breast cancer, which share clinical and molecular similarities with AVPC.

• Based on these data, Dr. Aparicio and team are initiating a trial in patients with AVPC to test the combination of checkpoint immunotherapy + carboplatin + cabazitaxel, followed by maintenance with a PARP inhibitor alone vs. a PARP inhibitor plus checkpoint immunotherapy.
• Of the AVPC clinical features, bulky lymph nodes and/or prostate mass are associated with the worst clinical outcomes. However, the standard of care treatment for men diagnosed after their disease has already metastasized is hormone therapy, and does not include local treatment of the primary tumor. Whether men with AVPC may benefit from the addition of local therapy (radiation or surgery) of the primary prostate tumor, is an important clinical question.

• Dr. Aparicio and team conducted a clinical trial to test the efficacy of 6 months of hormone therapy followed by hormone therapy alone versus with the addition of local treatment to the primary prostate tumor, in men newly diagnosed with metastatic prostate cancer. Analysis of this trial is ongoing.

• Thus far, the team has found that an AVPC molecular signature can be detected in a subset of men with newly diagnosed metastatic prostate cancer. Studies by others have found that some primary prostate cancer cases also exhibit low AR activity, suggesting these may represent early AVPC. These studies support testing for AVPC features earlier in the disease course, and the identification of more beneficial treatments.

• Altogether, these studies demonstrate that prostate cancer can be classified into different biological subsets with distinct clinical features and therapeutic responses. Platinum chemotherapy may serve as a backbone for the development of multi-modal therapeutic strategies for AVPC. Finally, AVPC may be detectable earlier in the disease course, and may represent an opportunity for the development of earlier and more effective interventions.

Figure: Aggressive Variant Prostate Cancer (AVPC) can be identified by a molecular signature consisting of combined defects (≥ 2) in the TP53, RB1 and PTEN tumor suppressor genes.
SPECIAL LECTURE: Real World Validation of Deep Learning Algorithms in the Assessment of Metastasis by Medical Imaging of Veterans with Prostate Cancer

Matthew Rettig, MD
University of California, Los Angeles; VA Greater Los Angeles Healthcare System

Nicholas Nickols, MD, PhD
University of California, Los Angeles; VA Greater Los Angeles Healthcare System

• New molecular imaging methods are being developed for prostate cancer in order to improve detection sensitivity and specificity. Artificial intelligence algorithms are also being developed to evaluate scan results, in order to improve accuracy and speed for obtaining results.

• The automated bone scan index (aBSI) is an artificial intelligence algorithm that has been developed to quantify the total tumor burden in a patient’s skeleton from bone scans. Studies have demonstrated that aBSI is prognostic for outcomes in patients with metastatic prostate cancer. Patients who have a higher tumor burden on the aBSI index have shorter overall survival and prostate cancer specific survival.

• Drs. Matthew Rettig and Nicholas Nickols conducted a study to determine the performance of the aBSI algorithm in a real-world setting, in veterans with prostate cancer. aBSI was applied to bone scans of 107 veterans with castration sensitive prostate cancer diagnosed and treated at the Greater Los Angeles VA since 2011. Only patients with bone-only metastatic disease were included in this study (no metastases in non-bone sites such as lung, liver, etc). Significantly shorter overall survival and prostate cancer specific survival was observed in patients with higher tumor burden on the aBSI index. The aBSI score was also significantly associated with higher Gleason scores and shorter time from diagnosis to first positive bone scan.

• These studies demonstrate a clinical value for the aBSI algorithm in men with prostate cancer.

• PSMA-PET imaging is a new imaging modality that is highly sensitive and specific for prostate cancer (Figure), and outperforms conventional imaging methods such as CT, bone scans, and MRI for detecting sites of prostate cancer metastases. FDA approval for PSMA-PET imaging for prostate cancer is currently being sought.

• Drs. Rettig and Nickols presented results from a study that compared PSMA-PET/CT (using the $^{18}$F-DCFPyL PSMA PET agent) vs conventional imaging (99mTc-MDP or NaF PET bone scan, CT or MRI of abdomen/pelvis) in 92 Veterans with high-risk prostate cancer at initial staging. The patients in this study had all undergone or planned to undergo conventional imaging, and the study sought to determine whether and how results from PSMA PET/CT scans might change their diagnosis and treatment management decisions.

• In 35% of patients, PSMA-PET imaging findings identified an altered risk group/stage that resulted in a major change in treatment recommendations (29.7% upstaged; 5.5% downstaged). Patients that were upstaged were recommended an increase in duration of ADT and added or increased duration of abiraterone. Patients that were downstaged were
recommended a decrease in duration of ADT and removal of abiraterone. PSMA PET findings also resulted in a change in the radiation target volumes in 35% of patients.

- Artificial intelligence algorithms are also being developed to evaluate images from PSMA-PET.

- Drs. Rettig and Nickols conducted a study to determine if metastatic disease can be predicted using PSMA-PET images of just the prostate area. An artificial intelligence algorithm using prostate-only PSMA-PET/CT imaging in veterans with prostate cancer was found to be highly predictive of co-existing metastatic disease.

- The PSMA-PET artificial intelligence prediction was superior to clinical predictors alone (clinical T stage, biopsy Gleason, % positive cores, PSA), and was not improved by the addition of clinical predictors.

- In summary, PSMA-PET imaging is a new imaging technology for prostate cancer that is highly sensitive and will likely soon be FDA-approved. These studies demonstrate the clinical impact of PSMA-PET, including directing treatment recommendations, and having the ability to predict metastatic disease from prostate-only imaging.

![Figure: Left: examples of PSMA PET/CT imaging of the prostate. Right: Chemical structure of the PSMA-PET imaging agent 18F-DCFPyL.](image)

**[18F] DCFPyL PSMA PET/CT for diagnosis and management of Veterans with prostate cancer at initial staging**
Session 6: New Drugs and Targets in Prostate Cancer: I

Targeting Oncogenic Transcription Factor Signaling Through p300/CBP

Karen Knudsen, MBA, PhD
Thomas Jefferson University

• New treatment strategies and therapeutic targets are urgently needed for men with advanced prostate cancer, a currently incurable disease state.
• CBP and p300 are transcription factors that are involved in a wide array of cellular activities, such as DNA repair, cell growth, differentiation and apoptosis, with unclear roles in cancer.
• Dr. Karen Knudsen and team found that CBP and p300 levels correlate with the activity of androgen receptor (AR) in prostate cancer, are associated with signatures of treatment resistance, and are associated with poorer clinical outcomes. These studies suggest CBP/p300 may be promising new therapeutic targets.
• In preclinical studies, Dr. Knudsen and colleagues found that a novel CBP/p300-inhibitor, CCS1477, has activity against various cancer types. In prostate cancer cell lines, CBP/p300-inhibition suppressed the activity of prostate cancer drivers AR and MYC. CCS1477 also suppressed the growth of prostate tumors in animal models. CCS1477 also suppressed DNA repair factor network activity, and sensitized tumors to treatment with radiation therapy.
• Based on these studies, Dr. Knudsen initiated a phase 1/2a clinical trial to test CCS1477 in patients with metastatic castration resistant prostate cancer (mCRPC) (Figure). This trial is being led by Dr. Johann de Bono in the UK. There are active plans to open the next phase of the study in the U.S.
• Altogether, Dr. Knudsen has identified CBP/p300 as a novel driver in prostate cancer and promising therapeutic target. These findings have already been translated into a clinical trial, and may lead to a new treatment for patients with advanced prostate cancer.
FGFR-Inhibition in Double Negative Prostate Cancer: Rationale and Future Directions

Michael Schweizer, MD
University of Washington

- Prostate cancer is primarily driven by signals from the androgen receptor (AR), which activate the expression of growth and survival genes. Because of this dependency, treatments that target AR have been a standard of care treatment for aggressive and advanced prostate cancer for decades.
- Unfortunately, nearly all cases of prostate cancer eventually develop resistance to AR-targeted therapies and progress to castration-resistant prostate cancer (CRPC). The development of CRPC can be driven by various mechanisms, including upregulation and/or mutations in the AR pathway, or transition into an alternate cell state that can receive growth and survival signals from non-AR pathways.
- Androgen Pathway Independent Prostate Cancer (APIPC) is a unique subset of advanced CRPC that are defined by a lack of expression of AR, AR-regulated genes such as PSA, and neuroendocrine genes. APIPC is therefore distinct from “typical” adenocarcinoma-type CRPC and from neuroendocrine prostate cancer (NEPC), an aggressive subtype of CRPC that express neuroendocrine genes.
• Dr. Michael Schweizer and team found that APIPC commonly express genes from the FGF pathway, and exhibit FGF pathway activation. Inhibition of the FGF pathway restricted growth of APIPC tumors in mice (Figure). Together, these data indicate that FGF pathways can drive APIPC tumor growth, and suggest that FGF may represent a promising therapeutic target in APIPC.

• To test this hypothesis, the team has initiated a clinical trial in which patients with APIPC (defined as CRPC lacking expression of AR and neuroendocrine genes) who have progressed on both abiraterone and enzalutamide will continue to receive the AR-targeted agent they most recently progressed on along with the FGF-inhibitor erdafitinib.

• An important clinical observation, is that significant variations in tumor subtypes can be seen in ~60% of advanced prostate cancer patients. Studies on tumor biopsies have found that some patients have APIPC and neuroendocrine prostate cancer cells, some have APIPC and AR-positive cancer cells, and some have all 3 subtypes of prostate cancer cells.

• These findings support efforts to develop combination therapy regimens that target these different prostate cancer subsets to improve the treatment of advanced prostate cancer.

The WNT/β-catenin pathway is an evolutionarily conserved pathway that plays a major role in fetal development and in the ongoing maintenance of tissue stem cells. WNTs are a family of secreted proteins that stimulate various WNT receptors on cells. This signal turns on the expression of genes involved in stem cell and developmental pathways.

Alterations in this pathway play a significant role in driving cancer development and progression, particularly colorectal cancer. In cancer, WNT signaling may support the maintenance and activities of cancer stem cells, which are a subset of cancer cells that are thought to continually self-renew and maintain tumor growth and recurrence.

The development of cancer therapies that target the WNT pathway has proven to be very difficult and several WNT-targeting agents have failed in clinical trials due to toxicity.

Recently, studies have found that the WNT pathway is commonly hyper-activated and/or mutated in advanced prostate cancer, suggesting WNT may be an important treatment target.

Dr. Christina Jamieson has found that WNT5a, a "non-canonical" WNT protein which does not signal through the typical β-catenin pathway, but instead signals through the ROR1 and ROR2 receptors, may be a promising target for the treatment of bone metastatic prostate cancer. WNT5A is important for the development of prostate tissue in the fetus.

Prostate cancer most commonly metastasizes to the bone, seen in >80% of patients with metastatic prostate cancer. Developing therapies to target and/or prevent bone metastasis is of critical importance.

The Jamieson lab has developed a series of patient-derived prostate cancer bone metastasis models and is using these models to study the biology of bone metastatic prostate cancer and identify promising new treatment strategies. These models maintain the donor patient’s genomic alterations and treatment resistance characteristics.

Studies using these models found that WNT5A and ROR1 are commonly highly expressed on bone metastatic prostate cancer.

These studies provide rationale for targeting the WNT5A/ROR1 pathway in prostate cancer.

Cirmtuzumab is a promising experimental therapy developed at UCSD that inhibits the WNT5A/ROR1 pathway, and is currently in clinical trials for the treatment of chronic lymphocytic leukemia (CLL) and metastatic breast cancer. Early results from these trials have been promising.

Cirmtuzumab treatment was effective at limiting growth of patient-derived prostate cancer models that are resistant to enzalutamide and docetaxel (Figure).

These studies demonstrate that the WNT5A/ROR1 pathway may have promise as a treatment target in advanced prostate cancer.

Additional preclinical studies are underway to support translation of cirmtuzumab into the clinic for metastatic prostate cancer patients. Dr. Jamieson is planning to open a phase 1b clinical trial to test cirmtuzumab + docetaxel in patients with mCRPC.
Cirmtuzumab treatment decreased the size of PCSD1 3D organoids that were resistant to enzalutamide plus docetaxel treatment.

**Prostate Cancer Organoids: Testing Cirmtuzumab (C) +/- Docetaxel (Do), +/- Enzalutamide (En)**

Figure: Cirmtuzumab treatment was effective at limiting growth of patient-derived prostate cancer models that are resistant to enzalutamide and docetaxel.

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**Targeting Androgen Receptor and ACK1 Signaling with Novel Epigenetic Therapeutics (R)-9b in Castration-Resistant Prostate Cancer**

Nupam Mahajan, PhD
Washington University

- The androgen receptor (AR) is the primary driver of the growth and survival of prostate cancer and is the primary treatment target in men with advanced disease. However, resistance to current AR-targeted therapies is common, necessitating the development of new treatment approaches to target this pathway.
- Dr. Nupam Mahajan and team have identified ACK1 as a regulator of the AR pathway. ACK1 is an enzyme (a kinase) that is expressed in all cell types, but is commonly upregulated in cancer cells by gene amplification, mutations and other mechanisms.
- Dr. Mahajan and team found that expression of ACK1 tends to increase with disease progression in patients with prostate cancer, with highest levels in castration resistant prostate cancer (CRPC). Higher levels of ACK1 activity were associated with shorter survival times in patients with CRPC.
ACK1 activation promoted the growth of CRPC tumors in animal models. In contrast, CRPC cells with an enzymatically-dead version of the ACK1 gene were unable to form tumors in mice. These studies suggest that ACK1 may be a promising new treatment target in prostate cancer.

The team developed a novel, potent, and highly selective ACK1 inhibitor, (R)-9b. Treatment with (R)-9b suppressed the activity of ACK1 in prostate cancer cells in laboratory cultures. By suppressing ACK1, (R)-9b also repressed the expression and activity of AR. Studies suggest that ACK1 may regulate AR both by regulating AR expression and by acting as a functional partner of AR.

(R)-9b treatment suppressed the growth of enzalutamide-resistant CRPC tumors in animal models (Figure). No evidence of toxicity was seen in tissue samples from treated animals.

Preclinical pharmacokinetic, metabolic and toxicological studies necessary to credential testing of the ACK1 inhibitor in prostate cancer clinical trials are underway. Results thus far have demonstrated that (R)-9b is able to reach the prostate in rats after injection, and appears to have a promising safety profile. A phase 1 trial testing (R)-9b in prostate cancer patients is being planned.

Figure: (R)-9b treatment suppressed the growth of enzalutamide-resistant CRPC tumors (C4-2B) in animal models (left, growth curves of tumors with or without (R)-9b treatment). No evidence of toxicity was seen in tissue samples from treated animals (right).
**BXCL701, an Orally Available Innate Immune Activator, in Combination with Pembrolizumab for Patients with NEPC (NEPC; SCPC)**

Vincent O’Neill, MD
Bioxcel Therapeutics

- Neuroendocrine prostate cancer (NEPC) is a highly aggressive and lethal form of advanced castration-resistant prostate cancer (CRPC). There are currently no effective treatments for NEPC and new strategies are urgently needed.
- DPP8 and DPP9 are enzymes that when inhibited, activate macrophages, a type of innate immune cell that can activate the rest of the immune system.
- The DPP8/9 genes are amplified in various cancer types including ~17% of NEPC cases and ~11% of pancreatic cancer cases. DPP8 and DDP9 may have potential as immunotherapy targets in prostate cancer.
- Dr. Vincent O’Neill presented studies on a novel inhibitor of DPP8/9, BXCL701, which also inhibits FAP, a protein expressed on fibroblasts cells that are often found within tumors and support tumor growth. This inhibitor is thus proposed to have dual mechanisms of activity as a cancer treatment.
- In preclinical cancer models, BXCL701 was synergistic with anti-PD1 checkpoint immunotherapy and activated anti-tumor immune responses.
- Over 700 individuals have been treated with BXCL701 in phase 1-3 clinical trials as single agent or in combination with chemotherapy.
- These trials found BCXL701 to be generally well-tolerated. The most frequently observed adverse events included edema/peripheral swelling, fever and rigors, dizziness, nausea, vomiting, rash (10%), and uncommon cases of hypotension. Adverse events tended to be manageable and reversible following discontinuation of drug use.
- A phase 1b/2 clinical trial was initiated to test BCXL701 + pembrolizumab in NEPC. The phase 1 portion of the trial which is evaluating safety and establishing the maximum tolerable dose has completed enrollment. Once evaluation has been completed, the phase 2 portion to evaluate efficacy will begin enrollment.
- In early data from 3 patients evaluable thus far, stable disease at 9 weeks (3 cycles of treatment) was observed in 2 patients (Figure). No severe adverse events or dose limiting toxicity was observed in the cohort treated at the lowest dose. Assessment of safety is ongoing for the final dose escalation cohort. All subjects remain on treatment.
- In summary, BCXL701 is a novel cancer therapy that has dual action against tumors by activating innate immune responses and suppressing cancer-associated fibroblasts. This treatment demonstrated promising anti-tumor activity in combination with pembrolizumab in preclinical models, and this combination is now being tested in a NEPC clinical trial.
## Disease Status

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<td>PSA decline &gt;50% by Week 12</td>
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*Pt #3 with only bone mets at baseline

**Figure**: Responses in NEPC patients on the phase 1 BCXL701 + pembrolizumab clinical trial lead-in cohort. Stable disease at 9 weeks (3 cycles) was observed in 2 of 3 evaluable patients.
Multi-Modal Learning for AI and IA: Applications to Prostate Cancer

Ganapati Srinivasa  
Omics Data Automation, Inc.

Anthony Chang, PhD  
Founder/CEO, BAMF Health

- There are numerous aspects of a patient’s clinical and biological data that contain information that can be used to identify the treatment strategies that will deliver the best possible outcomes for that individual. The types of medical data that can be obtained are rapidly expanding and include tumor genomic, molecular, and pathological features, information from new imaging technologies, and data on how these features change throughout the course of disease. The ability to collectively understand and optimally apply this information in the clinic is surpassing human cognitive capacity.

- Artificial intelligence algorithms are being developed to collectively evaluate and understand these different types of data.

- Mr. Ganapati Srinivasa and Dr. Anthony Chang discussed BAMF Health’s new artificial intelligence platform that is being developed to integrate and analyze data from patients’ electronic health records, labs, pathology, radiology, genomics, protein, and other data (Figure). The framework enables data to be continuous, in order to appropriately include time intervals. This type of “causal” artificial intelligence system is able to produce models which tell the researchers why the algorithm has reached a specific conclusion.

- The platform aims to provide an “intelligence assistance” framework that delivers understandable models that provide insight to clinicians and researchers about disease biology and predict optimal treatment strategies for individual patients.

- A study was performed that used comprehensive clinical, imaging, and molecular data from over 300 prostate cancer patients treated with various interventions to create an algorithm that will predict the best course of treatment for patients.

- With enough data, the algorithm could be used to model answers to various clinical questions, such as why certain treatments were chosen for patients and whether patients would have had better outcomes with an alternative treatment. For example, the algorithm predicted that a prostatectomy was not required for responses to PSMA-targeted radionuclide therapy.

- Such models generate hypotheses that may warrant testing in clinical trials.

- In summary, artificial intelligence systems are being developed to integrate and analyze complex and high dimensional patient data, in order to develop new models that can guide research and improve clinical practice.
Figure: Artificial intelligence frameworks are being designed to integrate and evaluate many types of patient data and create models to help clinicians and researchers better understand disease biology and predict optimal treatment strategies.
Synthesis of Biomedical Knowledge and Triangulation of Clinico-Omics Data Sets Over the Inference Platform for Prostate Cancer R&D Efforts

Venky Soundararajan, PhD
Inference and Qrativ: Mayo Clinic JV

- An estimated 90% of the world’s electronic medical data is in unstructured form, such as clinical notes entered by clinicians and medical staff into electronic health records and scientific research publications.
- Discussed by Dr. Venky Soundararajan, nference is developing an artificial intelligence-based platform to curate and merge all data from a swath of biomedical literature, clinical data from ~10 million de-identified patient medical records, genomic and other omic data, clinical trial data, insurance claims, and other sources into a single database that can be used to enable a far deeper understanding of disease biology (Figure).
- Natural language processing is being used to extract and harmonize the data from these documents.
- Questions that may be asked using this dataset include identifying new treatment targets and predictive or prognostic biomarkers.
- Built into the nference platform are several apps that allow visualization of different types and levels of data, such as clustering of patients with similar attributes (for instance, prostate cancer patients with mutations in a specific gene), and linking this information to other data about such attributes (for instance, the activity of the gene in other diseases, and scientific studies on the biological function of the gene in prostate cancer).
- The overall hope is that artificial intelligence-based triangulation of all of the available biomedical data that has been amassed by clinicians and researchers to date can be integrated and presented in a way that leads to new insights and understandings and will drive next steps in medical research and treatments.

**Figure:** The goal of nference is to triangulate large amounts of data from the biomedical literature, clinical data from ~10 million de-identified patient medical records, genomic and other omic data, clinical trial data, insurance claims, and other sources into a single database that can be used to enable a far deeper understanding of disease biology.
Pathology is a key medical practice that studies the microscopic features of patient tissues from biopsy or surgical samples in order to determine whether they are benign or malignant, to examine surgical margins, and to study the biology of disease. In many medical fields including oncology, while other tests contribute to screening, pathologists make the final disease diagnosis.

In traditional pathology, tissues from patients collected by biopsy or during surgery are thinly sliced and mounted onto glass slides. The slides are then stained with special dyes that label different molecules or proteins within the cell, and an experienced pathologist examines the slide under a microscope.

Based on the cells’ appearance, location, and staining with the dyes, pathologists are able to tell what kind of cells are present, whether they are normal or abnormal, and determine various aspects of biology.

Traditional pathology methods are highly time-consuming and tedious. At Memorial Sloan Kettering Cancer Center (MSKCC), ~1 million tissue slides are created each year from patient samples and must be analyzed.

The number of trained pathologists have been decreasing in the U.S. and worldwide, resulting in increased workload for existing pathologists in order to maintain the standard of care. Pathologists’ health and the accuracy of their work has suffered with the increasing workload and additional work hours necessitated by this crisis.

New digital and artificial intelligence based pathology systems are being developed to support pathologists, improve speed and accuracy of diagnoses, and enable new insights and biological understandings.

Dr. Thomas Fuchs discussed advancements in the field of computational pathology, a relatively new field which incorporates automated tissue processing and imaging technologies and artificial intelligence algorithms to analyze patient tissue slides.

Computational pathology algorithms have been developed to detect and classify cell nuclei, determine boundaries of different cell types in tissues (such as normal and tumor regions), and estimate the structure and morphology of tissues.

Digital imaging of tissue slides requires huge amounts of data storage capacity. A single tissue slide imaged with high resolution microscopy can take up 6 billion pixels. As a frame of reference, the entire database of CIFAR images (60,000 photos) are only 61.44 million pixels. This need for massive data storage and processing capacity represents a challenge for the field. High performance computing and improved machine learning algorithms are necessary.

Dr. Fuchs and team are developing computational pathology systems which are able to perform diagnosis, prognosis, and have an integrated large scale machine learning network.

Cancer tissues can be very messy and highly diverse. In order to develop highly accurate artificial intelligence systems that deliver accurate diagnoses in all instances, huge datasets that represent all possible cancer tissue variations are needed.

At MSKCC, ~40,000 cancer tissue slides are now being digitally imaged each month. Over one petabyte of compressed image data has already been generated.
• To process this data, MSKCC has developed a computational pathology portal in which digital imaging and clinical data is input and can be accessed and analyzed by MSKCC researchers and clinicians. Artificial intelligence algorithms for diagnosis of different types of cancers are being developed and trained using this portal. For instance, a clinical grade performance artificial intelligence system for prostate cancer was developed based on 12,000 slides.

• Artificial intelligence approaches have been used in which the computer is given two sets of slides (normal and cancer tissues) to compare and learn from. The use of more slides for training has resulted in significantly more accurate diagnostic algorithms.

• Paige.AI has developed a cancer diagnosis algorithm trained on ~100,000 slides that has achieved ~98% diagnostic accuracy for all cancer types. In 2019, this system received FDA breakthrough device designation for the clinical diagnosis of cancer.

• These computational pathology approaches have been able to significantly reduce the number of slides a pathologist has to look at by 75%, while maintaining 100% efficiency in diagnostic speed. These new technologies will also enable new understandings in disease biology and improve the clinical management of patients.

Artificial Intelligence at Concerto HealthAI

Francois Charest, PhD
Concerto HealthAI

- Much of healthcare data exists in a form that cannot be easily studied to understand trends in healthcare practices and gain insights into patient outcomes. This data contains rich information that would greatly enrich medical research.
- Dr. Francois Charest discussed Concerto HealthAI’s platform which uses artificial intelligence software to enrich and help curate large databases of patient data containing both structured and unstructured medical data.
- Concerto Health AI has compiled a database of over 2 million unique patient records and developed artificial intelligence models to study the data.
- Concerto HealthAI has an exclusive 10-year license rights to complete the ASCO CancerLinQ dataset. The goal of CancerLinQ is to generate a database containing real world data from over 1.5 Million cancer patients. Curation of these records involves both a trained nurse practitioner and natural language programming-based artificial intelligence evaluation of the patient records.
- Concerto HealthAI’s models are being used to predict clinical outcomes such as disease progression, survival, metastasis, and treatment responses.
- For example, an algorithm was developed that was able to impute a diagnosis of breast cancer metastasis cases 30% more frequently than using simple business rules alone (curated patient data stating patient as stage 4 or metastatic) with 98% accuracy. The additive predictive power of the model was due to data extracted from uncurated medical records such as diagnosis codes, medications, lab values, and age.
- In prostate cancer, algorithms are being developed to impute a diagnosis of metastasis, castration resistance status, biomarker status, and lines of treatment (Figure).
- These platforms will hopefully enable researchers to better predict patient outcomes and treatment responses and design improved clinical trials.
Prostate Cancer applications

*CHAI also has prior experience in prostate cancer (PC) and has ongoing work in PC.*

The framework developed for the Metastatic Breast Cancer AI model can be used to

<table>
<thead>
<tr>
<th>Refine and validate a <strong>Metastatic Prostate Cancer AI model</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impute Castration Resistant status</strong> of Prostate Cancer patients</td>
</tr>
<tr>
<td><strong>Facilitate imputation of biomarker</strong> status of Prostate Cancer patients</td>
</tr>
<tr>
<td>The output of metastatic imputation models is also used as an <strong>input of another model: Line of Therapy</strong></td>
</tr>
</tbody>
</table>

**Figure:** Prostate cancer applications being developed by Concerto HealthAI.
**Session 9: Attacking Prostate Cancer with T-Cell Engagers and Antibody-Drug Conjugates**

**STEAP1 as a Therapeutic and Diagnostic Target in Prostate Cancer**

Daniel Danila, MD  
Memorial Sloan Kettering Cancer Center

- There are numerous FDA-approved treatment options for men with advanced prostate cancer. However, while life-prolonging, these treatments are not curative as prostate cancer nearly always develops resistance to the treatment. The identification of new treatment targets and development of new treatments is an urgent unmet medical need.

- Dr. Daniel Danila presented data demonstrating promise for a new treatment for metastatic castration-resistant prostate cancer (mCRPC) targeting STEAP1.

- STEAP1 is a protein that is highly expressed on prostate tissues and most prostate cancers, but is not highly expressed on other normal tissues. STEAP1 is expressed on the surface of prostate cancer cells, and thus would be accessible to antibody-based drugs. These features suggest STEAP1 may be an optimal prostate cancer drug target.

- Antibody-drug conjugates (ADCs) are treatments composed of an antibody which targets a cancer-associated protein, attached to a toxic drug such as a chemotherapy agent.

- A STEAP1-targeting ADC, DST3086S, was developed that carries the cytotoxic agent monomethyl auristatin E (MMAE) via an enzyme-cleavable linker. The ADC is proposed to kill cells by binding to STEAP1 on the cell surface, followed by internalization of the ADC into the cell where naturally present cellular enzymes would cleave MMAE from the antibody, releasing it to kill the cell.

- A phase 1 clinical trial was initiated to establish the safety, tolerability, maximum tolerable dose, and recommended phase 2 dose level of DST3086S in men with mCRPC. To qualify for enrollment, patients had to have moderate to high levels of STEAP1 expression on their tumor samples (from biopsy or archival surgical tissues). A total of 77 patients were enrolled on the trial and treated at one of 7 dose levels.

- Promising results were observed, with DST3086S having acceptable safety and evidence of activity. PSA responses more likely and deeper in patients who received higher doses of DST3086S.

- A PSA reduction of $\geq 50\%$ was observed in 11 of 77 (14%) of patients overall and in 11 of 62 (18%) patients treated at the 3 highest dose levels (Figure).

- Of 46 patients who had measurable disease on scans, partial tumor shrinkage was observed in 2 (4%) patients, and stable disease was seen in 24 (52%) patients.

- PSA decreases and tumors shrinkage on scans were associated with reductions in levels of circulating tumor cells (CTCs).

- A STEAP1-targeted PET imaging probe has been developed and was used to evaluate the expression of STEAP1 in some of the patients on the trial. Use of this PET imaging agent may be useful in identifying patients who may be more likely to benefit from STEAP1-targeted treatment and for monitoring responses to treatment.

- Overall, these data demonstrate promise for a new STEAP1-targeted therapy and support further clinical development of STEAP1-targeted imaging and therapeutic agents.
CD46 as a Novel Target in Metastatic Castration Resistant Prostate Cancer

Rahul Aggarwal, MD
University of California, San Francisco

- The immune system has the remarkable capacity to recognize and kill cancer cells. However, cancer that progresses has typically evolved the ability to evade or suppress the immune system. Treatments that activate anti-cancer immune responses have been highly effective in many cancer types, but have yet to be optimized in prostate cancer.

- CD46 is a protein that helps cancer cells to evade killing by immune cells. CD46 functions by driving T cells to become immune-suppressive instead of having anti-cancer activity.

- CD46 is highly upregulated in various cancer types including prostate cancer. Amplification of the CD46 gene and high CD46 expression levels can be observed in prostate cancer, and these increase during disease progression. CD46 expression is particularly high in advanced prostate cancer including metastatic, castration resistant prostate cancer (CRPC) and neuroendocrine prostate cancer (NEPC) (Figure). Normal prostate cells also express CD46, but all other normal cells express CD46 at low levels or not at all.

- These data demonstrate that CD46 is highly specific for prostate cancer and could represent a promising target for prostate cancer immunotherapy.
• Dr. Rahul Aggarwal discussed the development of a CD46-targeting antibody-drug conjugate (ADC), FOR46, which carries the cytotoxic agent monomethyl auristatin E (MMAE), by researchers at the University of California, San Francisco (UCSF).

• FOR46 demonstrated potent anti-tumor activity in preclinical prostate cancer studies and had an acceptable toxicity profile in preclinical toxicology studies.

• Early studies suggest CD46-ADC may be synergistic with checkpoint immunotherapy and androgen receptor (AR)-targeted therapy.

• The team recently initiated a first-in-human phase I clinical trial to test the efficacy and safety of FOR46 in patients with metastatic CRPC.

• Based on results from this study, the team may conduct additional trials testing FOR46 in combination with checkpoint immunotherapy and AR-targeted therapy.

• Dr. Robert Flavell, a nuclear medicine physician scientist at UCSF, is developing a novel PET radiotracer targeting CD46 that may be used as a companion biomarker and theranostic agent to image CD46 expression. Studies in mice are promising thus far.

• In summary, CD46 has been identified as a promising new therapeutic target in advanced prostate cancer that may have synergy with checkpoint immunotherapy and AR-targeted therapy. A novel CD46-targeting agent is now being tested in a phase 1 trial in patients with metastatic CRPC.

**Figure:** CD46 gene amplification occurs in prostate cancer and increases during disease progression to metastatic and small cell neuroendocrine (SCNC) prostate cancer (left). High levels of CD46 expression can be observed in treatment-associated SCNC (right).
Phase 1 Trial of HPN424: A half-life extended, PSMA/CD3-specific TriTAC for the treatment of metastatic prostate cancer

Natalie Sacks, MD
Harpoon Therapeutics

- PSMA is a protein that is highly expressed on malignant prostate cancer cells and is a promising therapeutic target. Many new PSMA-targeted treatments are being developed, including PSMA-targeted immunotherapies.

- Dr. Natalie Sacks discussed the development of HPN424, a novel off-the-shelf T cell engaging immunotherapy agent that activates a patient’s own immune system and redirects T cells to target PSMA+ tumor cells. HPN424, is a “TriTAC” (TRI-specific T cell Activating Construct) – a small (50kD) globular protein optimized for CD3 recruitment at low target density, efficient solid tumor penetration with prolonged half-life and stability.

- The molecule has three targeting domains, each composed of an antibody fragment that binds to a specific target. HPN424 targets PSMA on prostate cancer cells, CD3 on T cells, and albumin in serum. The targeting of PSMA and CD3 is expected to bring T cells into close contact with PSMA-expressing prostate cancer cells and kill them. Targeting albumin is proposed to improve the length of time that the agent is able to remain in the circulation of patients after administration.

- In preclinical pharmacological studies, HPN424 had promising tumor-killing activity in prostate cancer models (Figure) and exhibited a long circulation time of over 80 hours in cynomolgus monkeys.

- A phase 1 trial was initiated to test HPN424 in mCRPC. The agent’s circulation time in patients supports a once-weekly dosing schedule.

- Patients exhibited expression of immune activation proteins consistent with similar classes of immunotherapeutic agents. Cytokine-mediated adverse events were transient and manageable. No dose limiting toxicities have yet been observed during dose-escalation.

- Overall, these data demonstrate the development of a novel PSMA-targeted T cell engager with a long circulation time that was designed to redirect T cells to kill prostate cancer cells. This agent is now being tested in Phase 1 prostate cancer clinical trials.

**HPN424 Potently Inhibits Growth in the 22Rv1 Prostate Cancer Model**

![Image](image_url)

**Figure:** The PSMA-targeted TriTAC HPH424 was able to reduce tumor volume in preclinical animal models.
Bispecific T-Cell Engager Immune Therapies for the Treatment of Prostate Cancer

Hosein Kouros-Mehr, MD, PhD
Amgen

- Immunotherapies have exhibited deep, long-term responses in many types of cancer but in prostate cancer their success has been limited to a small subset of patients. There is an urgent need for new immunotherapies that can harness the immune system to target and kill prostate cancers.
- Bispecific T-Cell Engager (BiTE®) molecules are immunotherapies consisting of two different antibody fragments that bind to proteins on T cells and tumor cells. The BiTE molecule brings the T cells in contact with the cancer cell, leading to T-cell directed tumor killing.
- Dr. Hosein Kouros-Mehr discussed the development of BiTEs to target prostate cancer.
- The AMG 212 BiTE is composed of antibody fragments that target the T cell protein CD3 and the prostate cancer protein PSMA.
- AMG 212 displayed potent activity against prostate cancer cells in preclinical studies. It has a 2-3 hour half-life in circulation and requires continuous IV infusion.
- A phase 1 trial was initiated to determine safety, tolerability and efficacy of AMG 212 in patients with metastatic castration resistant prostate cancer (mCRPC) (Figure). The trial tested doses ranging from 5–80 microgram/day via continuous IV infusion in mCRPC patients. No maximum tolerated dose (MTD) was identified.
- Of the 16 patients treated at various dose levels, two experienced long-term PSA responses and three patients exhibited stable disease on scans.
- 15 of 16 (94%) patients experienced adverse events including fever, chills, and low white blood cell count. Cytokine release syndrome, which is often associated with immunotherapies, was observed in three patients (19%), one with grade 3 and two with grade 2 severity.
- One patient who previously had no response to PSMA-targeted radionuclide therapy (177Lu-PSMA-617) experienced a durable PSA response, complete regression of PSMA-expressing metastatic tumors, reversal of disease related symptoms, and quality of life improvement.
- Because of the need for continuous IV infusion for AMG 212, a PSMA-targeted BiTE that has extended half-life (AMG 160) was developed. AMG 160 displayed potent anti-cancer activity in prostate cancer preclinical models and an acceptable safety profile in preclinical toxicology studies.
- A phase 1 trial testing AMG 160 in mCRPC patients is underway.
- Additional bispecific T-cell engager immunotherapies in development for prostate cancer at Amgen include a DLL3-targeting BiTE (AMG 757) and a STEAP1-targeting bi-specific antibody construct (AMG 509). DLL3 is a protein that is highly expressed on neuroendocrine prostate cancers and other neuroendocrine cancers such as small cell lung cancer. STEAP1 is highly expressed on the surface of > 80% of primary and metastatic prostate cancers. Additional clinical development of these BiTEs for prostate cancer is underway.
AMG 212: Consistent and Durable Response Across Indicators of Efficacy

- 2 patients with long term PSA responses (on treatment for 14 and 19 months) and 3 patients with stable disease by RECIST 1.1
- 15/16 patients (94%) had drug-related adverse events (most commonly fever, chills, decreased lymphocytes)
- Cytokine release syndrome (CRS) in 3/16 patients (19%) – 2 grade 2, 1 grade 3 (by CTCAE 4.03)
- 1 patient (80 µg/day) who did not respond to prior 177Lu-PSMA-617 had a durable PSA response, complete regression of PSMA disease in bone and soft-tissue, reversal of disease related symptoms, and OOL improvement

Figure: Results from a phase 1 trial testing AMG212 in patients with metastatic castration resistant prostate cancer (mCRPC). Figures at bottom show PSA levels, serum alkaline phosphatase levels and imaging scans from one patient who exhibited a response.
APPENDIX:

26th ANNUAL PROSTATE CANCER FOUNDATION
SCIENTIFIC RETREAT

OCTOBER 24-26, 2019

PROGRAM AGENDA
AGENDA
Thursday, October 24, 2019

GENERAL SESSIONS
Location: Costa Del Sol Ballroom

8:00 AM  Registration  Costa Del Sol Foyer

Welcome & Introduction
1:00 PM - 1:10 PM
Howard Soule, PhD
Prostate Cancer Foundation

Session 1: Population Science Studies to Inform Population and Patient Strategies to Reduce the Burden of Lethal Prostate Cancer
1:10 PM - 1:50 PM
Moderator: Elizabeth Platz, ScD, MPH
Johns Hopkins Bloomberg School of Public Health and the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

1:10 PM - 1:25 PM  Neighborhood Factors and Prostate Cancer Outcomes
Mindy C. DeRouen, PhD, MPH
University of California, San Francisco

1:25 PM - 1:30 PM  Discussion

1:30 PM - 1:45 PM  Exercise and Weight Management in the Supportive Care of Prostate Cancer Patients Undergoing Androgen Deprivation Therapy
Brian C. Focht, PhD, FACSM, CSCS
The Ohio State University

1:45 PM - 1:50 PM  Discussion
**Session 2: Immunotherapy for Prostate Cancer**

1:50 PM - 3:20 PM

**Moderator:** Charles Drake, MD, PhD  
Columbia University; NewYork-Presbyterian

1:50 PM - 1:55 PM  
**Introduction**

1:55 PM - 2:10 PM  
**The Biology and Therapeutic Impact of Targeting IL-23 in Prostate Cancer**  
Andrea Alimonti, MD  
Institute of Oncology Research, Switzerland

2:10 PM - 2:15 PM  
**Discussion**

2:15 PM - 2:30 PM  
**Precision Immunotherapy for CDK12-Biallelic Loss**  
Ajjai Alva, MBBS  
University of Michigan

2:30 PM - 2:35 PM  
**Discussion**

2:35 PM - 2:55 PM  
**Targeting Chronic cGAS-STING Signaling: A Novel Vulnerability in Chromosomally Unstable Tumors**  
Samuel Bakhoum, MD, PhD  
Memorial Sloan Kettering Cancer Center  
Eileen Parkes, MD, PhD  
University of Oxford, UK

2:55 PM - 3:00 PM  
**Discussion**

3:00 PM - 3:15 PM  
**Testosterone Effects on Innate Immunity; Implications for Combination Therapies**  
Samuel Denmeade, MD  
Johns Hopkins University  
Sushant Kachhap, PhD  
Johns Hopkins University

3:15 PM - 3:20 PM  
**Discussion**
**Session 3: Novel Insights from Prostate Cancer Genomics**

**3:20 PM - 4:20 PM**

**Moderator:** Himisha Beltran, MD  
Harvard: Dana-Farber Cancer Institute

3:20 PM - 3:35 PM  **Near-Mendelian Prostate Cancer Risk Variants of 8q24 and the HOXB Cluster**  
Jeffrey Smith, MD, PhD  
Vanderbilt University Medical Center

3:35 PM - 3:40 PM  **Discussion**

3:40 PM - 3:55 PM  **Circular RNA in Prostate Cancer**  
Housheng Hansen He, PhD  
Princess Margaret Cancer Centre, Canada

3:55 PM - 4:00 PM  **Discussion**

4:00 PM - 4:15 PM  **Insights from Integrated Whole-Genome, Whole-Transcriptome, and Whole-Methylome Sequencing of mCRPC**  
Shuang George Zhao, MD  
University of Michigan

4:15 PM - 4:20 PM  **Discussion**

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**SPECIAL LECTURE**

**4:20 PM - 4:35 PM**

**Cell Types of the Proximal Prostate are Enriched in Tumors, But Are They Progenitors?**

Douglas Strand, PhD  
The University of Texas Southwestern Medical Center

*Introduced by Howard Soule, PhD  
Prostate Cancer Foundation*

4:35 PM - 4:40 PM  **Discussion**

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4:40 PM - 4:45 PM  **Break**
**PANEL DISCUSSION**
4:45 PM - 5:45 PM

**Point-Counter Point:**
*Is there a Biological Basis for Racial Disparities in Prostate Cancer?*

**Precision Policy**

*Moderator: Lorelei Mucci, ScD*  
Harvard T.H. Chan School of Public Health

**Panelists:**

Daniel George, MD (Duke University)

Susan Halabi, PhD (Duke University)

Brandon Mahal, MD (Harvard: Dana-Farber Cancer Institute)

Elizabeth Platz, MPH, ScD (Johns Hopkins Bloomberg School of Public Health and the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins)

Westley Sholes, MPA (Member, California Prostate Cancer Coalition)

Kosj Yamoah, MD, PhD (Moffitt Cancer Center)

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**Dinner**
6:30 PM - 7:30 PM

*Dinner Location: Costa Del Sol Patio*

**Poster Session and Dessert**
7:30 PM - 10:30 PM

*Poster Session and Dessert Location: Costa Del Sol AB & Foyer*
6:00 AM - 7:45 AM  Breakfast
Location: Costa Del Sol Patio

7:45 AM - 8:00 AM  Move to Session

GENERAL SESSIONS
Location: Costa Del Sol Ballroom

**Session 4: Prostate Cancer Research in the VA**
8:00 AM - 9:05 AM

*Moderators:*
Bruce Montgomery, MD  
University of Washington; VA Puget Sound  
Matthew Rettig, MD  
University of California, Los Angeles; VA Greater Los Angeles Healthcare System

8:00 AM - 8:15 AM  **VA/PCF Precision Oncology Program for Cancer of the Prostate: POPCAP**
Bruce Montgomery, MD  
University of Washington; VA Puget Sound  
Matthew Rettig, MD  
University of California, Los Angeles; VA Greater Los Angeles Healthcare System

8:15 AM - 8:20 AM  Discussion

8:20 AM - 8:40 AM  **Special Lecture: Becoming a Great Partner in the Fight Against Prostate Cancer**
Rachel Ramoni, DMD, ScD  
Veterans Health Administration

8:40 AM - 8:45 AM  Discussion

8:45 AM - 9:00 AM  **Immunotherapy Associated Cardiotoxicities: Of Mice and Men**
Javid Moslehi, MD  
Vanderbilt University Medical Center

9:00 AM - 9:05 AM  Discussion
**SPECIAL LECTURE**
9:05 AM - 9:20 AM

"STAMPEDE Trial: What Have We Learnt and Where Next?"

Nicholas James, MBBS, PhD  
Institute of Cancer Research; Royal Marsden NHS Foundation Trust, UK

Introduced by Silke Gillessen, MD  
Istituto Oncologico della Svizzera Italiana (IOSI), Switzerland; University of Manchester, UK

9:20 AM - 9:25 AM  
Discussion

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**SPECIAL LECTURE**
9:25 AM - 9:45 AM

Molecular Stratification: PARP Inhibitors and Beyond

Johann de Bono, MD, PhD  
Institute of Cancer Research; Royal Marsden NHS Foundation Trust, UK

Introduced by Joaquin Mateo, MD, PhD  
Vall Hebron Institute of Oncology, Spain

9:45 AM - 9:50 AM  
Discussion
**DR. ANDREW HRUSZKEWYCZ, MD, PHD, MEMORIAL LECTURE**

9:50 AM - 10:05 AM

**DR. ANDREW HRUSZKEWYCZ: A Selfless Life**

William Dahut, MD
National Cancer Institute

*Introduced by Howard Soule, PhD
Prostate Cancer Foundation*

10:05 AM - 10:10 AM
Discussion

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**SPECIAL LECTURE**

10:10 AM - 10:40 AM

**State of the Science 2019**

Jonathan W. Simons, MD
Prostate Cancer Foundation

*Introduced by Howard Soule, PhD
Prostate Cancer Foundation*

10:40 AM - 10:45 AM
Discussion
KEYNOTE ADDRESS
10:45 AM - 11:45 AM

Michael Milken
Founder and Chairman
Prostate Cancer Foundation

Introduced by Stuart Holden, MD
Prostate Cancer Foundation

Group Photo
11:45 AM - 12:00 PM

Location: Costa Del Sol Foyer

Lunch
12:00 PM - 12:45 PM

Location: Costa Del Sol Patio

12:45 PM - 1:00 PM  Move to Session 5

Location: Costa Del Sol Ballroom
SPECIAL LECTURE
1:00 PM - 1:15 PM

Therapeutic Strategies Exploiting Synergies in Merkel Cell Carcinoma and Neuroendocrine Prostate Cancer

Paul Nghiem, MD, PhD
University of Washington

Introduced by Peter Nelson, MD
Fred Hutchinson Cancer Research Center

1:15 PM - 1:20 PM
Discussion

Session 5: Treatment Associated Small Cell/Neuroendocrine Prostate Cancer (t-SCNC) and Lineage Plasticity
1:20 PM - 2:40 PM

Moderator: Eric Small, MD
University of California, San Francisco

1:20 PM - 1:35 PM  Treatment-Associated Small Cell/Neuroendocrine Prostate Cancer: Defining the Syndrome
Eric Small, MD
University of California, San Francisco

1:35 PM - 1:40 PM  Discussion

1:40 PM - 1:55 PM  The Genomic Characterization of Treatment-Induced Small Cell Neuroendocrine Prostate Cancer
Himisha Beltran, MD
Harvard: Dana-Farber Cancer Institute

1:55 PM - 2:00 PM  Discussion

2:00 PM - 2:15 PM  Lineage Plasticity in Advanced Prostate Cancer: How Many Lineages? And How Plastic Are They?
Peter Nelson, MD
Fred Hutchinson Cancer Research Center

2:15 PM - 2:20 PM  Discussion
2:20 PM - 2:35 PM  
**Emerging Therapeutic Strategies for Aggressive Variant Prostate Cancers**
Ana Aparicio, MD
University of Texas MD Anderson Cancer Center

2:35 PM - 2:40 PM  
**Discussion**

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**SPECIAL LECTURE**
2:40 PM - 2:55 PM

**Real World Validation of Deep Learning Algorithms in the Assessment of Metastasis by Medical Imaging of Veterans with Prostate Cancer**

Matthew Rettig, MD
University of California, Los Angeles; VA Greater Los Angeles Healthcare System

Nicholas Nickols, MD, PhD
University of California, Los Angeles; VA Greater Los Angeles Healthcare System

*Introduced by Kenneth Pienta, MD*
*Johns Hopkins University*

2:55 PM - 3:00 PM  
**Discussion**

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**SPECIAL LECTURE**
3:00 PM - 3:10 PM

**The PSMA Walled Garden: Access for PCF Researchers to DCFPyL Images, Clinical Data and AI Tools to Accelerate Prostate Cancer AI Research**

Mark R. Baker
Progenics Pharmaceuticals

*Introduced by Nicholas Nickols, MD, PhD*
*University of California, Los Angeles; VA Greater Los Angeles Healthcare System*

3:10 PM - 3:15 PM  
**Discussion**
**Session 6: New Drugs and Targets in Prostate Cancer: I**

**3:15 PM - 4:15 PM**
Moderator: Karen Knudsen, MBA, PhD
Thomas Jefferson University

3:15 PM - 3:30 PM  **Targeting Oncogenic Transcription Factor Signaling Through p300/CBP**
Karen Knudsen, MBA, PhD
Thomas Jefferson University

3:30 PM - 3:35 PM  **Discussion**

3:35 PM - 3:50 PM  **FGFR-Inhibition in Double Negative Prostate Cancer: Rationale and Future Directions**
Michael Schweizer, MD
University of Washington

3:50 PM - 3:55 PM  **Discussion**

3:55 PM - 4:10 PM  **Glutamine Metabolism as a Therapeutic Target in Prostate Cancer**
Richard Lee, MD, PhD
Harvard: Massachusetts General Hospital

4:10 PM - 4:15 PM  **Discussion**
Dinner, Awards Ceremony, and Special Lecture
7:00 PM - 10:00 PM

Location: Costa Del Sol Ballroom

SPECIAL LECTURE:

*Accelerating Medical Product During a Crisis: Lessons from Ebola Outbreaks and Addressing Future Threats:*

8:00 PM - 8:20 PM
Matthew Hepburn, MD
Product Lead, Enabling Biotechnologies, U.S. Department of Defense

Introduced by: Howard Soule, PhD
Prostate Cancer Foundation

PCF Awards Ceremony
8:40 PM - 10:00 PM

2019 PCF Young Investigator Awards

2019 PCF VAlor Precision Oncology Center of Excellence Awards

2019 Movember Foundation-PCF Challenge Awards

MOVEMBER®

2018 PCF Challenge Awards

2019 PCF Challenge Awards
Saturday, October 26, 2019

6:00 AM - 7:15 AM  Breakfast
Location: Costa Del Sol Patio

7:15 AM - 7:30 AM  Move to Session

GENERAL SESSIONS
Location: Costa Del Sol Ballroom

Session 7: New Drugs and Targets in Prostate Cancer: II
7:00 AM - 8:30 AM
Moderator: Howard Soule, PhD
Prostate Cancer Foundation

7:30 AM - 7:45 AM  Targeting the WNT5A Receptor ROR1 in Prostate Cancer
Christina Jamieson, PhD
University of California, San Diego
Discussion

7:45 AM - 7:50 AM  Targeting Androgen Receptor and ACK1 Signaling with Novel Epigenetic Therapeutics (R)-9b in Castration-Resistant Prostate Cancer
Nupam Mahajan, PhD
Washington University
Discussion

8:05 AM - 8:10 AM  Discussion

8:10 AM - 8:25 AM  BXCL701, An Orally Available Innate Immune Activator, in Combination with Pembrolizumab for Patients with NEPC (NEPC; SCPC)
Vincent O’Neill, MD
Bioxcel Therapeutics
Discussion

8:25 AM - 8:30 AM  Discussion
**Session 8: AI and Machine Learning in Cancer Research and Development**

8:30 AM - 9:55 AM

**Moderator:** Marco Gottardis, PhD  
Janssen Research & Development, LLC

8:30 AM - 8:35 AM **Introduction**

8:35 AM - 8:50 AM **Multi-Modal Learning for AI and IA: Applications to Prostate Cancer**

Ganapati Srinivasa  
Omics Data Automation, Inc.  
**Anthony Chang, PhD**  
Founder/CEO, BAMF Health

8:50 AM - 8:55 AM **Discussion**

8:55 AM - 9:10 AM **Synthesis of Biomedical Knowledge and Triangulation of Clinico-Omics Data Sets Over the nference Platform for Prostate Cancer R&D Efforts**

Venky Soundararajan, PhD  
nference and Qrativ: Mayo Clinic JV

9:10 AM - 9:15 AM **Discussion**

9:15 AM - 9:30 AM **The First Clinical-Grade AI for Prostate Cancer Detection: Impact on Pathologists and Patients**

Thomas Fuchs, Dr. Sc.  
Paige

9:30 AM - 9:35 AM **Discussion**

9:35 AM - 9:50 AM **Artificial Intelligence at Concerto HealthAI**

Francois Charest, PhD  
Concerto HealthAI

9:50 AM - 9:55 AM **Discussion**

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**Session 9: Attacking Prostate Cancer with T-Cell Engagers and Antibody-Drug Conjugates**

9:55 AM - 11:15 AM

**Moderator:** Hosein Kouros-Mehr, MD, PhD  
Amgen

9:55 AM - 10:10 AM **STEAP1 as a Therapeutic and Diagnostic Target in Prostate Cancer**

Daniel Danila, MD  
Memorial Sloan Kettering Cancer Center

10:10 AM - 10:15 AM **Discussion**
10:15 AM - 10:30 AM CD46 as a Novel Target in Metastatic Castration Resistant Prostate Cancer
Rahul Aggarwal, MD
University of California, San Francisco

10:30 AM - 10:35 AM Discussion

10:35 AM - 10:50 AM Phase 1 Trial of HPN424: A half-life extended, PSMA/CD3-specific TriTAC
Natalie Sacks, MD
Harpoon Therapeutics

10:50 AM - 10:55 AM Discussion

10:55 AM - 11:10 AM Bispecific T-Cell Engager Immune Therapies for the Treatment of Prostate Cancer
Hosein Kouros-Mehr, MD, PhD
Amgen

11:10 AM - 11:15 AM Discussion

Closing Remarks
11:15 AM - 11:25 AM
Howard Soule, PhD
Prostate Cancer Foundation
Jonathan W. Simons, MD
Prostate Cancer Foundation

Meeting Adjourned
** A boxed lunch will be provided **
Program Committee:

Program Committee Co-Chair: Howard Soule, PhD (Prostate Cancer Foundation)
Program Committee Co-Chair: Andrea Miyahira, PhD (Prostate Cancer Foundation)

Jonathan W. Simons, MD (Prostate Cancer Foundation)
Marco Gottardis, PhD (Janssen Research & Development, LLC)
Hosein Kouros-Mehr, MD, PhD (Amgen)
Lorelei Mucci, ScD (Harvard T.H. Chan School of Public Health)
Elizabeth Platz, MPH, ScD (Johns Hopkins Bloomberg School of Public Health and the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins)
Eric Small, MD (University of California, San Francisco)
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