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REVIEW ARTICLE

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The 28th Annual Prostate Cancer Foundation Scientific Retreat report

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Abstract

Background: The 28th Annual Prostate Cancer Foundation (PCF) Scientific Retreat was held virtually over 4 days, on October 28–29 and November 4–5, 2021.

Methods: The Annual PCF Scientific Retreat is a leading global scientific conference that focuses on first-in-field, unpublished, and high-impact basic, translational, and clinical prostate cancer research, as well as research from other fields with high probability for impacting prostate cancer research and patient care.

Results: Primary areas of research discussed at the 2021 PCF Retreat included: (i) prostate cancer disparities; (ii) prostate cancer survivorship; (iii) next-generation precision medicine; (iv) PSMA theranostics; (v) prostate cancer lineage plasticity; (vi) tumor metabolism as a cancer driver and treatment target; (vii) prostate cancer genetics and polygenic risk scores; (viii) glucocorticoid receptor biology in castration-resistant prostate cancer (CRPC); (ix) therapeutic degraders; (x) new approaches for immunotherapy in prostate cancer; (xi) novel technologies to overcome the suppressive tumor microenvironment; and (xii) real-world evidence and synthetic/virtual control arms.

Conclusions: This article provides a summary of the presentations from the 2021 PCF Scientific Retreat. We hope that sharing this knowledge will help to improve the understanding of the current state of research and direct new advances in prostate cancer research and care.

KEYWORDS
androgen receptor, diagnosis, prognosis, therapy, tumor biology

1 | INTRODUCTION

The 28th Annual Prostate Cancer Foundation (PCF) Scientific Retreat was a virtual event held over 4 days, on October 28–29 and November 4–5, 2021. The Annual PCF Scientific Retreat features presentations on first-in-field, unpublished, and high-impact basic through clinical prostate cancer research, as well as research from other fields with significant potential for impacting prostate cancer research and patient care. The Retreat is PCF's primary annual global knowledge exchange event and aims to foster a collaborative research culture and accelerate research that will ultimately bring an end to death and suffering from prostate cancer.

The 2021 PCF Scientific Retreat had 52 presentations in the Plenary Session including the PCF Women in Science Award Lecture. There were 117 virtual poster presentations. Research was presented from an extensive number of fields, including cellular and molecular biology, tumor and germline genetics and genomics, epigenetics, liquid biopsies, metabolism, endocrinology, cancer immunology and immunotherapy, tumor microenvironment (TME), medical oncology, precision medicine, drug discovery and development, epidemiology and population sciences, disparities research, survivorship research,

molecular pharmacology, nuclear medicine, radiology and novel molecular imaging, radiation oncology, computational biology, artificial intelligence, pathology, surgery, urology, real-world evidence and synthetic/virtual control arms, and clinical trials. There were 1597 individuals from 33 countries who registered for the Retreat, representing over 213 academic institutions, 68 biopharmaceutical companies, 15 medical research foundations, and the NIH, NCI, Department of Defense, and Department of Veterans Affairs (VA). Fifty-three percent of the speakers were presenting at a PCF Scientific Retreat for the first time.

This article summarizes the presentations from the 28th Annual PCF Scientific Retreat. All of the presentations and discussions can be viewed in full here: https://www.pcf.org/scientific-retreat/28th-annual/video-replays/.

The 2021 PCF "State of Science" report (PDF), which includes a more detailed summary of each presentation and the Agenda from the 28th Annual PCF Scientific Retreat can be downloaded at: https://www.pcf.org/c/scientific-retreat-reports/.

2 | PROSTATE CANCER DISPARITIES

Global annual estimates for prostate cancer include ~1.4 million diagnoses and ~466,000 deaths each year, with the number of deaths estimated to double to ~740,000 by 2040. Black men experience significant prostate cancer disparities, including ~1.8-fold higher incidence rate and ~2.2-fold higher mortality rate compared with White men and ~2.9-fold higher incidence rate and ~4.6-fold higher mortality rate compared with Asian men. The highest rates of prostate cancer deaths occur in countries with larger African ancestry populations, particularly in Africa and South America. In addition, Black men are typically diagnosed at a younger age and with more aggressive and/or advanced disease, compared with White men.

Kosj Yamoah (Moffitt Cancer Center) and Isla Garraway (University of California, Los Angeles; VA Greater Los Angeles Healthcare System) gave an overview of prostate cancer disparities in African Americans and discussed studies in the VA aiming to identify factors that contribute to disparities. Many of these studies were led under the auspices of the PCF–VA Partnership, founded in 2016, which established a network of PCF–VA Centers of Excellence and programs to improve the care of Veterans with prostate cancer.

Multiple complex etiologies likely contribute and interact to drive racial health disparities. This includes access to and quality of medical care, other sociodemographic factors, and biologic factors. Factors impacting biology include inherited genetics, genomics, epigenetics, the immune system, environmental and occupational exposures, stress, diet, and metabolism. Factors impacting healthcare access and care delivery include structural racism, healthcare system inequalities, health policies, mistrust, health insurance, and low socioeconomic status (SES). Additional socioeconomic factors that impact health outcomes include education access and quality, neighborhood and built environments, economic stability, and social and community context. While racial disparities in prostate cancer incidence are considered largely attributable to factors that impact biology, racial disparities in mortality rates are attributed to the combined impact of higher incidence rates and suboptimal treatment delivery. Studies performed in equal access clinical settings such as the VA are key to understanding the drivers of disparities and developing strategies to overcome them.

The VanDAAM trial conducted in the Moffitt Cancer Center, James Haley VA Hospital, and Bay Pines VA HealthCare System, from 2018 to 2021, utilized a unique accrual strategy to maximize enrollment of African American patients with prostate cancer. For each self-identified African American patient enrolled, a CAPRA score-matched non-African American patient was enrolled. Altogether, of 276 patients approached, 243 (125 African American, 118 non-African American) were enrolled (88% accrual success rate), and genetic sequencing was performed for 233 (96%). Significant overlap was observed between ancestry proportions and self-identified race, with 9% of self-identified African American patients being classified as non-African American based on genomic ancestry proportions, and no self-identified non-African American patients reclassified based on genomic ancestry. Risk classification using NCCN guidelines versus Decipher found two- to five-fold higher disparate classification among African Americans compared with non-African American patients. For instance, 18.2% of African American patients classified as low-risk based on NCCN guidelines were reclassified as high-risk based on Decipher, while no such reclassification occurred in non-African American patients. These findings suggest that current clinical risk stratification systems are suboptimal in African American patients. Targeted accrual of African American patients is a feasible strategy for increasing diversity in clinical trials and will aid investigations on the diversity of prostate cancer.

The RESOLVE PCa (Rate Elements Skewing Outcomes Linked to Veteran Equity in Prostate Cancer) Consortium in the VA is investigating how interactions between social and biologic determinants influence prostate cancer incidence, aggressiveness, and clinical outcomes. Income, SES, marital status, social support, and education levels have been identified as social determinants of health linked to prostate cancer aggressiveness and clinical outcomes including survival. SES and environmental disparities continue to be persistent in Black communities. For instance, the predominantly Black neighborhoods that were subjected to redlining in the 1930s had the highest social vulnerability in a 2020 study. Another study found that in the United States, people of color are disproportionately and systematically exposed to higher levels of $PM_{2.5}$ pollutants in their neighborhoods. As discussed in more detail by Lynch (below), a prostate cancer core was developed in the VA VINCI (VA Informatics and Computing Infrastructure) database, which included Veterans diagnosed or treated for prostate cancer in the VA. The development required the abstraction of structured electronic health records data as well as the development of natural language processing tools to identify patients with metastatic disease, and extract and harmonize clinical and demographic factors. Overall, 488,984 living and 592,153 deceased patients with prostate cancer were identified in the VA between 2000 and 2018. These

include 16,618 patients living with metastatic prostate cancer. Geocoding is being used to map location densities of VA patient characteristics, and identify associations with other mapped factors, including environmental exposures such as daily $PM_{2.5}$ exposure levels, and SES. These multidimensional studies will enable the creation of complex predictive models and improve understanding of the etiologies of prostate cancer disparities.

A study by the PCF-VA Health Disparity Working Group evaluated racial disparities in prostate cancer diagnostics and biopsies in the VA.[1] Among ~8 million veterans undergoing routine care in VA hospitals between 2005 and 2019, ~259,000 underwent a diagnostic biopsy and ~137,000 were diagnosed with prostate cancer. No differences were observed in time from the first elevated PSA (>4.0) test result to biopsy, and from the time of the PSA test to treatment initiation. However, a twofold higher prostate cancer incidence rate was observed for Black eterans compared with White Veterans. Black Veterans also tended to be younger and have more advanced disease at diagnosis, including higher PSA levels, more aggressive prostate cancer, and higher rates of metastatic disease. Long-term outcomes following definitive primary treatment were evaluated in a subcohort of ~92,000 Veterans diagnosed with prostate cancer between 2005 and 2015 with at least 5 years of follow-up. The 10-year cumulative rate of prostate cancer-specific mortality was lower among Black than White veterans (4.0% vs. 4.8%) in this subset. This demonstrates that equal healthcare access and quality can effectively eliminate racial health disparities. However, the ~2-fold higher incidence rate in Black veterans compared with White veterans resulted in disproportionately higher overall prostate cancer metastasis and mortality rates in Black veterans. These data suggest that racial disparities in prostate cancer incidence continue to drive disparities in outcomes in equal access healthcare settings such as the VA. A better understanding of the factors and dynamics that contribute to racial disparities in prostate cancer incidence, as well as policies for equalizing access in all healthcare systems, are necessary for advancing health equity.

Lorelei Mucci (Harvard T.H. Chan School of Public Health) discussed studies on epidemiologic factors contributing to prostate cancer disparities in Black men and men of African ancestry. Epidemiologic studies have found that risk factors for prostate cancer incidence include older age, family history, genetic risk loci, and taller height. Risk factors for aggressive prostate cancer include genetic risk loci, taller height, and lifestyle factors including obesity, low vitamin D levels, low lycopene intake (from tomatoes), smoking, and reduced physical activity. Studies including the polygenic risk score (PRS) discussed by Haiman (below) have demonstrated that inherited genetic factors play a strong role in prostate cancer incidence in men of European and African ancestry. Whether the prevalence of lifestyle factors that affect prostate cancer risk differ between Black and White men, and whether they contribute to disparities is an important question.

A study in National Health and Nutrition Examination Study and the Health Professionals Follow-up Study cohorts evaluated the multivariable relative risks for lifestyle factors and lethal prostate cancer, and the prevalence of lifestyle and dietary factors in Black and White men, to determine the population attributable fraction differences in lifestyle and diet risks for lethal prostate cancer by race. A higher prevalence of smoking and low vitamin D levels were observed in Black compared with White men. There were smaller differences in the prevalence of physical inactivity and lycopene intake, while obesity rates were similar. These data suggest that increasing vitamin D levels and not smoking represent potential opportunities for prostate cancer interception and reduction of disparities. While physical inactivity and obesity did not significantly contribute to racial disparities, these are important risk factors for lethal prostate cancer overall. There is a relative paucity of epidemiologic studies among Black men, particularly on role of contextual factors, and there is an urgent need to identify opportunities for intervention to reduce disparities.

Brandon Mahal (University of Miami) discussed the role of equitable healthcare access in prostate cancer disparities. Race and ethnicity are social constructs that include many aspects beyond ancestry and genomics, such as culture, behavior, environment, and social influences. These factors can interact to influence the risk for disease development and outcomes. While the role of biological differences in prostate cancer racial disparities remains unclear, the role of access to care and other social-economic impacts of systemic racism have been demonstrated.

Several clinical trials and equal access studies have demonstrated that in equal-access healthcare settings, Black patients with prostate cancer have equal and sometimes even better outcomes than White patients. For instance, a meta-analysis of RTOG randomized controlled clinical trials found an association between Black race and lower risk of prostate cancer mortality in patients diagnosed with localized prostate cancer. A meta-analysis of Phase 3 trials of docetaxel-regimens in CRPC found that Black patients experienced similar or slightly better OS than White patients. A study by Mahal and colleagues found that among patients newly diagnosed with intermediate to high-risk prostate who did not have medical insurance, more Black than White men did not receive treatment (27.8% vs. 15.7%). Even among newly diagnosed patients with medical insurance, nontreatment rates were higher for Black versus White men (15.5% vs. 10.6%). The Affordable Care Act (ACA) has been demonstrated to have effectively eliminated racial disparities in medical coverage. Before the ACA, 13.9% of Black patients were uninsured versus 10.4% of White patients. Post-ACA, these numbers were equalized, with 6.9% of Black patients and 6.2% of White patients being uninsured. Thus, policies that improve access to insurance can effectively reduce health disparities.

Racial disparities are also prevalent in genomics studies. For instance, Whites comprise ~16% of the global population, but represent ~80% of participants in GWAS studies. White patients are also overrepresented among The Cancer Genome Atlas (TCGA) samples, while there are insufficient samples to detect a 10% mutational frequency over background somatic mutation frequencies, for all other races and ethnicities, over all cancer types, with the exception of Black women with breast cancer. Ancestry-specific

differences in somatic prostate cancer alterations identified in TCGA include higher frequencies of *TP53* alterations and *SCNA/CCNE1* amplifications and lower frequencies of PI3K pathway alterations in patients of African ancestry relative to patients of European ancestry. Ongoing studies by Mahal and colleagues include evaluation of racial differences in rates and timing of comprehensive genomic testing, and whether these differences impact OS.

Solutions to disparities will require multipronged approaches, including increasing diversity in trans-disciplinary and clinical research, active community outreach programs to improve care delivery and overcome distrust, transparency, education, acknowledgment of the history and impact of racism, and establishment of a racially, ethnically, culturally and linguistically diverse oncology workforce.[2,3] As an example, at the University of Miami, a cancer education and prevention initiative has been established, which includes a community outreach program with multicultural and multilingual staff, who are integrated with the cancer center.

Franklin Huang (University of California, San Francisco) discussed a study on prostate cancer genomic alterations in patients of European and African ancestry. Genomic sequencing was performed on prostate tumor samples from a cohort of 3454 patients, including 251 African ancestry and 1940 European ancestry individuals with localized disease, and 185 African ancestry and 1078 European ancestry individuals with metastatic disease. *TMPRSS2-ERG* fusions and *PTEN*-deletions occurred at higher frequencies in prostate cancer from European ancestry patients, while alterations in the *MYC*, *SPOP*, and *KMT2D* genes were more frequent in prostate cancer from African ancestry patients. In African ancestry prostate cancer, *AR*, *MYC*, and *RB1* alterations were more frequent in metastatic versus localized disease. The frequency of targetable somatic alterations and biomarkers (*ATM*, *BRCA2*, or DNA repair gene alterations, tumor mutational burden [TMB] and micro-satellite instability [MSI]) were similar in European and African ancestry patients. While this study represents the largest effort to date to identify somatic alterations in metastatic prostate cancer from patients of African ancestry, collectively there have been relatively fewer cases reported on, compared with European ancestry cases. Significantly more studies are needed to better define the genomic landscape of prostate cancer in diverse populations, to better determine any ancestry-based genomic differences, inform treatment selection, and understand the factors that contribute to prostate cancer disparities. Equitable inclusion of diverse populations in treatment and research settings including clinical trials and genomics studies is key to delivering precision oncology. Some of these data have been published.[4]

3 | THE IMPORTANCE OF CLINICAL TRIAL DIVERSITY AND LESSONS FROM THE COVID-19 VACCINE TRIAL

Sandra Amaro (Pfizer) discussed clinical trial diversity, and the methods used by Pfizer to enroll a diverse cohort onto their COVID-19 vaccine trial. Diverse representation in clinical trials is essential for equity and reducing healthcare disparities and understanding how race, ethnicity, age, and gender may impact the efficacy and safety of medicines and vaccines. It is critical that clinical trial enrollees represent the diversity of individuals impacted by the disease under study.

Before the COVID-19 pandemic, as part of an effort to achieve equity in clinical trials, Pfizer established a Multicultural Equity Health Collective of external stakeholders including advocacy organizations and legislators, who disseminate English and Spanish language educational materials about trial opportunities to communities. This Collective played a significant role in the ability of Pfizer to rapidly reach and enroll diverse volunteers onto the COVID-19 clinical trial. For example, one of Pfizer's Multicultural Equity Health partners Dr. Elena Rios (National Hispanic Medical Association) spoke on a Southern California radio station's Strength Thru Unity show about the trial and website URL, resulting in over 1000 website visitors completing the trial pre-screener, over 90 of whom were ultimately enrolled on the trial. This demonstrates the significant influence that a trusted voice can have on medical behaviors in underserved and underrepresented communities.

Baseline diversity and demographic data from 213 Pfizer US clinical pharmacology and vaccine trials with 103,103 participants conducted between 2011 and 2020, was recently published.[5] The study found that 56% of trials had participant levels at or above US census levels for Black or African Americans, and 53% of trials had participant levels at or above US census levels for Hispanic or Latino individuals. Only 16%, 14%, and 8.5% of trials had participant levels at or above census levels for Asian, Native Hawaiian or Pacific Islander, and American Indian or Alaska Native individuals, respectively. US Census levels versus Pfizer Trial participant levels were reported for White (76.3% vs. 80.4%), Black or African American (13.4% vs. 14.3%), Hispanic or Latino (18.5% vs. 15.9%), Asian (5.9% vs. 3.1%), American Indian or Alaska Native (1.3% vs. 0.6%), and Native Hawaiian or Pacific Islanders (0.2% vs. 0.2%).

Pfizer has also developed policies to embed the importance of diversity within the organization, select and develop clinical trial site partnerships committed to participant and site staff diversity, develop programs to build trust and awareness in communities, develop digital tools to overcome practical barriers to trial participation, and share knowledge transparently on representation in clinical trials.

4 | PROSTATE CANCER SURVIVORSHIP

Cancer survivorship is a branch of oncology that manages quality of life issues in cancer patients and survivors. These needs begin at diagnosis, and continue throughout the disease course, including during ongoing and subsequent treatment, long-term disease remission, and end-of-life care. Survivorship research aims to rigorously test and identify optimal quality-of-life treatment and management strategies, and to define the biology of survivorship issues. Survivorship care teams include nurses, oncologists, and specialty care by cardio-oncologists, nephrologists, onco-endocrinologists, tobacco counselors, sleep insomnia experts, psychologists, and sexual health

experts. Survivorship care also requires clear communication between patients and care providers, to optimally determine and respond to patients' needs. The following speakers discussed various issues related to prostate cancer survivorship.

Alicia Morgans (Dana-Farber Cancer Institute) discussed survivorship programs and research. PCF-SURECaP is a working group composed of prostate cancer researchers focused on improving prostate cancer survivorship care. A PCF-SURECaP white paper highlighted critical areas of need in prostate cancer survivorship.[6] Priority areas include determining the subjective patient experience, which includes assessing quality of life, patient-reported outcomes, caregiver–patient interactions, social functioning, financial toxicity, racial disparities, and minority engagement. Areas where clinical research is needed include treatment-related cardiovascular and metabolic health toxicities, frailty and exercise tolerance, cognitive and psychological health, and skeletal and bone health. Studies to better define the biology and heterogeneity of survivorship issues are also needed to improve care and advance precision survivorship. For instance, better understandings are needed on how adverse events and quality of life may be impacted by inflammation and stress responses, aging and senescence, somatic genomics, germline genetics, the microbiome, and clonal hematopoiesis.

Artificial intelligence (AI)-based methods are being developed to monitor outcomes and adverse events in patients, and to identify candidates for survivorship clinical trials. As an example, a pilot AI program followed ~1400 men to ensure every 3-monthly PSA testing and patient-reported outcome surveys were done, and automatically identify patients with rising PSA or symptom development and issue immediate clinician referrals for follow-up diagnostics and care.[7] The automated triage provided by this system was found to improve well visits and increase clinician time for acute care.

4.1 | Survivorship management of adt-associated hot flashes

Morgans also discussed a study on a wearable device that aims to reduce hot flashes from hormonal therapy in patients with prostate cancer. Hot flashes are a common adverse event affecting ~80% of patients with prostate cancer receiving hormonal therapy and are reported as the most troubling side effect in ~25% of patients. Hot flashes often worsen with treatment duration and younger age at diagnosis, and negatively impact sleep and quality of life. Current treatment options are limited.

Morgans et al.[8] conducted a pilot clinical trial to test the impact of a novel wrist-wearable phasic cooling or warming thermal wave-delivering device in 50 men with prostate cancer undergoing hormonal therapy (luprolide, abiraterone, or enzalutamide) and bothersome hot flashes. This device (Embr) can change perception of environmental temperatures by up to 5°F and is app-controlled for the personalization of duration, frequency, and intensity of thermal waves. Enrolled patients received the device to use for 4 weeks and were followed for device usage and surveys to measure hot flashes, hot flash interference, sleep, temperature symptoms, and perceived efficacy. Preliminary results from the first 32 patients found the device was used on average for 3 h per day over eight sessions, and patients experienced a ~22% average reduction in hot flashes over 4 weeks, independent of the type of hormonal therapy. In addition, patients experienced improvements in hot flash quantity, bothersome ratings, interference with activities or sleep, and control over interference with activities or sleep. A slight improvement in sleep disturbance and sleep-related fatigue was observed, as well as a trend toward improvement in hot flash-related temperature symptoms. Approximately 67% of patients felt the device was somewhat to extremely effective at managing hot flashes; positive experiences were associated with more frequent or regular usage. These preliminary data suggest this device may have promise for managing hot flashes and improving hot flash-impacted quality of life measures, and warrant further study. In a prior study in women with hot flashes caused by menopause, the device was found to reduce hot flash interference, improve control over hot flashes, and improve sleep quality.

4.2 | Evaluating the cognitive impact of ar-targeted therapy

Charles J. Ryan (University of Minnesota; Prostate Cancer Foundation) discussed preliminary results from the PCF-SURECaP Working Group initiatives, COGCaP, and ARACOG, which evaluated the cognitive effects of ADT in patients with prostate cancer. While ADT is an effective backbone treatment for prostate cancer, it is associated with a range of side effects including fatigue, weight gain, and depression, and may increase the risk for cognitive impairment and dementia. Understanding the biology underlying these side effects, and identifying biomarkers for risk, and mitigation and management strategies, are critical for improving prostate cancer survivorship.

AR is expressed in the brain and has functions including regulation of memory, executive functions, visual and spatial cognition, neuron protection, and removal of waste products from the brain. AR blockade or the natural reduction of androgens that occur with age may contribute to cognitive decline, dementia, and Alzheimer's disease. For instance, in patients with Alzheimer's disease, low brain testosterone levels have been associated with increased levels of β-amyloid. A study by Gonzalez et al. found higher rates of impaired cognitive performance over time in prostate cancer patients on ADT compared with patients undergoing prostatectomy only and with healthy controls. However, other studies have not consistently validated links between ADT and impaired cognitive function. A polygenetic hazard score that estimates an individual's genetic risk for Alzheimer's disease has been developed. Whether this score may be a biomarker for identifying patients at higher risk for developing cognitive disorders after ADT is unknown. Further studies are needed to determine the cognitive effects of various

forms of AR-targeted therapies that have different mechanisms of action.

The multicenter COGCaP trial, led by Morgans, Ryan, and colleagues, is evaluating the cognitive effects of abiraterone versus enzalutamide in patients with mCRPC. In COGCAP, patients with mCRPC without dementia or prior chemotherapy who are initiating AR-directed therapy receive the clinician's choice of abiraterone versus enzalutamide. Cognitive testing is performed at baseline, 3, 6, and 12 months. Correlative analyses include advanced neuroimaging techniques including diffusion tensor imaging (DTI), blood-oxygenation-level-dependent (BOLD) functional magnetic resonance imaging (fMRI), and arterial spin labeling (ASL) imaging at baseline and 3 months, and blood sample collection for SNP analysis. At the time of this presentation, 58 total patients had been enrolled out of a target of 100; 19 are on enzalutamide and 37 are on abiraterone.

The ARACOG trial is comparing the cognitive effects of darolutamide versus enzalutamide in patients with mCRPC. This trial is evaluating the hypothesis that differential CNS penetration of darolutamide and enzalutamide may be associated with differences in cognitive testing results measured during therapy. The trial is enrolling mCRPC patients who have not had prior darolutamide or enzalutamide, and randomizing them to receive darolutamide versus enzalutamide for up to 52 weeks. Cross-over to the other treatment arm is allowed if patients display symptoms of cognitive decline. Patients will be evaluated by cognitive assessments using Cambridge Neuropsychological Test Automated Battery (CANTAB), a cognitive function and impairment assessment software that tests learning, executive function, working memory, visual, verbal and episodic memory, and attention, information and processing time. The primary endpoint is the comparison of percentage change in the maximally changed cognitive domain from baseline at 24 weeks. Additional correlative evaluations include fMRI, Timed Up and Go (TUG) times, subjective surveys on cognitive function, and genomics for AR CAG repeat length, Alzheimer's disease polygenetic hazard score, and exosome analysis. This trial is active and ongoing.

These trials will enable a better understanding of the association between different types of AR-targeted therapies and cognitive risks, enable and validate cognitive evaluation tests in oncology clinics, and help to identify biomarkers and the biology associated with cognitive decline during hormone therapy. Challenges in oncology cognitive trials include patient self-selection biases, testing commitments of sites and test scalability, and the validity of biomarkers.

4.3 | Survivorship research to improve cardiovascular and bone health

In addition to cognitive effects and hot flashes, treatment with AR-targeted therapy can have cardiometabolic side effects including atherogenesis, myocardial infarction, dyslipidemia and diabetes, bone health side effects such as osteopenia and fragility fractures, and other side effects including sarcopenia, decreased exercise tolerance, hypertension, and potentially mental health-related consequences.

Studies have found that ADT exacerbates cardiovascular disease risk, with changes in cardiometabolic health observed as early as 12–24 weeks after initiation of ADT. Early intervention is critical to reducing these side effects, and for reducing early mortality from cardiovascular disease-related complications in patients with prostate cancer. The FDA has issued a black box warning that GnRH agonists increase the risk for diabetes and cardiovascular diseases, and recommends periodic monitoring of blood glucose and/or hemoglobin A1c levels in patients being treated with GnRH agonists.

Ravi Parikh (University of Pennsylvania; The Corporal Michael J. Crescenz VA Medical Center) discussed survivorship research in the VA to improve cardiovascular and bone health in patients with prostate cancer. Parikh and colleagues assembled a registry-like curated data cohort of >150,000 veterans diagnosed with prostate cancer between 2004 and 2020, from the VA Corporate Data Warehouse, which includes data on lab tests, imaging, mental health, socioeconomic burden, and cause of death, as a resource for survivorship studies.

Parikh and colleagues used data on >90,000 veterans diagnosed with prostate cancer between 2010 and 2017 from this cohort, to investigate cardiovascular risk factor screening and management in veterans with prostate cancer initiating treatment with GnRH agonists.[9] Cardiovascular outcomes that were assessed included hypertension, dyslipidemia, and impaired glucose tolerance. The study found that cardiovascular risk factors tended to be under-assessed and under-treated in men with prostate cancer. Men with pre-existing cardiovascular risk factors experienced higher rates of cardiovascular risk factor assessments; however, no significant differences were observed between assessments in patients starting ADT versus not starting ADT. These data suggest that ADT initiation did not play a role in physician decisions to perform cardiovascular risk factor assessments. Overall, comprehensive cardiovascular risk factor assessment occurred in ~68% of patients undergoing ADT, and 54% of those assessed had uncontrolled cardiovascular risk factors, of which ~30% did not receive corresponding risk-reducing medication.

ADT is also associated with accelerated bone loss and a 10%–20% risk of significant fracture after 5 years. ADT-associated fractures decrease quality of life and functional status and may increase prostate cancer-related mortality by up to 40%. Unfortunately, while anti-resorptive therapies are commonly recommended in patients with mCRPC, they are not routinely recommended in mHSPC. Survivorship guidelines recommend that patients undergo baseline and periodic assessment of bone mineral density using bone density scans (DXA) and the World Health Organization Fracture Risk Assessment Tool (FRAX) before initiating ADT. However, in a VA study, Parikh and colleagues found that <1/3 of eligible veterans with prostate cancer received DXA screening, including <50% of patients with mHSPC. Measures to increase and improve early bone health assessments are needed.

Biomechanical Computed Tomography analysis (BCT), an analysis that can be made using spine or hip regions from standard computed tomography (CT) scans can provide measurements of bone strength

and DXA-equivalent bone mineral density T-score at the hip and a volumetric bone mineral density of trabecular bone at the spine. Prostate cancer patients routinely undergo baseline and surveillance prostate cancer imaging, suggesting this method may offer an opportunistic approach for bone health screening. Parikh and colleagues evaluated the ability of BCT to determine changes in bone strength and bone density in 140 patients with mHSPC undergoing ADT. BCT was applied to baseline CT images taken within 48 weeks before ADT initiation versus CT images taken up to 96 weeks after ADT initiation, and at least 48 weeks after baseline. In preliminary results, BCT assessments found an average 22% decrease in bone strength, 60% decrease in femoral neck T-score, and 20% decrease in hip bone density, after ~1 year of ADT, compared with baseline. Virtual stress testing is being performed using these data to estimate the risk for fractures if a patient were to fall. Future studies in the VA will evaluate type I collagen C-telopeptide (CTX) as a blood-based biomarker for fracture risk. The development of imaging or blood-based biomarkers of bone health that can be routinely performed and integrated into guidelines for anti-resorptive therapy will be critical steps toward improving prostate cancer survivorship.

4.4 | Cardiovascular disease risk with gnrh antagonists versus lhrh agonists

Neal Shore (Carolina Urologic Research Center, GenesisCare, USA) discussed cardiovascular risks associated with various forms of AR-targeted therapy. LHRH agonists are thought to increase the risk for cardiovascular disease by stimulating immune cells in atherosclerotic plaques to promote plaque instability and rupture, leading to thrombotic complications. Multiple prior studies including meta-analyses, a prospective Phase 2 trial, real-world data analyses, and an analysis of data from the FDA Adverse Events Reporting System (FAERS), have found reduced risks of cardiovascular events and deaths with GnRH antagonists versus LHRH agonists in prostate cancer patients with pre-existing cardiovascular disease. However, the injectable GnRH antagonist is associated with a higher rate of injection site reactions which has contributed to a high rate of crossover to LHRH agonists, which would not be anticipated with an oral GNRH antagonist. Unfortunately, there are caveats and flaws in many of these prior studies, and more studies are needed. Studies are also needed that focus on African American populations, who experience disparately higher prostate cancer and cardiovascular mortality rates. Prospective studies with cardiovascular events as the primary endpoint are needed. Overall, these data suggest that screening and regular monitoring for metabolic and cardiovascular risk factors may be critical for guiding ADT choices and determining whether other lifestyle and pharmacological interventions are needed to mitigate risk.

The pivotal randomized Phase 3 HERO trial evaluated the oral LHRH antagonist relugolix (orally once daily) versus leuprolide (subcutaneous injection every 3 months) in 934 patients with advanced prostate cancer.[10] The trial met its primary endpoint of sustained castration (<50 ng/dl) from Day 29 through 48 weeks and was FDA-approved in 2020. Cardiovascular events were a pre-specified safety endpoint. Ninety-two percent of patients on the relugolix arm and 94% of patients on the leuprolide arm had at least one cardiovascular risk factor: lifestyle risk factors (67.8%, 65.6%, respectively), cardiovascular or cerebrovascular risk factors (78.5%, 82.5%, respectively), or a history of major adverse cardiovascular events (MACE) more than 6 months before enrollment (13.5%, 14.6%, respectively). Patients with a history of MACE in the 6 months preceding enrollment were excluded from the trial. A 54% lower cumulative incidence of new MACE events in the first 48 weeks was observed in patients treated with relugolix versus leuprolide (2.8% vs. 5.6%). Among patients treated with leuprolide, new MACE events were significantly higher in patients with a history of MACE versus no history of MACE (17.8% vs. 4.2%). Among patients treated with relugolix, new MACE events occurred in 3.6% of patients with a history of MACE versus 2.8% of patients with no history of MACE. Overall, this represents a 5.8-fold lower risk for new MACE events in patients with a history of MACE if treated with relugolix versus leuprolide, and a 1.5-fold lower risk for new MACE events in patients with no history of MACE with relugolix versus leuprolide. No statistically significant associations were observed between cardiovascular risk and any metabolic biomarkers evaluated (FSH levels, dyslipidemia, HbA1c, weight, BMI, blood pressure, Gleason score, global geographic region, race, ethnicity, testosterone at baseline, prior ADT use, and lifestyle-related risk).

PRONOUNCE was the first randomized trial to prospectively compare the cardiovascular safety of a GnRH antagonist and an LHRH agonist in patients with prostate cancer initiating ADT who had pre-existing atherosclerotic cardiovascular disease.[11] Unfortunately, the study was prematurely terminated due to smaller than planned numbers of participants and events. The primary outcome, time to first adjudicated MACE (myocardial infarction, stroke, or death) through 12 months, was not significantly different between patients treated with degarelix versus leuprolide. Thus, conclusions on cardiovascular safety between degarelix and leuprolide could not be drawn from this study. Nonetheless, PRONOUNCE provides a model for interdisciplinary collaboration between urologists, oncologists, and cardiologists for the evaluation of cardiovascular outcomes in patients with prostate cancer. A recently published retrospective analysis of real-world claims-based data going back 10 years also observed no significant differences in cardiovascular events in patients with prostate cancer treated with a GnRH antagonist versus LHRH agonist.

Prospective, well-designed trials that evaluate cardiovascular and other safety measures as primary endpoints in prostate cancer patients being treated with different types of AR-targeted therapies, as well as validated biomarkers and cardiovascular risk assessment tools for such assessments, remain an unmet need.

4.5 | Sleep dysfunction and prostate cancer

Stacy Loeb (New York University; Manhattan Veterans Affairs Hospital) discussed studies on the association between sleep

dysfunction and prostate cancer. Sleep disturbances are common. Of US adults, ~35% sleep under 7 h per night, 10%–30% experience insomnia, and 2%–30% experience obstructive sleep apnea. Multiple mental and physical health consequences have been linked to sleep and circadian disturbances, including depression, poorer quality of life and well-being, increased risk for chronic diseases including cancer, hypertension, diabetes, obesity, depression, heart attack, stroke, fatigue, erectile dysfunction, and increased risk of accidents and injuries. The IARC Monographs Working Group has classified night shift work as "probably carcinogenic to humans" (Group 2A), although this is based primarily on evidence from experimental and mechanistic cancer animal models, with limited clinical evidence. Several mechanisms have been proposed on how sleep disturbances may impact cancer, including possible roles for the circadian system and melatonin as tumor suppressors, and hypoxia caused by sleep apnea as a possible driver of tumor progression.

In a systematic literature review by Sigurdardottir and colleagues,[12] 15 of 16 epidemiologic studies (10 statistically significant) found a positive association between prostate cancer risk and circadian rhythm or sleep disrupters including countries with more light at night, shorter sleep duration, shift work, and occupations with circadian disruptions. Another epidemiological study found that below-median morning urinary melatonin levels were associated with fourfold increased risk for advanced prostate cancer. Genetic studies in a cancer consortium data set found associations between genetic variations in circadian rhythm and melatonin pathway genes and risk for prostate and several other cancers. However, other studies have not found consistent associations between melatonin levels, sleep duration or sleep quality, and prostate cancer risk.

Robbins et al.[13] conducted a "social listening" study to evaluate sleep-related concerns and unmet needs among patients with prostate cancer and caregivers. Of 685 posts evaluated in an online prostate cancer patient community, 86% were posted by patients and 14% were posted by caregivers. Posts about sleep were more common among patients with advanced disease versus localized disease and were associated with more negative emotions. Co-existing complaints included fatigue, pain, and hot flashes. Sleeping medications were mentioned in 22% of posts.

Robbins and colleagues also performed a systematic review of studies in patients with prostate cancer and caregivers that included sleep as an endpoint. Eighty-three studies were identified, including three in caregivers; these studies were primarily about other topics but included subjective and/or objective measures of sleep as secondary endpoints.[14] Sleep disturbances were commonly associated with physical issues including night sweats, urination, and pain, and psychological issues, including distress, depression, and anxiety. Few studies evaluated sleep disturbance interventions, but some limited data suggested acupuncture, hypnotic therapy, mindfulness-based cognitive therapy, and educational information may provide short-term benefits.

Preliminary results from the survey of patients with prostate cancer and caregivers conducted by Loeb and colleagues found high rates of poor sleep quality, poor sleep habits, and clinical insomnia. There was also a high prevalence of using sleeping medicines. Despite this, a recent survey of urologists by Loeb and colleagues found that most do not document sleep quality, and rarely/never discuss sleep hygiene recommendations with patients. There are several quality of life instruments that include measures for sleep. These include EORTC QLQ C30, Functional Assessment of Cancer Therapy—Prostate (FACT-P), and Memorial Anxiety Scale for Prostate Cancer (MAX-PC). In addition, specific measures for sleep disturbances include the Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, STOP-BANG, Apnea Risk Evaluation System (ARES), Insomnia Severity Index (ISI), Sleep Hygiene Index (SHI), actigraphy and polysomnography.

The high frequency of sleep medication usage found in these studies is concerning, as some have black box warnings for the risk of serious injury caused by sleepwalking. Cognitive-behavioral therapy for insomnia (CBT-I) is a widely available structured intervention that addresses thoughts and behaviors about sleep and is recommended as the initial approach for the management of chronic insomnia by the American College of Physicians. If CBT-I fails, then shared decision-making about pharmacologic therapy may be recommended. In addition, treatable secondary causes of insomnia should be considered (e.g., depression, pain, urinary problems, and other sleep disorders like sleep apnea).

Sleep hygiene recommendations to promote healthy sleep include maintaining regular sleep and wake time, regular physical activity in the morning or afternoon, avoidance of naps, limiting caffeine consumption at night, avoiding big meals and limiting fluid within 3 h of bedtime, to have a bright light in the morning and avoid bright light at night, turning off electronics at night, avoid looking at the clock if awakened, and to enhance the sleep environment (temperature, comfort, and using the bed for sleep and sex only). Cognitive therapy and relaxation training such as deep breathing, yoga, and bio-feedback are also recommended.

Ongoing observational studies that are evaluating sleep in prostate cancer patients include IRONMAN, the Health Professionals Follow-Up Study, and "Eat-Move-Sleep," a Digital Survivorship study that is examining lifestyle after a cancer diagnosis. The Sleep Health & Lifestyle Improvement Program (SHIP) is a pilot interventional study led by Loeb and colleagues that will test a 3-month tailored digital sleep and lifestyle intervention. Questionnaires and actigraphy will be done at baseline and post-intervention.

Overall, these studies demonstrate that sleep disturbances are common among prostate cancer survivors and caregivers; however, assessments and interventions are understudied and underutilized. More studies are needed to better understand the impact of sleep disturbance on clinical and quality of life outcomes in patients with prostate cancer. Sleep is not mentioned in the American Cancer Society prostate cancer survivorship guidelines or other common guidelines for patients with prostate cancer. Establishing survivorship guidelines that address sleep is a critical need.

4.6 | Exercise as an approach to optimize treatment and health outcomes among prostate cancer survivors

There is strong evidence for the benefits of exercise in patients and survivors of prostate and other cancers. These include improvements in mental and physical quality of life, and improved survival and clinical outcomes. Prostate cancer patients may especially benefit from exercise, as ADT-associated side effects include reduction in lean mass, increase in fat, reduced physical function, and ~2-fold increased risk for metabolic diseases including diabetes and cardiovascular disease. Current cancer survivorship guidelines recommend aerobic exercise (30 min of moderate intensity physical activity, three times per week) plus resistance exercise (30 min per session, two times per week). However, ~25% of cancer survivors are physically active, ~65% are overweight or obese, and many are at increased risk for comorbidities. Survivorship research to determine optimal exercise recommendations and how to encourage adherence remains needed.

Christina Dieli-Conwright (Dana-Farber Cancer Institute) discussed a series of clinical studies her team has led, investigating the benefits of exercise in cancer patients and survivors.

A trial led by Jackie Dawson tested a 12-week periodized resistance training regimen in patients with prostate cancer undergoing ADT.[15,16] The regimen consisted of 3 months of three times per week, 45-min, supervised machine-based total body exercises which periodically progressed in intensity. Periodized resistance training was found to significantly increase lean muscle mass by an average of ~1.1 kg, and significantly reduced fat mass, waist circumference, and triglyceride levels, while total body mass did not change. The prevalence of sarcopenia was significantly reduced by the exercise regimen from 38.5% to 15.4%. In addition, there was a trend toward improved physical function including walking speed and speed of time to get up and go. The exercise group also experienced significantly improved overall quality of life scores and a trend toward reductions in fatigue and depression. Over 90% of patients completed the prescribed exercise, demonstrating good compliance.

ACTIVATE is a recently completed follow-up pilot trial that tested circuit-based intervals of aerobic and resistance exercise in sedentary overweight/obese patients with prostate cancer undergoing ADT. This trial evaluated changes in cardio-metabolic health, fitness, quality of life, and sarcopenic obesity measures. In preliminary results, the exercise regimen was found to decrease the prevalence of metabolic syndrome from 90% to 10% after 17 weeks. In patients that did not undertake exercise, the prevalence of metabolic syndrome increased from 75% at baseline to 85% at Week 17.

The randomized ERASE trial, led by Derek Kang, tested 12 weeks of usual care versus aerobic high-intensity interval training in 52 prostate cancer patients on active surveillance. The exercise regimen was found to significantly improve cardiorespiratory fitness and improved PSA velocity.

A trial led by Rebekah Wilson tested a combination of exercise and diet modifications in obese patients with prostate cancer undergoing ADT. The regimen was found to reduce fat mass and improve fitness. Good patient adherence was also seen in this trial, with 89% attending supervised exercise regimens and 100% attending dietary consultations.

THRIVE is an ongoing trial that is testing home-based exercise regimens in underserved minority patients with prostate, breast or colorectal cancer, who are undergoing chemotherapy. Enrolled participants receive exercise equipment delivered to their homes, and virtually supervised exercise regimens. Outcome measures include exercise participation and cardiovascular health.

Exercise oncology studies that remain needed include investigations into virtual outreach and access programs, novel exercise modalities, and effects on treatment efficacy, skeletal muscle quality, and tumor biomarkers. Establishing accessible exercise guidelines for patients and survivors will be critical toward improving prostate cancer survivorship and reducing disparities in underrepresented populations.

Mr. Joël Pointon (Patient and Advocate) discussed the development of an exercise initiative to preserve and improve the quality of life in prostate cancer patients undergoing ADT. Patient resources for managing quality of life and mental health consequences of prostate cancer diagnosis and treatment, particularly exercise programs appropriate for patients undergoing ADT, remain limited. A recent cancer survivorship survey found that exercise was a primary concern in ~2/3 of patients with metastatic cancer. To address this unmet need, Pointon partnered with personal trainer Justin Fassio to develop a home-based core resistance training exercise program for patients undergoing ADT. Exercises were developed that could be done with minimal equipment and across varying levels of difficulty. A website (www.exrx4adt.com) was developed that includes instructional videos and photos, as well as a patient support group section. The development of a personalized one-on-one training access program is under consideration. This project is seeking partnership with prostate cancer organizations for support, patient awareness, and to obtain patient feedback on the program and website. Accessible exercise programs such as this are critical for improving patient quality of life and survivorship. Questions can be emailed to Rt4adt@gmail. com.

5 | PREDICTING RISK OF PROSTATE CANCER WITH POLYGENIC SCORES

Epidemiologic studies have demonstrated that prostate cancer is one of the most heritable forms of cancer. Genetic and genome-wide association studies (GWAS) have been performed to identify the heritable factors that affect the risk of developing prostate cancer. The following speakers discussed studies to develop improved tools to predict who is at the highest genetic risk and may benefit from interventions such as early or more intensive screening and whether modifiable lifestyle factors can impact genetic risk.

Christopher Haiman (University of Southern California) discussed the use of GWAS data to develop a polygenic risk score (PRS) that can predict genetic risk for prostate cancer across multiethnic populations. A GWAS meta-analysis was performed using a cohort of 110,406 patients with prostate cancer and 126,974 controls, which included 10,368 cases and 10,986 controls of African Ancestry, 8610 cases and 18,809 controls of Asian ancestry, 2714 cases and 5239 controls of Latino ancestry, and 88,714 cases and 91,940 controls of European ancestry. Two hundred and sixty-nine genetic prostate cancer risk variants were identified; 86 were novel and 183 were previously known. Together, the 269 risk variants explained ~40% of familial relative risk for prostate cancer, a significant improvement over the ~28% of familial relative risk for prostate cancer accounted for by the previous 183 risk variants. A PRS developed using the 269 variants demonstrated high performance in stratifying lifetime risk for prostate cancer in White and Black populations. Compared with individuals with average risk (40%–60% of PRS scores), individuals with the top 80%–90% PRS scores had a 2.5-fold increase in risk, and individuals in the top 90%–100% of PRS scores had a 4.0-fold increase in risk for prostate cancer. Similar risk stratification was seen across African, Asian, Latino, and European populations. Age-specific absolute risk stratification found that individuals in the top 1% of PRS scores had a lifetime risk of prostate cancer of >60% for White men and >50% for Black men. Individuals in the lowest 10% of PRS scores had a lifetime risk for prostate cancer of under 5% in both White and Black populations. The performance of the PRS has been validated in several additional independent cohort studies. The PRS can also estimate risk based on a man's age. The PRS was unable to discriminate between risk for aggressive versus nonaggressive prostate cancer. However, 60% of lethal prostate cancer cases in White men and 55% of lethal prostate cancer cases in Black men were found to occur in men with the top 30% PRS scores. While pathogenic risk variants in *BRCA2*, *ATM*, and *CHEK2* are known to increase the risk for prostate cancer in European ancestry populations and pathogenic risk variants in *BRCA2*, *ATM*, *NBN*, and *PALB2* increase risk in African ancestry populations, PRS was found to modify this risk. For example, among European men with risk genes, those in the lowest 10% of PRS scores had an average population risk for prostate cancer, while those in the highest 10% of PRS scores had an 11-fold increase in risk over average. Because these GWAS studies were performed in predominantly European populations, additional studies in larger, trans-ancestry populations are being done. A trans-ancestry meta-analysis of 152,610 prostate cancer cases and 775,990 controls is underway. In a whole-exome sequencing study of 8361 nonaggressive versus 9185 metastatic prostate cancer cases, pathogenic germline variants in 17 of 23 DNA repair genes evaluated were found to be present at higher frequencies in metastatic versus nonaggressive prostate cancer cases (16.4% vs. 8.9%). Pathogenic variants in *BRCA2*, *ATM*, *NBN*, *MRE11A*, and *SLX4* were significantly higher in metastatic prostate cancer, suggesting these may act as genetic biomarkers for the early identification of patients who are more likely to develop metastatic disease. Future work by Haiman and colleagues includes expanding GWAS cohorts to be more inclusive of underrepresented ethnic and racial populations. For instance, the RESPOND study is aiming to perform exome and whole-genome sequencing on 20,000 exomes from prostate cancer patients of African ancestry. In addition, studies are needed to validate the PRS and inform how these tools can be improved and clinically implemented for guiding individualized prostate cancer screening strategies for men of all races and ethnicities. Some of these data have been published.[17–19]

Tyler Seibert (University of California, San Diego) discussed the development of a polygenic hazard score (PHS) based on genetic prostate cancer risk variants identified in GWAS studies, to predict genetic risk for aggressive prostate cancer and guide individualized screening strategies. The PHS is similar in principle to the PRS discussed by Haiman but incorporates an age dependence within a survival analysis framework, in which controls are censored in a way that the future potential to become a case is retained and cases are censored at the time of treatment of low-risk prostate cancer for the endpoint of diagnosis of aggressive prostate cancer. A PHS was developed using 46 genetic prostate cancer risk variants identified in GWAS studies in a largely European cohort. In an independent validation study using the UK ProtecT cohort, the 46-variant PHS was significantly able to predict age at diagnosis of aggressive cancer, and when added to PSA testing, improved its positive predictive value for identifying men at risk for aggressive prostate cancer. In a multiethnic cohort of 80,491 individuals, including 71,856 European, 6253 African, and 2382 Asian ancestry participants (based on genetic ancestry) the 46-variant PHS was found to perform well in predicting aggressive and lethal prostate cancer in the overall cohort, but underperformed in populations of African ancestry, compared with European and Asian ancestry . The hazard ratio (HR) for prediction of age at diagnosis of clinically significant prostate cancer (individuals in the top 20% vs. bottom 20% of PHS) was 5.6 in European, 5.2 in Asian, and 2.4 in African populations. To improve performance in African ancestry populations, an African ancestry data set was used to identify new prostate cancer SNPs; three were identified, all in 8q24. The addition of the three variants to the 46-variant PHS improved the HR from 2.4 to 4.7 for prediction of age at diagnosis of clinically significant prostate cancer in African ancestry populations (top 20% vs. bottom 20% of PHS). As an alternate approach to socially defined ancestry categories, an AI-based approach was used to agnostically infer “ancestries” from genomics data from a cohort of 71,856 European, 6253 African, and 2382 Asian ancestry individuals. The AI method identified two inferred ancestral groups and one admixed group. One group comprised largely individuals of European ancestry and the second group was largely composed of individuals of African ancestry. The admixed group included most of the individuals of Asian ancestry and ~1/3 of the individuals of African ancestry. The performance of the 46-variant PHS for identifying individuals at risk for aggressive prostate cancer was tested in AI-inferred ancestral groups and was similar to socially defined ancestral groups, with good performance in the largely European group (HR = 5.60) and the admixed group (HR = 5.05), but poorer performance in the largely African ancestry group (HR = 2.06) (HR = hazard

ratio of top 20% vs. bottom 20% of PHS). A new 290-variant PHS was developed by combining the 46 variants from the original PHS with those from the 269-variant PRS score developed by Haiman et al., using machine learning to determine a final optimal model of 290 variants. The HR (top 20% vs. bottom 20% of PHS) for the 290-variant PHS for predicting age at diagnosis of clinically significant prostate cancer was 13.7 in European, 10.3 in Asian, and 7.1 in African populations. However, this cohort was not entirely independent because while the model was developed in a training data set independent of the testing set, some individuals in the testing set had been included in the Haiman et al. GWAS meta-analysis that identified the 269 variants. An independent validation study of the 290-variant PHS was performed using the population-based and ancestrally diverse VA Million Veteran Program cohort, consisting of 582,515 veterans, including 68,538 with a prostate cancer diagnosis. In a multivariable model, the 290-variant PHS had an HR (top 20% vs. bottom 20% of PHS) of 4.15 for lifetime risk of prostate cancer-specific mortality, which was stronger than associations with family history (first-degree relative) (HR = 1.67) or African ancestry (HR = 1.97). These data demonstrate that PHS is associated with age at diagnosis of clinically significant/aggressive prostate cancer, age at diagnosis of metastatic prostate cancer, and lifetime prostate cancer-specific mortality. More data from non-European ancestry individuals are needed to improve the PRS for risk stratification in men of various genetic ancestries. Prospective trials will be needed in the future to validate the PHS. Some of these data have been published.[20–24]

Anna Plym (Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health) discussed the potential for a healthy lifestyle to modulate the risk for prostate cancer in men with a high prostate cancer polygenic risk score.[25] Previous studies have supported the general role of healthy lifestyles in prostate cancer prevention. Kenfield et al.[26] previously developed and validated a six-component-based "healthy lifestyle score," which Plym used to stratify men into unhealthy (0–2), moderate (3), and healthy (4–6) categories based on how many components are present. The six components are: healthy weight (BMI < 30); vigorous physical activity (≥3 h/week or ≥7 h/week brisk walking); not smoking (never smoked or quit ≥ 10 years ago); high consumption of tomatoes (≥7 servings/week); high consumption of fatty fish (≥1 serving/week); and reduced intake of processed meat (<3 servings/week). To investigate whether a healthy lifestyle may be able to attenuate prostate cancer risk in men with high genetic risk, Plym and colleagues applied the "healthy lifestyle score" and the 269-variant PRS developed by Haiman et al.[17] to an independent cohort of 12,441 men from The Health Professionals Follow-up Study and the Physicians' Health Study, who had genotyping data available. This cohort included 3005 prostate cancer events and 435 lethal prostate cancer events during a follow-up of 27 years. In this cohort, the 269-variant PRS was validated to stratify men for overall prostate cancer risk, but also enabled risk stratification for lethal prostate cancer. For example, men in the top quartile (75%–100%) of PRS scores had a hazard ratio (HR) of 5.65 for overall prostate cancer and 4.32 for lethal prostate cancer, compared with men in the bottom quartile (0%–25%) of PRS scores. No significant differences were observed in the risk of overall prostate cancer between men with healthy, moderate, and unhealthy lifestyles, in different PRS quartiles. However, among men in the top PRS quartile, adhering to a healthy or moderately healthy lifestyle was associated with a significantly reduced risk of lethal prostate cancer (HR = 0.55 and 0.61, respectively). However, healthy or moderately healthy lifestyle adherence did not impact the risk for lethal prostate cancer in those in lower genetic risk quartiles. In a case-only analysis following 2111 prostate cancer cases for lethal disease, similar results were found, in which a healthy or moderately healthy lifestyle was associated with a significantly reduced risk of lethal prostate cancer (HR = 0.51 and 0.60, respectively) among patients in the top 25% of PRS scores. In this cohort, 85% had T1–T2 disease, 82% were Gleason ≤ 7, 41% underwent radical prostatectomy, and 36% underwent radiation therapy at diagnosis. Among the individual components of the healthy lifestyle score, BMI, high physical activity, and not smoking appeared to be the strongest contributors to the modification of risk for lethal prostate cancer. Importantly, a healthy lifestyle was associated with a 24%–46% reduced risk of non-prostate cancer death across all PRS quartiles. Together, these data validate the 269-variant PRS score for stratifying risk for prostate cancer and demonstrate that a healthy lifestyle may significantly reduce the risk of lethal prostate cancer among men at the highest genetic risk. Additional studies are needed to validate these findings. Ongoing studies are evaluating the impact of other lifestyle factors, validating these findings in other populations, and evaluating the interaction with rare germline genetic prostate cancer risk variants.

6 | NEXT-GENERATION PRECISION MEDICINE

Genomics and other molecular studies have demonstrated that prostate and other cancers can be stratified into various molecular subtypes that may share clinical features and may benefit from similar treatment strategies, including precision medicine and targeted therapies.

Felix Feng (University of California, San Francisco) discussed multi-omic studies on metastatic castration-resistant prostate cancer (mCRPC) by the PCF-SU2C West Coast Prostate Cancer Dream Team. Since 2012, this multi-institutional team has collected metastatic tissue biopsies and liquid biopsies from over 400 patients with mCRPC. Studies done on these samples include whole-genome sequencing,[27] whole-genome bisulfite sequencing,[28] transcriptome sequencing,[29–32] 5hmc sequencing (Sjöström et al., in progress), ATAC sequencing (Shrestha et al., in progress), circulating tumor DNA analysis[33] (Herberts et al., in progress) and autoantibody analysis.[34] Whole-genome sequencing studies were performed on 100 mCRPC samples to define the landscape of structural variants in mCRPC. This study identified a site 624 kb upstream of AR which was amplified in ~80% of mCRPC cases. These amplifications were found to be driven

by tandem duplication events. The site was identified as a novel AR enhancer, as it corresponded with a ChipSeq peak for H3K27ac and was associated with significantly higher AR expression levels. Whole-genome bisulfite sequencing to identify sites of repressive 5-methyl-Cytosine (5mC) marks was performed on the 100 mCRPC cases. This study found lower 5mC levels on the *AR* gene and *AR* enhancer were common in mCRPC and identified several foci of recurrent hypomethylation upstream of *AR* as additional *AR* enhancers. A whole-genome 5hmC sequencing study found that *AR* and *AR* response genes are preferentially marked by 5hmC in mCRPC. Together, these studies demonstrate that altered AR activation through genomic and epigenomic alterations is the most common driver of mCRPC. LNCaP cells carrying an endogenous chimeric neon-green AR reporter developed by CRISPR knock-in to the *AR* locus were used in a genome-wide CRISPRi screen to identify regulators of AR expression. Top hits included known AR regulators (*AR*, *HOXB13*, *GATA2*, and *GRHL2*) and *PTGES3*, which was not previously identified as an AR regulator. Knockdown of *PTGES3* inhibited proliferation of AR-positive prostate cancer cell lines and growth of an AR-positive xenograft but had no effect on growth in AR-negative prostate cancer cell lines. *PTGES3* knockdown reduced chromatin accessibility at ~80% of AR binding sites. Together, these data suggest that PTGES3 may function as an AR co-regulator and may be a promising therapeutic target in AR-driven prostate cancer. Using small molecule screens, Feng and colleagues have identified several PTGES3-targeting lead compounds. Further development of these compounds is underway. In addition, studies are ongoing to integrate clinical genomic and epigenomic sequencing data with functional genome-wide screens, to identify novel key drivers and mediators of treatment response/resistance in mCRPC.

Joel Greshock (Janssen Oncology) discussed the development of genomics and histopathology biomarkers to predict therapeutic responses in patients with prostate cancer. SPARTAN was a pivotal Phase 3 trial that randomized patients with nonmetastatic CRPC (2:1) to receive ongoing ADT + apalutamide versus ADT + placebo. The trial found that the addition of apalutamide to ADT significantly improved metastasis-free survival (MFS), time to symptomatic progression, time to second progression (PFS2), and overall survival (OS), compared to placebo + ADT,[35] and led to FDA approval of apalutamide in this setting. Greshock and colleagues performed a retrospective biomarker analysis using samples from 233 patients enrolled in SPARTAN (154 who received apalutamide + ADT vs. 79 who received placebo + ADT) to determine whether the PAM50 gene expression panel (determined using Decipher gene expression microarrays) could differentiate patients who would versus would not benefit from the addition of apalutamide to ADT. PAM50, developed for breast cancer to subgroup patients into Luminal A, Luminal B, and Basal subgroups, has been previously adapted for prostate cancer.[36] Compared with samples from the Decipher GRID database, SPARTAN samples were highly enriched for basal tumors (152 basal; 70 luminal B; 11 luminal A), which was expected since SPARTAN patients were required to be castrate-resistant. Apalutamide + ADT was associated with a significantly longer MFS compared with placebo + ADT in both basal and luminal subtypes. However, within the apalutamide + ADT arm, significantly longer MFS was seen for patients with luminal subtypes versus those with basal subtypes. Similar trends were seen for OS and progression-free survival.

Greshock also presented studies and highlighted the future potential of developing AI-based classifiers for diagnosing and prognosing prostate cancer from histopathology slides. An AI algorithm trained on over 1000 whole-slide prostate images from a manually curated public data set (Kaggle PANDA) to detect prostate cancer achieved an AUC of 0.905. The algorithm also identified specific areas on the slides that drove cell classifications. A machine learning AI-based algorithm was also developed that was able to predict Gleason score, which strongly correlated with pathologist-determined ISUP scores (Pearson r = ~0.75). AI algorithms that are able to incorporate genomic, transcriptomic, and other features along with pathology are under development for predicting clinically relevant features of prostate cancer, including how patients may respond to particular therapies. Challenges for AI and machine learning-based "digital assays" include the possible need for a lot of high-quality data, the ability to recognize futility, gaining regulatory engagement and guidance, and avoiding uninterpretable models, which can lead to mistrust and underuse.

Rebecca Fitzgerald (University of Cambridge, UK) discussed omics studies in esophageal adenocarcinoma that may serve as lessons for the prostate cancer research community. Esophageal adenocarcinoma typically occurs in the lower esophagus, often in the background of Barrett's esophagus. Early detection and intervention are possible and result in excellent long-term outcomes and less treatment-associated side effects, while 5-year survival rates are ~20% in patients who are diagnosed after cancer symptoms have developed. As part of the ICGC, the UK Oesophageal Cancer Clinical and Molecular Stratification (OCCAMS) consortium has recruited over 3000 patients with esophageal adenocarcinoma and performed whole-genome sequencing on over 600 esophageal cancer samples thus far, and where possible matched these with RNA-seq and methylation profiling. An initial analysis of 129 tumors determined the genomic landscape of esophageal adenocarcinoma. A large number of low prevalence driver mutations were identified, demonstrating significant disease heterogeneity. These findings were confirmed and expanded upon in a follow-up study on 551 esophageal adenocarcinomas, which included samples from TCGA. Integrated analyses of whole-genome and RNA sequencing combined with improved bioinformatic analysis methods in this study enabled the determination of mutation recurrence frequencies, mutational clustering, copy number alterations, extrachromosomal amplifications, passenger mutations, and the functional impact of alterations. Aside from confirming known driver gene mutations, including *TP53* which was by far the most prevalent, being altered in ~70% of esophageal adenocarcinomas, this study identified 76 additional driver genes, 69% of which were known drivers in pan-cancer analyses and 86% of which were not previously reported in esophageal cancer. The incorporation of clinical outcomes data enabled the identification of mutations with prognostic significance.

For example, *GATA4* amplification and *SMAD4* mutation or deletion were associated with significantly shorter overall survival times. To characterize the genomic evolution from Barret's esophagus to esophageal adenocarcinoma, the genomics of pre-cancerous Barrett's esophagus samples were compared between patients who never progressed to dysplasia, who developed high-grade dysplasia with Barrett's esophagus, and who eventually progressed to esophageal adenocarcinoma. Mutations in cancer driver genes were identified even in non-dysplastic Barrett's that never progressed to cancer. Alterations in DNA copy number and *TP53* were found to be the most specific in identifying Barrett's esophagus cases that would be likely to progress, suggesting that *TP53* alterations are likely an early, initiating event in the development of esophageal adenocarcinoma and may be a useful biomarker for identifying at-risk individuals requiring early intervention. Another study sequenced samples from multiple metastatic sites and over time in the same patients to develop spatial maps of tumor evolution. Results from this study suggest that metastatic sites are seeded by multiple tumor subclones, as opposed to a step-wise fashion in which only one metastatic site seeds another. ctDNA tests are being developed to detect minimal residual disease posttreatment and for these analyses, elimination of signals from clonal hematopoiesis of indeterminate potential (CHIP) results in greatly increased accuracy. As we develop an improved understanding of esophageal adenocarcinoma biology, new precision medicine treatment strategies will follow, and the lessons learned may help to drive advances in other cancer types. Some of the data presented have been published.[37–39]

7 | MEASURING AND TARGETING LINEAGE PLASTICITY TO PREVENT LETHAL PROSTATE CANCER

The androgen receptor (AR) is the primary driver of prostate cancer growth and survival, and systemic therapy targeting the AR axis is the backbone of treatment for patients with aggressive or advanced disease. Unfortunately, in patients receiving these treatments, the development of AR therapy resistance and progression to CRPC is nearly inevitable. While alterations that reactivate the AR pathway are the driver of progression to CRPC in the majority of cases (~60%–80%), several other mechanisms can drive AR independence and castration resistance. Lineage plasticity enables a stem-like state which can be followed by trans-differentiation to neuroendocrine (NE) prostate cancer (NEPC) or $AR^{-}NE^{-}$ lineages, and has been observed in up to ~27% of mCRPC cases, a dramatic increase over the ~11% rate seen in the era before second-generation AR-targeted therapy became standard of care. Known drivers of lineage plasticity include combined loss of *TP53* and *RB1*, which is observed in ~10% of CRPC cases, as well as alterations in PTEN/p53, N-MYC, AURKA, BRN2, PEG10, Sox11, and SMARCA4 pathways. Several presentations focused on identifying mechanisms and treatment strategies for lineage plastic and NE prostate cancer.

Eliezer Van Allen (Dana-Farber Cancer Institute) discussed single-cell sequencing studies in metastatic biopsies taken before and after treatment with enzalutamide, to investigate tumor and immune programs in patients with CRPC and NEPC. In these studies, single-cell suspensions from metastatic biopsies from 14 patients were separated into $CD45^{-}EPCAM^{+}$, $CD45^{+}EPCAM^{-}$, and $CD45^{-}EPCAM^{-}$ populations by FACS, followed by full-length single-cell RNA-seq. As an example of a finding from this study, TGF-beta was identified as a top transcriptional program upregulated in tumor cells after exposure to enzalutamide. No recurrent somatic mutations were discovered to explain this, although convergence in this process was observed across patients. The upregulation of TGF-beta pathways post-enzalutamide was validated by immunohistochemistry (IHC) in pre- and post-enzalutamide clinical specimens and in mouse models. Single-cell analysis of a single biopsy from a patient with small cell NEPC found upregulation of previously developed NEPC signatures and downregulation of AR signatures compared with adenocarcinoma samples. Gene expression analysis of the NEPC sample identified upregulation of known NEPC regulons SOX2 and EZH2, as well as novel lineage plasticity-promoting regulons including HOX5, HOX6, and NR1D2. NR1D2 is a circadian rhythm gene that is targetable by existing agents. Downregulated regulons included ERG, EV1, EHF, and HOXB13. Upregulation of HOX5, HOX6, and NR1D2 genes in NEPC was validated in a clinical NEPC gene expression data set published by Beltran and colleagues, as well as by IHC in a panel of patient-derived NEPC organoids. These data demonstrate that single-cell studies from a single patient biopsy can identify novel and potentially targetable regulons that are commonly upregulated in NEPC. Single-cell analyses of matched pre- and post-enzalutamide biopsies were used to investigate the impact of enzalutamide on immune microenvironmental programs. A subset of patients was found to exhibit T-cell clonal expansion after enzalutamide. Whether this phenomenon may be a biomarker for identifying patients likely to benefit from checkpoint immunotherapy deserves further study. Some of these data have been published.[40] Ongoing studies are collecting matched pre-, on-, and post-treatment tumor and liquid biopsies, and performing single-cell whole-genome, whole-exome, and single-cell RNA sequencing studies, to better understand the spatial and temporal dynamics of the TME. In addition, the Metastatic Prostate Cancer Project (mpcproject.org), an initiative in which patients can self-enroll and contribute their data and archival or fresh tumor and blood samples, offer an opportunity to study a broader and more representative patient population.

Andrew Armstrong (Duke University) discussed the use of liquid biopsies to inform treatment and measure lineage plasticity and heterogeneity in patients with mCRPC. The multicenter PROPHECY trial had the primary aim of prospectively evaluating the expression of AR-V7 in CTCs as a biomarker for treatment responses in patients with CRPC. The trial enrolled 120 patients with taxane-naïve progressive mCRPC who were candidates for abiraterone or enzalutamide, and collected liquid and tumor biopsies at enrollment, at the time of progression on abiraterone or enzalutamide, and at the time of progression in a subset of patients who received subsequent

taxane therapy. Assays performed on liquid biopsy samples included ARV-7 CTC assays (Adna mRNA test and Epic nuclear protein test), CTC whole-exome sequencing (WES), comparative genomic hybridization (CGH), RNA-Seq, and ctDNA sequencing. Updated results from PROPHECY were presented.[41–43] Compared with patients with AR-V7-positive CTCs, patients with AR-V7-negative CTCs on AR-targeted therapy had significantly prolonged progression-free survival (median of 3.7 vs. 7.2 months, respectively, for Adnatest; median of 3.7 vs. 6.0 months, respectively, for Epic test) and overall survival (median of 11.1 vs. 24.8 months, respectively, for Adnatest; median of 8.4 vs. 20.5 months, respectively, for Epic test). In contrast, similar outcomes were seen with taxane chemotherapy for AR-V7-positive versus AR-V7-negative groups; progression-free survival (median of 4.0 vs. 6.1 months, respectively, for Adnatest; median of 4.5 vs. 5.3 months, respectively, for Epic test) and overall survival (median of 8.2 vs. 12.6 months, respectively, for Adnatest; median of 6.8 vs. 11.1 months, respectively, for Epic test). These data suggest that patients with AR-V7-positive CTCs have a low chance of benefitting from hormonal therapies and would likely have greater benefit with chemotherapy or a clinical trial. In many patients, AR-V7 heterogeneity was observed, with both AR-V7-positive and AR-V7-negative CTCs detected. Poor outcomes with AR-targeted therapy were observed in a subset of patients with only AR-V7-negative CTCs, suggesting the need to identify new biomarkers for guiding treatment selection in AR-negative mCRPC. A comparative analysis of genomic alterations in matched CTCs versus ctDNA from 140 patients in PROPHECY found that CTCs were often better indicators of the presence of oncogenic driver alterations including *MYC-N* amplification, *RB*-loss, and *PTEN*-loss. Among AR-V7-negative patients, *MYC-N*-amplification and *PTEN*-loss in CTCs were strongly associated with shorter progression-free survival, versus *MYC-N*-WT and *PTEN*-WT CTCs, respectively. To identify novel biomarkers of treatment response in AR-V7-negative patients, genomic alterations in CTCs were compared between AR-V7-negative patients who responded versus did not respond to treatment with abiraterone or enzalutamide. CTC genomic alterations that were commonly associated with poor clinical outcomes in patients with AR-V7-negative mCRPC treated with abiraterone or enzalutamide, included *TP53*, *PTEN*, *BRD4*, *WNT*, DNA repair, epigenetic, AR signaling, and lineage plasticity pathways (*CHD1* loss). In ongoing studies, CTC assays that can evaluate both phenotype and genotype are being developed as predictive biomarkers. Using the Epic platform, a CTC neuroendocrine (NE) phenotype was developed, which includes high nuclear:cytoplasmic ratio and a small, circular morphology, independent of AR expression. The CTC-NE phenotype was strongly predictive of poorer overall survival among patients in PROPHECY and in an MSKCC cohort. These data suggest that CTC-NE phenotyping may help to identify AR-V7-negative patients likely to have poor responses to AR-targeted therapy and who should be considered for alternative approaches. A ctDNA genomic-methylation test that can identify patients with NEPC has been developed by Beltran and colleagues. This test evaluates genomic alterations including in *AR*, *RB1*, *TP53*, and *CYLD*, and hyper-and hypo-methylation alterations on 20 genomic sites, including in *SPDEF*, *ASXL3*, and *N-cadherin*. These studies demonstrate that CTCs and ctDNA biomarkers can help to guide treatment selection in some patients with mCRPC; however, additional studies are needed to better identify and determine optimal therapies for patients with more aggressive and heterogenous lineage-plastic subsets of prostate cancer.

Ping Mu (UT Southwestern Medical Center at Dallas) discussed the role of CHD1 in prostate cancer lineage plasticity and tumor heterogeneity. To identify gene-deletions that confer resistance to AR-targeted therapy, an shRNA library consisting of 4324 hairpins targeting 730 most frequently deleted genes in human prostate cancer was developed. The library was retrovirally transduced into LNCaP cells that were injected into immunocompromised mice. Mice were treated with enzalutamide, and the resistant tumor clones were obtained and subjected to deep sequencing. One of the top candidate genes identified in this screen was the ATP-dependent chromatin remodeler *CHD1* (Chromodomain Helicase DNA Binding Protein 1). *CHD1* is deleted in ~8%–10% of prostate cancer and has a context-specific role. A study in 56 patients treated with abiraterone or enzalutamide from the PCF-SU2C mCRPC cohort found an association between CHD1 expression levels and time on treatment, suggesting patients with low CHD1 levels developed resistance significantly faster than patients with high CHD1 levels. Knockdown of *CHD1* by shRNA or CRISPR in prostate cancer cell lines conferred resistance to enzalutamide in vitro and in xenograft models, which could be reversed by the reintroduction of *CHD1* cDNA. *CHD1* knockdown alone in LNCaP xenografts did not lead to more aggressive growth in vehicle-treated mice. Expression of canonical AR-regulated genes such as KLK3, NKX3.1, TMPRSS2, and NDGR1 remained repressed by enzalutamide in *CHD1*-knockdown cells, suggesting that the mechanism of enzalutamide resistance conferred by *CHD1*-loss is not via restoration of AR activity. To identify transcription factors that may be driving enzalutamide resistance in *CHD1*-null cells, combined analysis of RNA-seq and ATAC-seq were used. Twenty-two candidate transcription factors were identified, four of which were confirmed in a CRISPR-based functional library screen in *CHD1*-null cells: GR, BRN2, TBX2, and NR2F1. Interestingly, evaluation of enzalutamide-resistant subclones derived from *CHD1*-null cell lines found marked heterogeneity in the expression of GR, BRN2, TBX2, and NR2F1. With an increased time of enzalutamide treatment, different subclonal lines appeared to commit to the expression of only one of the factors. This suggests that *CHD1*-loss induces a state of epigenetic plasticity, in which cells driven by different enzalutamide-resistance mechanisms compete until one dominant clone remains. An RNA-seq analysis in 212 metastatic prostate cancer cases found similar results; patient tumors could be stratified into 5 distinct groups: CHD1-high tumors, and 4 CHD1-low subtypes, each with high expression of either GR, BRN2, TBX2, or NR2F1. Evaluation of gene expression in 10 *CHD1*-loss subclones expressing different resistance drivers found that all exhibited downregulation of luminal gene signatures and upregulation of EMT signatures. Using doxycycline-inducible sh-CHD1 cell lines, it

was found that lineage plasticity and EMT genes were rapidly induced following the loss of CHD1, and expression was reversible following re-expression of CHD1. These data suggest epigenetic control of lineage plasticity. Finally, the growth of enzalutamide-resistant *CHD1*-null xenografts was slowed by the treatment of mice with the BET inhibitor CPI. While enzalutamide alone had little effect, synergy was observed with the combination of CPI and enzalutamide in this model.[44] Together, these data demonstrate how CHD1 functions as a key gatekeeper of epigenetic plasticity in prostate cancer, and how the loss of CHD1 leads to resistance to AR-targeted therapy by enabling upregulation of various lineage plasticity programs.

Amina Zoubeidi (Vancouver Prostate Centre) discussed studies on the identification of drivers of NEPC, the role of AR in NEPC, and the preclinical development of a BRN2-inhibitor. As discussed above, the expression of AR can sometimes persist during the evolution to NEPC. Zoubeidi and team performed an AR cistrome analysis of CRPC and treatment-induced NEPC cells, which found that AR bound to a slightly overlapping but larger number of sites in NEPC versus CRPC. CRPC-unique sites included hallmark estrogen response genes, IL2-STAT5 signaling, and Notch signaling pathways. Shared sites included hallmark AR-response and UV response pathways. NEPC-unique sites included neuronal, developmental, and epithelial–mesenchymal transition pathways, suggesting a role for AR in promoting a "lineage infidelity" phenotype in the NEPC setting. In NEPC, AR binding was proximal to stem cell and neuronal transcription factor motifs. Combined analysis of AR ChIP-seq and ATAC-seq data from CRPC versus NEPC found that hyper-accessible regions were concordant with the reprogrammed AR cistrome. Genes that were epigenetically open and bound by AR in NEPC included GATA, FOXA, LHX1, NeuroD1, Pct4, and ASCL1. Analysis of samples from the DARANA trial, which tested a 3-month course of neoadjuvant enzalutamide, followed by prostatectomy, found that AR drove expression of an expanded gene set including neuronal genes after enzalutamide, suggesting a shift toward support of lineage plasticity. A treatment-induced NEPC model was used to study epigenetic changes during the transition from adenocarcinoma-CRPC to NEPC. In this study, CRPC cells were treated with enzalutamide, and ATAC-seq and RNAseq were performed at times 0, 3, and 10 days after the start of enzalutamide, and in a treatment-induced NEPC model. Before enzalutamide treatment, ~2700 open DNA regions were observed as ATAC-seq peaks, which increased to ~26,000 regions after 10 days of enzalutamide. Before treatment, there were few ATAC-seq binding sites in promoters; however, enzalutamide promoted a strong bias toward ATAC-seq peaks forming in promoters. Integration of ATAC-seq and RNA-seq data demonstrated that enzalutamide redirected chromatin accessibility from a canonical AR-driven transcriptional program to stem cell plasticity and neuronal programs. For example, PSA was highly expressed in adenocarcinoma-CRPC cells but repressed in NEPC cells, while WNT5A and BRN2 were low in CRPC and highly expressed in NEPC. BRN2 (POU3F2) is a master transcription factor that controls neuronal differentiation during development, is sufficient to drive neuronal differentiation in embryonic stem cells and fibroblasts, and is highly expressed in neuroendocrine/small cell lung cancer. High expression of BRN2 was confirmed in clinical NEPC gene expression data sets,[32,45] and at the protein level by IHC. BRN2 ChIP-seq performed in treatment-induced NEPC and de novo NEPC cell lines found that BRN2 bound to enhancers in closed chromatin regions and to promoters in open chromatin regions, suggesting it acts as a pioneer factor. Overexpression of BRN2 in CRPC cells induced neuronal gene expression and phenotypic neuronal differentiation. BRN2 knockdown by siRNA in NEPC cells reduced proliferation in vitro and reduced tumor growth and expression of neuroendocrine genes in mouse tumor models. Zoubeidi and colleagues solved the 3D structure of the BRN2 DNA binding domain and used this to screen for small molecule BRN2 inhibitors. A candidate BRN2 inhibitor (BRN2i) was identified which could strongly bind BRN2, and prevented its function, as measured by BRN2 reporter assays, expression of NEPC target genes, and DNA-binding assays. Treatment with BRN2i reduced the growth of NEPC cells but not adenocarcinoma-CRPC cells. Concordant gene expression was seen between cells in which BRN2 was knocked down by CRISPR and cells treated with BRN2i, demonstrating the specificity of BRN2i for BRN2. Furthermore, treatment with BRN2i significantly slowed the growth of both de novo and treatment-induced NEPC tumors in mice, and significantly decreased the expression of proliferation markers (Ki67), and NEPC genes (BRN2, SOX2, ASCL1, and PEG10). Together, these studies demonstrate that AR-pathway inhibition potentiates NEPC trans-differentiation by promoting changes in the chromatin landscape and an alternative AR-transcriptional program. BRN2 was identified as a driver and promising therapeutic target in NEPC. Some of these data have been published.[46–48] Further development of the the first-in field BRN2 inhibitor is underway.

8 | PCF WOMEN IN SCIENCE AWARD LECTURE: TUMOR SUPPRESSORS REIMAGINED: CONVERTING UNDERSTANDING OF RB ACTION INTO TRANSLATIONAL POTENTIAL

Karen Knudsen (American Cancer Society) was awarded the 2021 PCF Women in Science Award and Lecture, in recognition of her many impactful scientific achievements and her exemplary leadership, mentorship, and advocacy for advancing the professional growth of women in cancer research and medicine. During her tenure at Thomas Jefferson University and Sidney Kimmel Cancer Center at Jefferson Health (SKCC), Knudsen became one of only a very few women Directors of an NCI-designated cancer center, as Executive Vice President of Oncology Services and Enterprise Director. Under her leadership, SKCC expanded its care region, became ranked as one of the top cancer centers in the nation by US

News & World Report, significantly increased the number of women faculty, and created one of the most diverse leadership teams. Knudsen also co-founded the PCF Women in Science Forum in 2016 and led the development of the Forum and its agenda over the years. This Forum has created a strong and supportive network and pipeline of women in the cancer research field, including programs for high school students from underrepresented minority backgrounds with an interest in STEM. In 2021, Knudsen became the Chief Executive Officer of the American Cancer Society and the ACS Cancer Action Network, where she continues to break glass ceilings for women in science.

Knudsen's research in steroid hormone pharmacology, cell cycle, DNA repair, and targeted therapies has ultimately led to new oncology treatments for patients. Her early work demonstrating PARP as a driver and possible therapeutic target in CRPC set the stage for the clinical development of PARP inhibitors, of which two were FDA-approved for patients with mCRPC with certain DNA repair gene alterations in 2020. Knudsen's research has elucidated the oncogenic roles of many molecular pathways, including PARP1, DNA-PKcs, P300/CBP, CRY1, and RB1. For her PCF Women in Science Award lecture, Knudsen discussed prostate cancer incidence and disparities in the SKCC catchment area, and studies on the role of RB1 in prostate cancer.

SKCC is located in Philadelphia, Pennsylvania. Approximately 80% of SKCC patients live in a densely populated seven-county area that suffers from significant health and racial disparities. The prostate cancer incidence rate in the overall SKCC catchment area is 130.1 per 100,000, which is significantly higher than the Philadelphia State (103.7 per 100,000) and US (104.5 per 100,000) averages. The prostate cancer mortality rate in the SKCC catchment area is 21.9 per 100,000, also significantly higher than the Philadelphia State (18.6 per 100,000) and US (19.0 per 100,000) averages. Racial health disparities in the SKCC region are significant. Higher rates of cancer mortality are seen for Blacks compared with Whites for many cancer types, prostate cancer being the most disparate. An over twofold higher prostate cancer mortality rate is seen for Black men compared to White men in the SKCC region.

Loss of the RB1 tumor suppressor commonly occurs in various cancers including prostate. *RB1* is intact in most primary prostate cases, but is increasingly lost during progression, and observed in ~30% of mCRPC cases. *RB1*-loss is associated with poor outcomes, including earlier disease recurrence and reduced overall survival. Gene expression data from 951 cancer cell lines with known *RB1* genomic status were used to develop an *RB1*-loss gene expression signature consisting of 186 genes; this signature was able to identify tumors with intact versus lost *RB1*. Loss of RB pathway function most commonly occurs due to *RB1* gene deletion, but can also be caused by rare deletions in genes including *RBL1*, *RBL2*, *E2F1*, *CDK2*, *CDK4*, *CCND1*, and *CDKN2A*. However, even in prostate cancer cells with monoallelic *RB1* loss, RB protein expression can be lost. Comprehensive identification of prostate cancer cases with an RB1 loss phenotype will require assays beyond genomics or protein expression alone.

In mCRPC, two downstream effects of RB1-loss are upregulation of AR and the E2F1 transcription factor. This suggests a tumor-suppressive role of RB1 is to constrain the transcriptional activity of E2F1 and AR. The genome-wide impact of RB1 loss on AR and E2F1 was investigated using ChIP-Seq in isogenic *RB1*-intact and *RB1*-loss hormone-sensitive prostate cancer (HSPC) cell lines. An expansion of E2F binding in the genome was observed when *RB1* was lost, which was enriched for enhancers including AR. A gene expression signature based on these RB/E2F1-regulated genes was able to identify tumors with RB1-loss from the PCF-SU2C Dream Team data set. These data suggest that altered E2F1 activity is associated with poor outcomes in RB1-loss mCRPC.

Whether RB1-loss would be advantageous in tumors that had already achieved CRPC was investigated by generating isogenic *RB1*-WT and *RB1*-loss CRPC lines. In the CRPC setting, loss of RB1 also led to aberrant expanded E2F1 binding, summing ~1600 genes. These sites were distinct from those caused by RB1-loss in the HSPC setting and enriched with sites co-bound by AR. A major AR/E2F1 coregulated target was TNF-AIP8, a negative regulator of caspase activation downstream from TNF-α signaling. Correspondingly, *RB1*-loss CRPC cells exhibited a reduced apoptotic response following treatment with platinum chemotherapy or TNF-α. This suggests that if RB1 is lost in CRPC, E2F1 and AR can cooperate to activate a new pattern of gene expression and increase resistance to apoptosis.

The enhanced E2F1 function caused by RB1-loss in CRPC also led to altered metabolism gene expression. Whole-scale metabolomics profiling identified seven altered metabolic pathways associated with RB1/E2F1 alterations in CRPC, including five amino acid metabolism pathways and two lipid metabolism pathways. For instance, glutathione synthesis was upregulated, a feature which was also observed in breast, non-small cell lung, and bladder cancers with RB1-loss. Increased glutathione synthesis led to decreased intracellular ROS production, resulting in increased resistance to cytotoxic agents such as doxorubicin. In a clinical CRPC cohort, a correlation was observed between levels of E2F1 and glutathione synthesis enzymes in RB1-loss tumors, while no relationship was seen in RB1-intact tumors. These data suggest that targeting glutathione synthesis may be a treatment strategy in tumors with RB1-loss. CRPC cells with RB1-loss had enhanced sensitivity to treatment with Erastin, which blocks early events required for glutathione production but not to BSO, which blocks later steps in glutathione production. Together these data demonstrate that the expanded E2F1 cistrome that occurs as a result of RB1-loss in CRPC can drive metabolomic alterations and chemotherapy resistance. Some of these data have been published.[49]

Clinical trials based on RB1 status are underway. ABICABAZI is a Phase 2 trial testing abiraterone alone versus with cabazitaxel in RB-low CRPC. RIBOX is a Phase 2 trial testing enzalutamide alone versus with the CDK4/6-inhibitor ribociclib in RB-intact CRPC. These studies will help to elucidate whether RB status is an actionable treatment selection biomarker in patients with advanced prostate cancer.

9 | NUCLEAR RECEPTOR BIOLOGY IN CRPC

The nuclear receptor family includes AR, estrogen receptor (ER), glucocorticoid receptor (GR), progesterone receptor (PR), and mineralocorticoid receptor (MR)—all are hormone receptors with distinct but related and overlapping functions. There is cross-talk between different nuclear receptor pathways, as they can regulate each other's activity through gene expression and posttranslational modification. For instance, AR can repress the expression of GR, while AR inhibition results in increased GR expression. Upregulation of GR expression and activity is observed in patients with mCRPC, where it appears to drive resistance to AR-targeted therapy, likely due to GR's ability to reactivate some AR-mediated gene expression. This session focused on nuclear receptor biology, including the role of GR in CRPC and its potential as a therapeutic target, and the impact of AR agonism in prostate cancer and ER-positive breast cancer.

Nima Sharifi (Cleveland Clinic) discussed the mechanisms and role of GR activation in CRPC. GR is activated by cortisol (or corticosterone in mice). Under normal conditions, cortisol is continually converted by 11β-HSD2 to cortisone (11-dehydrocorticosterone in mice), an inactive form that is unable to bind GR. This process prevents the hyperactivation of GR. The opposing process, conversion of cortisone to cortisol, is performed by 11β-HSD1. 11β-HSD1 activity requires NADPH, which is produced from NADP by the enzyme hexose-6-phosphate dehydrogenase (H6PD). Sharifi and colleagues found that continual conversion of cortisol to cortisone occurs in prostate cancer cells; however, this process was impeded by treatment with enzalutamide, resulting in high levels of cortisol. Enzalutamide treatment was found to greatly reduce levels of 11β-HSD2 in several human prostate cancer cell lines. Overexpression of 11β-HSD2 alone did not affect the growth of prostate tumor xenografts in mice; however, 11β-HSD2 overexpression greatly increased sensitivity to enzalutamide, resulting in significantly slower tumor growth and prolonged survival of mice. These data suggest that 11β-HSD2 reinstatement restores enzalutamide sensitivity. The impact of targeting H6PD as a way to inhibit 11β-HSD1 and increase 11β-HSD2 activity was investigated. Genetic silencing of H6PD in prostate cancer cells resulted in the restored conversion of cortisol to cortisone in vitro and restored sensitivity to enzalutamide in xenograft models. Generation of NADPH by H6PD in prostate cancer cells was blocked by treatment with the PARP-inhibitor rucaparib, while olaparib had no effect. Rucaparib but not olaparib synergized with enzalutamide in blocking prostate tumor growth and prolonging survival in xenograft models. Together, these data suggest that in treatment-naïve prostate cancer, the conversion between cortisol and cortisone are balanced, limiting the activity of GR. However, enzalutamide treatment downregulates 11β-HSD2, resulting in increased levels of cortisol and GR activation. Targeting H6PD in this setting may increase sensitivity to enzalutamide. While abiraterone has a different mechanism of action than enzalutamide, expression of GR and increased levels of cortisol were observed in ~30% of abiraterone-resistant prostate cancer cases, suggesting that upregulation of cortisol and GR may also play a role in resistance to abiraterone. Further studies into the role and mechanisms of GR activation in CRPC, and the therapeutic potential for H6PD inhibition, including by rucaparib, are underway. Some of these data have been published.[50,51]

Suzanne D. Conzen (UT Southwestern Medical Center) discussed preclinical and clinical studies on targeting the GR pathway in CRPC. Conzen and colleagues investigated the expression of GR in prostate cancer cell lines and found that some castrate-resistant cell lines expressed high GR at a steady state, while GR-low cells consistently upregulated GR expression after treatment with enzalutamide.[52] The team has examined a series of selective GR modulators (SGRMs) able to block GR activity in prostate cancer cells without broad toxicity, and are evaluating their therapeutic potential in GR-positive mCRPC. For example, the nonsteroidal SGRMs CORT-(108)297 and CORT-(118)335 have potent activity against GR without blocking PR. Treatment of mice with CORT-297 or CORT-335 delayed growth of tumor xenografts after castration and repressed GR-target genes, including cell proliferation genes.[53] This suggests that GR signaling contributes to castration resistance, and that GR inhibitors can delay progression to CRPC. Clinical trials have been initiated to test SGRMs with AR-targeted therapy in patients with CRPC. CORT-125134 (relacorilant) is currently being tested in combination with enzalutamide in patients with enzalutamide-resistant CRPC. The Phase 1 portion, which evaluated the safety and identified an optimal Phase 2 dose for the combination, has been completed. An expansion phase that will also evaluate GR activity using geospatial profiling of patient biopsies is ongoing. In another trial, CORT-125281 (exacorilant) is being tested in combination with enzalutamide in patients with CRPC resistant to abiraterone or AR-antagonists. A clinical trial testing the steroidal GR-inhibitor mifepristone + enzalutamide in patients with enzalutamide-resistant CRPC has been completed. However, mifepristone is limited by cross-reactivity with other nuclear receptors. ORIC-101 is a mifepristone-derivative with similar activity against GR but reduced activity against AR and other nuclear receptors. Further studies are needed to investigate tumor GR activity as a biomarker for identifying patients likely to benefit from treatment with GR inhibitors, to better understand the role and mechanisms of GR in prostate cancer, and to determine whether treatment with GR inhibitors may be more effective earlier in prostate cancer disease history. Therefore, a trial is being planned to test the addition of an SGRM to neoadjuvant intense AR-inhibition (ADT + enzalutamide) versus AR inhibition alone in patients with newly diagnosed high-risk prostate cancer, followed by prostatectomy.

Wayne Tilley (University of Adelaide) discussed the roles of AR in breast and prostate cancer. Approximately 80% of breast cancers are driven by estrogens and ER. AR expression has been observed in nearly all breast cancers and is independently prognostic. However, the role of AR and its potential as a therapeutic target in breast cancer remain controversial, in part because AR is antagonized in prostate cancer; hence both AR agonists and AR antagonists have been concurrently tested in trials of ER-positive breast cancer. Tilley and colleagues evaluated the impact of AR agonists (DHT and

enobosarm, a selective AR modulator) versus AR antagonists (enzalutamide) in various breast cancer patient-derived xenograft models, including metastatic ER-targeted therapy-resistant disease and ER-positive estrogen-independent disease. In these models, treatment with either DHT or enobosarm durably inhibited tumor growth, while enzalutamide had no effect. Mechanistic studies found that activated AR is able to displace the binding of ER to chromatin and sequester the ER coactivators p300 and SRC-3, thereby preventing activation of ER-regulated oncogenic cell cycle genes while simultaneously inducing expression of AR-regulated tumor suppressor genes. These data strongly support AR acting as a tumor suppressor in breast cancer (see Hickey et al.[54]). To investigate whether AR can be reprogrammed to act as a tumor suppressor in prostate cancer, Tilley and colleagues screened a library of ~3200 nuclear receptor ligand analogs and known receptor agonists to identify candidate compounds with the ability to prevent growth and alter the morphology of four androgen-dependent and castration-resistant prostate cancer cell lines. Ten candidate AR-modulating compounds were identified, including CB003 and methyl-testosterone (methyl-T). The most potent was CB003, which inhibited growth and altered morphology of three prostate cancer cell lines, including two lines resistant to the current standard of care therapies. Methyl-T potently suppressed the growth of the AR + LNCaP cells but did not affect the growth of the AR-independent PC3 and R1-D567 prostate cancer cell lines. AR ChIP-seq assays found that treatment of prostate cancer cells with Methyl-T resulted in AR binding to nearly all the same sites as DHT, plus a large number of additional sites that were associated with genes potently inhibited by Methyl-T. These data are being interrogated to understand the mechanism of growth inhibition by Methyl-T. The findings demonstrate that Methyl-T is a more potent activator of AR than DHT and suggests a role for potent AR agonists in the treatment of prostate cancer. These data warrant further study into the potential for selective AR modulators in the treatment of breast and prostate cancer. Some of these data have been published.[54]

10 | TUMOR METABOLISM AS A DRIVER AND TREATMENT TARGET IN PROSTATE CANCER

Massimo Loda (Weill Cornell Medicine) discussed studies on the biology and therapeutic potential of targeting prostate cancer metabolism. Alterations in cellular metabolism pathways are a hallmark of cancer, enabling rapid cell growth and survival in nutrient-poor environments. Unlike many other cancer types, primary prostate cancers often do not exhibit increased glucose utilization (aerobic glycolysis), and thus molecular imaging with ^{18}F-FDG PET is often negative. Instead, prostate cancers commonly exhibit an unusual Zn/aconitase metabolism resulting in the abundance of citrate, which fuels de novo lipogenesis and the Krebs cycle. FASN, the rate-limiting enzyme in fatty acid metabolism, is expressed at low levels in most normal tissues (except for liver and lactating mammary glands) but is overexpressed in prostate cancer. Loda and colleagues have found that FASN is regulated by AR, and is amplified/overexpressed in mCRPC. FASN germline polymorphisms were associated with the risk of lethal prostate cancer in patients with metabolic syndrome. FASN overexpression was shown to increase the proliferation and growth of immortalized prostate cells and promote progression to PIN with a long latency. In addition, genetic ablation of FASN in prostate-specific PTEN KO prostate cancer transgenic mouse models prevented the development of invasive disease. Together, these studies suggest that lipogenesis and FASN, in particular, may be a promising therapeutic target in advanced prostate cancer.

A key role of oncogenes is to alter tumor metabolism to support rapid and ongoing growth. MYC and AKT1 are two of the most common prostate cancer drivers. Metabolomic profiling studies in MYC versus AKT1-driven prostate cells, transgenic prostate cancer mouse models, and human prostate cancers found that MYC-driven tumors were predominantly fueled by lipogenesis, while AKT-driven tumors were mainly fueled by glycolysis. Studies in MYC-driven prostate cancer mouse models found that high-fat diets fuel prostate cancer progression by rewiring the metabolome and amplifying the MYC program. In this model, a high-fat diet led to a decrease in the production of S-Adenosyl methionine (SAM), resulting in histone hypomethylation, decreased H4K20me1 marks in MYC-driven gene promoters, increased recruitment and activity of PHF8 (a Jumonji histone demethylase and the only enzyme known to demethylate the H4K20me1 mark), and increased MYC-driven transcription. A study that examined health professionals with over 25 years of health outcomes and demographic data from the Physicians' Health Study and Health Professionals Study registries found that prostate cancer patients with increased saturated fat intake had significantly increased risks of prostate cancer metastasis and prostate cancer mortality.

An orally bioavailable small molecule inhibitor of FASN (IPI-9119) was co-developed with Infinity Pharmaceuticals. In LNCaP and 22Rv1 cells, IPI-9119 potently blocked growth, FASN expression, and FASN activity including ^{14}C-glucose incorporation into lipids. While IPI-9119-treated cells displayed downregulation of lipogenic metabolites and accumulation of metabolic precursors, there was increased expression of lipogenic genes including FASN, and increased uptake of environmental poly-unsaturated fatty acids (PUFAs), suggesting an attempt to compensate for FASN inhibition. Accumulation of PUFAs resulted in increased ROS sensitivity and ER stress, resulting in cell death. Treatment of prostate cancer cell lines, organoid cultures, and xenograft models with IPI-9119 reduced tumor cell growth, which was further potentiated by supplementation with DHA-ω-3 PUFAs. IPI-9119 treatment also downregulated the levels and transcriptional activity of AR and AR-V7. Treatment of prostate cancer cell lines with IPI-9119 plus enzalutamide or darolutamide had an additive antigrowth effect. RNAseq and metabolomics studies found that AR binding on lipid metabolism genes is enriched in prostate cancers from African American patients relative to European American patients, and this differential AR

binding drives upregulation of lipid metabolism gene expression, including FASN, in African American prostate cancer. These data suggest that FASN inhibition may have a stronger effect in patients of African ancestry. Together, these studies demonstrate the rationale for testing FASN-inhibitors in the treatment of prostate cancer and suggest dietary intervention and AR antagonists as potential combination strategies to achieve greater efficacy. Some of the data presented have been published.[55–57]

The FASN-inhibitor TVB-2640 has been tested in a Phase 1 clinical trial for astrocytomas, breast cancer, and colon cancer. A randomized trial testing TVB-2640 in combination with enzalutamide in patients with mCRPC is being planned. The trial will evaluate the safety and determine the recommended Phase 2 dose for the combination and will include correlative studies to evaluate the impact of FASN inhibition on tumor biology and metabolism.

11 | PSMA THERANOSTICS: THE NEW AGE OF PROSTATE CANCER IMAGING AND TREATMENT

PSMA (prostate-specific membrane antigen) is a protein present on the surface of most prostate cancer cells and a highly promising target for imaging and therapeutic purposes. PSMA theranostics have made significant headway recently, with PET imaging agents ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL, and the beta-emitting molecular radiotherapy (MRT) ^{177}Lu-PSMA-617 (LuPSMA), receiving FDA approval. A history of PSMA theranostics has recently been published.[58]

Michael Hofman (Peter MacCallum Cancer Centre; Prostate Cancer Theranostics and Imaging Centre of Excellence (ProSTIC)) reviewed some of the key clinical studies in the development of PSMA PET and LuPSMA.

The ProPSMA study,[59] led by Hofman, compared the performance of ^{68}Ga-PSMA-11 PET imaging vs. conventional imaging (CT + bone scans) in 302 patients with newly diagnosed prostate cancer. Compared with conventional imaging, ^{68}Ga-PSMA-11 PET achieved higher accuracy (65% vs. 92%), a higher likelihood to change treatment decisions (15% vs. 28%), and fewer uncertain results (23% vs. 7%). In 2020, ^{68}Ga-PSMA-11 became FDA-approved for use at UCLA and UCSF. This has since been followed by FDA approval of two commercial kits for generating the agent.

Two randomized trials, TheraP and VISION, have been completed that test LuPSMA in patients with mCRPC. Led by Hofman, the Phase 2 TheraP trial tested LuPSMA versus cabazitaxel in 200 patients with mCRPC.[60,61] Patients enrolled in the trial had progressive mCRPC, had previously received docetaxel, may have had novel antiandrogen therapy, and were screened by PSMA PET and FDG PET. Patients with PSMA-negative FDG-positive lesions were ineligible. Patients who received LuPSMA experienced significantly more PSA ≥ 50% responses (66% vs. 37%), objective responses (49% vs. 24%), and progression-free survival rates at 12 months (19% vs. 3%), with fewer grade 3–4 adverse events (33% vs. 53%), compared to patients who received cabazitaxel. Recently, data from TheraP after a median of 3 years of follow-up were presented, which found that OS analyzed by intention-to-treat and summarized by restricted mean survival time (RMST) was not significantly different between patients who received LuPSMA versus cabazitaxel (19.1 vs. 19.6 months, respectively).[62] Accordingly, LuPSMA had less toxicity with consequent improvement in quality of life of parameters compared to cabaxitaxel, a proven life-prolonging therapy.

The international randomized Phase 3 VISION trial tested LuPSMA + standard of care (SOC) versus SOC alone in patients with PSMA-positive mCRPC who had been previously treated with taxane chemotherapy (1–2 regimens) and 1 or more novel antiandrogens.[63] Protocol-permitted SOC was determined before randomization, but excluded chemotherapy, immunotherapy, radium-223, and investigational drugs. LuPSMA was delivered in 7.4 GBq (200 mCi) doses every 6 weeks for four cycles and could be increased to six cycles. Both co-primary endpoints, overall survival (OS) and radiographic progression-free survival (rPFS), were significantly longer among patients who revived LuPSMA + SOC vs. SOC alone (OS: median of 15.3 months vs. 11.3 months, HR = 0.62 (N = 831); rPFS: median 8.7 vs. 3.4 months, HR = 0.40 (N = 581)).

LuPSMA was demonstrated to be well tolerated. Notable adverse events observed in TheraP and VISION included dry mouth (mostly Grades 1–2, affecting 39%–60% of patients), nausea (mostly Grades 1–2, affecting 34%–40% of patients), and anemia and thrombocytopenia (mostly Grades 1–2 affecting 9%–19% of patients, with ~10% of patients experiencing Grades 3–4). In VISION, patients receiving LuPSMA + SOC also reported significantly prolonged maintenance of the quality of life (median 9.7 vs. 2.4 months in time to ≥10-point decrease in FACT-P total from baseline) and prolonged time to pain progression (median 14.3 vs. 2.9 months in time to the first occurrence of ≥30% or ≥2-point increase in BPI-SF pain intensity from baseline), compared with patients who received SOC alone. TheraP demonstrated that patients treated with LuPSMA experienced fewer side effects than patients treated with cabazitaxel, including diarrhea, fatigue, hair loss, urinary symptoms, dizziness, skin rash, pain in hands and feet, and insomnia. LuPSMA (Lutetium Lu 177 vipivotide tetraxetan; Pluvicto®) received FDA approval on March 23, 2022, for the treatment of patients with PSMA-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy.

Despite these highly promising results and ~4-month average improvement in OS in this advanced patient group, LuPSMA is not curative. Further advancements in PSMA theranostics are needed, including better biomarkers for identifying patients most likely to benefit, individualized dosing strategies, testing novel radioisotopes, and combination treatment strategies. For instance, whole-body dose delivery has been found to correlate with PSA response and tumor SUVmean of PSMA PET, suggesting that patients who received a dose below a certain threshold (<10 Gy) to tumors are unlikely to respond. In the TheraP study, an FDG volume ≥200 ml was associated with shorter OS, while PSMA SUVmean ≥ 10 was associated with longer OS and was a predictive biomarker for response (LuPSMA vs. cabazitaxel). In addition, ongoing clinical trials are testing the efficacy

of LuPSMA earlier in prostate cancer disease history, including in hormone-sensitive metastatic prostate cancer and as a neoadjuvant treatment in patients with localized disease.

Neil Bander (Weill Cornell Medical College) discussed insights and future predictions from 25 years of PSMA research, and the rationale for MRT using alpha-emitting PSMA-targeted antibodies as monotherapy and in combination with beta-emitting PSMA-targeted small molecules.

PSMA PET imaging is significantly more sensitive than conventional imaging (CT, MR, bone scan) for determining sites of prostate cancer metastases. Ongoing studies suggest PSMA PET may also have the potential for diagnosis of localized prostate cancer. PSMA levels strongly correlate with Gleason grade, thus PSMA PET may be prognostic for recurrence after localized therapy and risk for lethal prostate cancer. Other applications under investigation for PSMA PET in diagnostic settings include the selection of patients for biopsy, improving targeted biopsy, inferring Gleason score and risk, active surveillance monitoring, focal ablation and radiation therapy planning, and screening in high-risk individuals. Because of the predominance of bone lesions in prostate cancer, which are not measurable on conventional imaging, current radiographic response assessment is suboptimal in prostate cancer. Validation of PSMA PET as a treatment response biomarker could speed clinical trials and reduce the cost and duration of drug development. Optical imaging with PSMA is being tested in intraoperative surgical settings to visualize tumor margins and identify tumor-positive lymph nodes for resection.

As discussed above, the beta particle-emitting PSMA-targeted MRT agent LuPSMA was recently granted FDA approval. Another beta particle-emitting MRT agent, ^{177}Lu-PSMA I&T is currently being tested in the Phase 3 SPLASH trial. MRT with the alpha-emitting agent ^{225}Ac-PSMA-617 has also shown promise in non-trial settings, but has also caused cases of severe and intolerable xerostomia. Urea-based PSMA small molecule imaging studies have demonstrated uptake in lacrimal and salivary glands, and spleen, liver, kidneys, small bowel, and bladder, due to urinary excretion. PSMA-targeted antibodies (such as J591) exhibit different pharmacokinetics and bio-distribution compared with small molecules, with molecular imaging finding no uptake in lacrimal or salivary glands, longer vascular persistence, and excretion via the liver and GI tract. This suggests that xerostomia may not occur with alpha-emitting MRT using PSMA-targeted antibodies.

Bander, Tagawa, and colleagues recently completed a Phase 1 trial testing a single dose of ^{225}Ac-J591, at 7 ascending doses, in 32 patients unselected by PSMA PET. ^{225}Ac-J591 was well-tolerated, and no maximum tolerated dose was identified. Twelve patients exhibited Grade 1 xerostomia, but no higher grades were observed, and most cases occurred in patients previously treated with LuPSMA. Fourteen of 31 (44%) patients experienced PSA ≥ 50% responses, including 7 of 13 (54%) patients previously treated with LuPSMA. A trial testing multiple ascending doses is currently underway.

The nonoverlapping bio-distribution of PSMA-targeted antibody and small molecule-based MRT based on imaging studies, combined with data that J591 and the urea-based small molecules bind nonoverlapping sites on PSMA, suggest that combining these agents for MRT may improve antitumor efficacy without increasing toxicity. In preclinical mouse studies, complete tumor regression occurred following treatment with the combination of alpha-emitting PSMA-antibodies and beta-emitting PSMA-small molecules, suggesting synergy. Further, this may be a favorable combination based on tumor geometry and isotope path length. Beta radiation poorly targets micro-metastatic lesions, and trials of ^{177}Lu-MRT commonly report progression due to previously nonvisualized lesions, often in the bone marrow. However, the short, focused emissions range of alpha particles effectively radiate micro-metastatic lesions. A trial testing ^{225}Ac-J591 in combination with ^{177}Lu-PSMA-I&T has recently been opened at Weill Cornell Medicine.

In addition to radioligand-based PMSA targeting agents, other PSMA-targeted treatments are being developed. These include PSMA-targeted antibody–drug conjugates, bispecific antibodies, CAR T cells, and other novel approaches. Future investigations will focus on additional combination PSMA therapeutics approaches. The earlier use of PSMA-targeted treatments in the prostate cancer disease history is also being investigated, including neo-adjuvant or adjuvant treatment in localized high-risk disease settings with curative intent.

Shahneen Sandhu (Peter MacCallum Cancer Centre) discussed results from the PRINCE Trial, which tested the combination of LuPSMA with pembrolizumab in mCRPC. Radiation therapy has the potential to induce immunogenic cell death, and targeted delivery of beta particle radiation by LuPSMA may release tumor-associated antigens from multiple sites, suggesting rationale for combining LuPSMA with immunotherapy. The phase 1/2 PRINCE trial tested the combination of LuPSMA (six cycles, every 6 weeks, at a starting dose of 8.5 GBq, decreasing by 0.5 GBq with each cycle) with pembrolizumab (200 mg, up to 35 cycles, every 3 weeks) in 37 patients with mCRPC, who had received prior AR-antagonist therapy (enzalutamide, abiraterone or apalutamide), may have had prior docetaxel, and had ECOG scores of 0–1. Patients were screened by ^{68}Ga-PSMA-11 + FDG PET/CT, and to be eligible must have PSMA SUVmax > 20 at any site and SUVmax > 10 at other sites of disease ≥10 mm, and no FDG-positive/PSMA-negative sites of disease. Enrolled patients underwent serial PSMA PET scans, bone scan, and CT chest/abdomen/pelvis scans at baseline and every 12 weeks. Serial PBMC, ctDNA, CTC, and plasma samples were collected at baseline, every 12 weeks, and at disease progression. Tumor biopsies were mandatory at baseline, weeks 3–4, and at radiological progression. The co-primary endpoints were PSA ≥ 50% response (PSA-RR) and safety. Secondary endpoints included rPFS, PSA progression-free survival (PSA-PFS), overall response rate (ORR), and OS.

Treatment-related adverse events (TEAEs) in patients treated with LuPSMA + pembrolizumab were consistent with TEAEs seen with single-agent LuPSMA and pembrolizumab. Grade 1–2 TEAEs included xerostomia (76%), fatigue (37%), rash (25%), nausea (24%), and pruritis (19%). Hematological toxicities were largely Grades 1–2 and managable, and included anemia (5% Grade 2, 3% Grade 3), thrombocytopenia (14% Grades 1–2), and neutropenia (3% Grade 1).

Immune-related adverse events (irAEs) were also primarily Grades 1–2 including rash (25%), pruritis (19%), aspartate aminotransferase elevation (11%), alanine aminotransferase elevation (8%), arthralgia (8%), and myalgia (5%). Several patients experienced more severe (Grades 2–3) and co-occurring irAEs, including colitis (two Grade 3 events), mucosal pemphigus (one Grade 3 event), ocular myasthenia gravis (one Grade 3 event), optic neuritis (one Grade 2 event), and myocarditis (one Grade 3 event). There were no Grade 4 TEAEs or treatment-related deaths. Four patients (11%) discontinued pembrolizumab due to toxicities; none discontinued LuPSMA due to toxicities.

PSA ≥ 50% response, the primary endpoint, was seen in 73% (27/37) of patients. ORR by RECIST 1.1 was seen in 78% (7/9) of patients with measurable disease. Despite stringent patient selection criteria, four patients had no PSA decreases. At a median follow-up of 38 weeks, median 24-week rPFS was estimated at 65%, and 24-week PSA-PFS was estimated at 68%. At the time of this presentation, 23 of 37 enrolled patients were still on treatment. A CTC analysis compared paired baseline versus week 12 samples in 29 patients. In 18 patients who had detectable PSMA-positive CTCs at baseline, 61% (11/18) had cleared PSMA-positive CTCs to zero at 12 weeks, and 83% (15/18) had decreases in PSMA-positive CTCs at 12 weeks. Of 11 patients who had zero PSMA-positive CTCs at screening, 100% (11/11) maintained zero CTCs at 12 weeks. Many patients had PSMA-positive and PSMA-negative CTCs at baseline; the relevance of this heterogeneity in LuPSMA responsiveness is yet unclear. Correlative studies are ongoing to investigate the impact of LuPSMA + pembrolizumab on the TME and define predictive biomarkers of response and resistance.

Ana Kiess (Johns Hopkins University) discussed the potential for targeting micro-metastatic disease with Auger versus alpha-emitting MRT. Auger emitters decay by ejection of low-energy outer shell Auger electrons. Auger electrons have a shorter path (<10 µM range) than alpha (50–100 µM range) or beta (0.05–12 mm range) particles and an intermediate LET (4-26 keV/µM for Auger; 0.2 keV/µM for beta; 80–100 keV/µM for alpha). This suggests that PSMA-MRT using Auger emitters may have increased antitumor efficacy and decreased toxicity, and particularly efficacy against micro-metastases, compared with alpha or beta emitters. PSMA-positive vs PSMA-negative prostate tumor-bearing mice were treated with PSMA-targeted small molecules (PSMA-6, DCIBzL) labeled with Auger (^{125}I) or alpha (^{211}At) emitters (developed by Pomper and colleagues, Johns Hopkins University); both agents improved survival in mice with PSMA-positive tumors, including micro-metastatic models, but not PSMA-negative tumors. However, significant renal toxicity was seen in mice treated with the alpha emitter ^{211}At-PSMA-6, including subcortical atrophy and degenerative loss of proximal tubules, and dosimetry studies revealed significantly higher mean absorbed doses of ^{211}At-PSMA-6 in kidney and kidney proximal tubules than PSMA-positive tumors. ^{211}At-PSMA-6 also led to eventual lethal toxicity in a dose-dependent manner. In contrast, significant antitumor efficacy with no short- or long-term kidney toxicity was seen in mice treated with the Auger-emitting PSMA-targeting agent ^{125}I-DCIBzL, even after 1 year at doses 100× higher than given for ^{211}At-PSMA-6. Dosimetry modeling of ^{125}I-DCIBzL demonstrated lower mean absorbed doses in kidneys than PSMA-positive tumors. Together, these studies demonstrate the promising antitumor activity with potential low toxicity for Auger-emitting PSMA MRT in the treatment of prostate cancer, including in patients with micro-metastatic disease; some data have been published.[64,65] Further studies are strongly warranted.

Cristina Müller (Paul Scherrer Institute) discussed the use of the "four sisters of terbium" in PET and SPECT imaging and targeted alpha- and beta-MRT. Terbium (Tb) is a unique element that comprises four radioisotopes with decay properties optimal for variable theranostic applications: ^{152}Tb for PET imaging, ^{155}Tb for SPECT imaging, ^{149}Tb for alpha particle-based MRT, and ^{161}Tb for beta particle-based MRT.

^{161}Tb and ^{177}Lu have similar half-lives, and emit beta particles of a similar medium energy, and gamma radiation, making them useful for both MRT and SPECT imaging. The chemical similarity of ^{161}Tb and ^{177}Lu allows stable chelation using DOTA. Importantly, ^{161}Tb but not ^{177}Lu emits a substantial number of conversion and Auger electrons. ^{161}Tb is produced via irradiation of ^{160}Gd targets, in a process analogous to the production of ^{177}Lu from ^{176}Yb. A ^{161}Tb production facility has been established at the Paul Scherrer Institute in Switzerland, and other global production sites are planned. Theoretical dose calculation studies demonstrated the potential for smaller targets to absorb significantly higher radiation doses from ^{161}Tb versus ^{177}Lu or other next-generation beta-emitting radioisotopes (^{67}Cu or ^{47}Sc), suggesting promise for ^{161}Tb-based MRT in the treatment of micro-metastatic cancer. A study comparing the properties of ^{177}Lu-PSMA-617 and ^{161}Tb-PSMA-617 found both could be produced efficiently with >98% purity, and exhibited similar uptake and internalization in PSMA-positive prostate cancer cells but not PSMA-negative prostate cancer cells in vitro. In mice, equivalent pharmacokinetic profiles were observed with ^{177}Lu-PSMA-617 and ^{161}Tb-PSMA-617, including equivalent uptake levels in tumors versus normal tissues, and ready ability to view accumulation in PSMA-positive tumors on SPECT imaging. These data demonstrate ^{177}Lu-PSMA-617 and ^{161}Tb-PSMA-617 are interchangeable without affecting tissue distribution and uptake of PSMA-617. Human phantom and first-in-human studies have demonstrated clinical feasibility for SPECT with ^{161}Tb using low-energy-high-resolution (LEHR) collimators.

Preclinically, a stronger antitumor in vitro and in vivo efficacy was seen for ^{161}Tb-PSMA-617 (due to Auger electrons emission) compared with ^{177}Lu-PSMA-617 applied at the same activity levels.

Preclinical studies testing ^{149}Tb-PSMA-617 as an alpha-emitting MRT demonstrated antitumor efficacy and prolonged survival in mice bearing PSMA-positive prostate tumors. ^{149}Tb does not produce alpha-emitting daughters during decay, suggesting it may have improved safety compared with other alpha emitters such as ^{225}Ac. ^{149}Tb also emits positrons, and PET imaging was successfully performed in mice bearing PSMA-positive prostate tumors treated with ^{149}Tb-PSMA-617.

^{152}Tb-PSMA-617 and ^{155}Tb-PSMA-617 have potential as diagnostic PET and SPECT agents, respectively; both have been successfully used for imaging in prostate cancer mouse models. These agents are also of interest in combination with long-circulating targeting agents, for delayed imaging, and for dosimetry for PSMA-targeted MRT.

Altogether, these studies demonstrate that terbium radioisotopes have promise for multiple theranostic purposes, and may have improved antitumor activity and/or safety compared with currently used PSMA-targeted MRT agents. However, while ^{161}Tb production is well established, production of ^{149}Tb, ^{152}Tb, and ^{155}Tb remains a challenge, and new production methods and facilities are needed. ^{161}Tb is the most advanced in terms of preclinical investigations; yet, further studies are needed to better understand the Auger electron effects in the treatment of metastatic disease. Clinical trials testing ^{161}Tb-based PSMA-targeted MRT are being planned.

Discussed by Aseem Anand (EXINI Diagnostics AB. Sweden; a wholly owned subsidiary of Lantheus Holdings), AIenabled quantitative imaging biomarkers are algorithms that automate and standardize determinations of cancer burden from medical images. Quantitative imaging biomarkers can be developed for use in several contexts: prognostic (to predict a patient's outcome independent of treatment), predictive (to predict if a patient will or won't respond to a treatment), and response (to measure a patient's response to a treatment).

The FDA-cleared and AI-enabled automated bone scan index (aBSI) quantitates prostate cancer from technetium bone scans and has been translated into clinical use. aBSI was prospectively validated in a Phase 3 trial as an independent prognostic biomarker for overall survival in patients with mCRPC and had additive predictive value with other known prognostic biomarkers such as LDH, hemoglobin, PSA, and albumin.[66] aBSI has further been demonstrated to predict response to radiation therapy and to identify patients with newly diagnosed prostate cancer likely to benefit from radiation therapy.[67]

Similarly, aPROMISE is a deep learning-based method developed to standardize localization and quantification of tumor burden from PSMA PET/CT scans. The Progenics program, PyL ACCESS, provided free or ^{18}F-labeled DCFPyL at no cost to clinicians in exchange for PET/CT patient images. ^{18}F-DCFPyL-PSMA PET/CT images from over 3000 patients were collected through this program and used for AI training. An automated PSMA-Score, which represents the total tumor burden by tissue type is reported at the patient level. aPROMISE was validated in a prospectively planned analysis of the OSPREY study.[68] Further validation of aPROMISE was demonstrated in a PCF-VA study in veterans diagnosed with localized high-risk prostate cancer imaged with PSMA PET/CT.[69]

Additional studies are ongoing to validate quantitative PSMA-Score as a prognostic biomarker in patients with metastatic prostate cancer, and as a response imaging biomarker in patients with mCRPC undergoing treatment with ^{177}Lu-PSMA and with Radium-223. Preliminary results from these studies are promising. Together, these studies demonstrate rigorous performance valuation of aPROMISE, with the goal of providing a standardized method for efficient, consistent, and accurate prostate cancer quantification, to improve patient management and outcomes. Appropriate validation studies will be required for use in additional clinical settings. ^{18}F-DCFPyL (Pylarify®) was FDA approved for prostate cancer imaging in 2021. aPROMISE v1.2.1 was the first AI-enabled application to receive FDA clearance for PSMA PET quantification in 2021.

12 | FIBROBLAST ACTIVATION PROTEIN-ALPHA (FAP) AS A THERANOSTIC TARGET IN PROSTATE CANCER

Andy Simmons (Clovis Oncology) discussed the potential of fibroblast activation protein-alpha (FAP) as a theranostic target in prostate cancer. FAP is a membrane-bound protease expressed at high levels on cancer-associated fibroblasts (CAFs) abundant in the stroma of most tumors. FAP has limited expression on normal tissues, with the exception of sites of tissue remodeling such as wound healing and fibrosis. These features make FAP an attractive imaging and theranostic target. Studies in TCGA and a small IHC study suggest that FAP RNA and protein expression are relatively low in primary and metastatic prostate cancer compared with other cancer types.

A series of quinoline-based FAP inhibitors (FAPI-04, FAPI-46, and FAPI-74) were developed that can be labeled with different radioisotopes, including for diagnostic imaging (e.g., ^{68}Ga) and therapy (e.g., ^{177}Lu). In preclinical studies, these FAP inhibitors were rapidly taken up by FAP-expressing cells in the tumor stroma with low accumulation in normal tissues. A study led by Kratochwil tested ^{68}Ga-FAPI-04 PET/CT in 80 patients in 28 primary and metastatic cancer types. Fifty-four primary tumors and 229 metastatic tumors were included in the study. Tumors with the highest average ^{68}Ga-FAPI-04 SUV_{max} included sarcoma, esophageal, breast, cholangiocarcinoma, and lung cancer. In the prostate cancer patients evaluated ($n = 13$), uptake was intermediate to high, with an SUV_{max} ~10. However, all prostate cancer patients were PSMA-negative; whether PSMA expression may have an inverse relationship with FAP expression is unknown. A case report of a patient with PSMA-negative mCRPC found qualitatively similar ^{18}F-FDG and ^{68}Ga-FAPI-04 tracer uptake in lymph node and bone lesions, suggesting potential for FAP-targeted therapy in patients with PSMA-negative prostate cancer.

In addition to the molecules in the FAPI series, other small molecules targeting FAP are being developed. FAP-2286 is a novel FAP-targeted low molecular weight cyclic polypeptide linked to DOTA, allowing for chelation to radionuclides, including ^{68}Ga and ^{177}Lu. FAP-2286 was found to be potent and selective for FAP and stable in human plasma. Treatment of mice bearing FAP-expressing tumor cell lines and patient-derived xenografts (PDX) with a single dose of ^{177}Lu-FAP-2286 significantly inhibited tumor growth, with no significant body weight loss observed. ^{177}Lu-FAP-2286 outperformed the FAP-targeted agent ^{177}Lu-FAPI-46 at repressing tumor growth in xenograft models. SPECT/CT imaging found longer retention times of ^{177}Lu-FAP-2286 versus ^{177}Lu-FAPI-46 in tumor

sites, which may underlie its improved antitumor activity. A Phase 1/2 clinical trial (LuMIERE; NCT04939610) is investigating FAP-2286 theranostics in multiple solid tumors. In this trial, ^{68}Ga-FAP-2286 PET is used to identify FAP-positive patients who will receive treatment with ^{177}Lu-FAP-2286. An investigator-initiated study led by Tom Hope (UCSF) will evaluate the ability of ^{68}Ga-FAP-2286 to detect metastatic cancer in patients with solid tumors.

Key questions remaining on the utility of FAP theranostics in prostate cancer include whether there is a subset of prostate cancer patients with FAP-high tumors who may benefit from FAP-targeted MRT and whether PSMA, clinical factors, or other biomarkers correlate with FAP expression.

13 | THERAPEUTIC DEGRADERS AS A NEW CLASS OF PROSTATE CANCER TREATMENTS

Arul M. Chinnaiyan (University of Michigan, Michigan Center for Translational Pathology) discussed the development of therapeutic degraders targeting the SWI/SNF chromatin remodeling complex as a new approach to blocking oncogenic transcription factors in prostate cancer. Studies by Chinnaiyan and colleagues identified the multi-protein SWI/SNF chromatin remodeling complex as an interaction partner with AR, FOXA1, and ERG. SWI/SNF is altered in ~20% of various cancers, though rarely in prostate cancer.

The activity of the proteolysis-targeting chimera (PROTAC) degrader, AU-15330, which targets the SWI/SNF ATPase subunits SMARCA2 and SMARCA4, was tested in a series of 65 human-derived normal and cancer cell lines from 14 different lineages. Growth of several AR-dependent prostate cancer, ER and/or AR-positive breast cancer, and MYC-driven multiple myeloma lines were preferentially sensitive to AU-15330, while normal cell lines including normal prostate were resistant. AU-15330 was observed to strongly degrade SMARCA2 and SMARCA4 proteins in various cell lines. These data suggest that cancers driven by AR or certain other transcription factors are specifically sensitive to SMARCA2/4-targeting. ATAC-sequencing studies found significant loss in chromatin accessibility in prostate cancer cells treated with AU-15330, which was not observed following treatment with a BRD4-targeted PROTAC. Chromatin regions compacted by AU-15330 included enhancer regions regulated by FOXA, ETS, and AR, while promoter regions were largely unaffected. ChIP-seq studies found that AU-15330 significantly reduced DNA binding by AR, FOXA1, and ERG. The expression of genes regulated by AR, FOXA1, and ERG was also significantly reduced. Hi-ChIP studies found that 3D interactions between promoter and enhancer sites on the *AR* gene were lost after AU-15330 treatment. AU-15330 treatment significantly inhibited tumor growth in murine AR-positive CRPC xenograft models, and further synergized with enzalutamide; in the VCaP CRPC model, this combination resulted in tumor regression, an effect that has never been previously attained in this highly aggressive model. AU-15330 was well tolerated in mice, with no body weight or organ weight loss, organ toxicities, or complete blood count changes observed. Together, these data demonstrate significant promise for SMARCA2/4-targeting PROTACs in the treatment of enhancer-addicted prostate and other cancers. Much of these data were recently published.[70]

14 | NEW APPROACHES FOR IMMUNOTHERAPY IN PROSTATE CANCER

14.1 | The role of AR in T cells and immunotherapy responses

Amy Moran (Oregon Health & Science University) discussed a T-cell intrinsic role for AR signaling in immunotherapy resistance. In epidemiologic studies, the immune system demonstrates a sexual dimorphism, with tmale sex appearing protective against auto-immunity, but increased susceptibility to cancer and COVID-19 mortality, compared with the female sex. Moran and others have observed that lymphocytes in normal and prostate cancer tissues express AR. To investigate whether AR in T cells impacts antitumor immune responses, Moran and colleagues evaluated baseline tumor biopsy samples from a Phase 2 trial testing the addition of pembrolizumab in mCRPC patients progressing on enzalutamide. Of eight patients evaluated, three exhibited a response to pembrolizumab (PSA reductions >25%), while five were nonresponders. Biopsy samples were subjected to single-cell and bulk RNA-seq analyses. Unbiased single-cell gene expression analyses identified two major subsets of CD8 T cells, which highly overlapped with CD8 T cells from responders versus nonresponders. Responder CD8 T-cell signatures exhibited low AR activity and increased functional activity compared with nonresponder CD8 T cells. An AR activity score was developed and found to negatively correlate with pembrolizumab response among patients on the trial. The AR activity score also negatively correlated with CD8/IFNγ activity in additional gene expression data sets from patients with prostate cancer (PCF West Coast Dream Team cohort) or melanoma. CRISPR-mediated deletion of AR in CD8 T cells enhanced the expression of IFNγ response pathways. AR ChIP in mouse T cells found AR binds to open chromatin regions in IFNγ, granzyme B, and other immune effector genes. The role of AR in T-cell activity was evaluated in chronic antigen exposure models, using LCMV-specific TCR transgenic P14 mice infected with LCMV Cl13. Mice were adoptively transferred with P14 T cells from which AR was deleted by CRISPR before LCMV infection, or mice were treated with degarelix + enzalutamide following LCMV infection. Both T-cell intrinsic AR deletion or degarelix + enzalutamide treatment did not impact acute effector responses of T cells to LCMV. However, AR deletion/inhibition maintained the functional capacity, including IFNγ production, of T cells after chronic exposure to LCMV. Together, these results suggest that AR signaling in T cells promotes exhaustion, while AR blockade may enhance T-cell activity and immunotherapy responses in patients with prostate cancer. Much of these data have recently been published.[71]

14.2 | Advances in checkpoint immunotherapy for prostate cancer

Ajjai Alva (University of Michigan) discussed the efficacy of checkpoint Immunotherapy in patients with mCRPC with *CDK12*-loss. *CDK12*-loss prostate cancer was recently described as a distinct molecular subtype, characterized by genomic instability, focal tandem duplications, and high levels of gene fusions.[72] *CDK12*-loss is present in ~7% of patients with metastatic prostate cancer and appears to be exclusive from SPOP-mutations, ETS gene fusions, and mismatch repair gene defects. The high levels of neoantigens generated by gene fusions have led to the hypothesis that *CDK12*-loss may sensitize tumors to treatment with checkpoint immunotherapy. Anecdotal data from the University of Michigan have supported this, with two of four patients with *CDK12*-loss who received checkpoint immunotherapy exhibiting responses, one of which was deep and durable. Case series reports found that patients with *CDK12*-loss mCRPC tended to have more aggressive disease, faster time to metastasis, reduced benefit from hormone therapy, and reduced time to castration-resistance, compared to patients with mCRPC with alterations in *BRCA1/2* or *ATM*.

Alva and colleagues initiated a three-cohort multicenter clinical trial to test ipilimumab + nivolumab in patients with *CDK12*-loss tumors. Cohort A is testing ipilimumab + nivolumab in patients with *CDK12*-loss mCRPC. Cohort B is testing ipilimumab + nivolumab in patients with *CDK12*-loss solid tumors. Cohort C is testing nivolumab alone in patients with *CDK12*-loss mCRPC. *CDK12*-loss was determined by genomic sequencing in tumor or blood samples and could be mono-allelic or bi-allelic.

Preliminary results were reported for Cohort A ($N = 33$). The primary endpoint was overall response rate (ORR) as measured by PSA > 50% decline from baseline. Secondary endpoints included safety, rPFS, duration of response, duration of therapy, time to progression, OS, PSA-PFS, and quality of life measures. Correlative studies are evaluating tumor genomics and immune biology. At the time of this presentation, PSA > 50% decline was observed in 4 of 23 evaluable patients, for an ORR of 17.4%. Hyper-progression, in which PSA levels increased over 10-fold, was observed in several patients. Nine of 25 evaluable patients (36%) experienced Grades 3–5 serious adverse events. Nineteen of 33 evaluable patients experienced treatment-emergent adverse events of any grade, which were consistent with known adverse effects with these treatments. This study is ongoing and represents the first precision genomic selection study for immunotherapy in mCRPC. Whether biallelic CDK12-loss may confer better sensitivity to immunotherapy, whether immunotherapy may work better if given earlier in the disease course, and mechanisms and biomarkers of hyper-progression, remain important questions.

Chet Bohac (MacroGenics, Inc.) discussed the preliminary results of a Phase 1 cohort expansion trial testing the anti-B7-H3 antibody –drug conjugate (ADC) MGC018, in patients with mCRPC.[73] B7-H3 is a negative-regulatory immune "checkpoint" protein highly expressed on prostate and other solid tumor cells, tumor vasculature, and tumor stroma, but has limited expression on normal tissues, and is under investigation as a new target for cancer immunotherapy. MGC018 is a B7-H3-targeted ADC, conjugated to the DNA-alkylating agent duocarmycin by a cleavable linker. On average, each MGC018 molecule carries an average of 2.7 molecules of duocarmycin. Preclinical studies demonstrated immunogenic killing by MGC018 against multidrug-resistant tumor cell lines. Treatment with MGC018 suppressed the growth of B7-H3-expressing prostate, breast, ovarian, lung, head and neck, and melanoma tumors in mice. MGC018 exhibited an acceptable safety profile in preclinical toxicology studies. Side effects in cynomolgus monkeys after several doses of MGC018 included transient low blood cell counts, dry skin, and hyperpigmentation. A Phase 1/2 dose-escalation trial was performed to evaluate safety and establish the recommended Phase 2 dose (RP2D) for MGC018, given intravenously every 3 weeks, in patients with certain advanced solid tumors. Two dose-limiting toxicities were observed in the dose-escalation cohort: one Grade 4 neutropenia event and one Grade 3 fatigue event. Five of 9 (55.5%) patients with mCRPC in the dose-escalation cohort experienced ≥50% PSA reductions. Some melanoma patients also experienced a response. A Phase 1 cohort expansion testing the RP2D is ongoing. At the time of this presentation, 88 patients had been enrolled in the expansion cohort, including 40 patients with mCRPC. Ninety-three percent of the mCRPC patients had high B7-H3 levels in tumor samples by IHC. TEAEs were observed in 83 of 88 (96.5%) patients, including 48 (55.8%) with Grade 3 or higher TEAEs, and 29 (33.7%) with at least 1 serious TEAE. There were two on-study deaths, one due to COVID-19, and one of undetermined cause. Toxicities led to the discontinuation of MGC018 in four mCRPC patients. Common TEAEs (any grade) included fatigue (37%), neutropenia (34%), hand-foot syndrome (31%), pleural effusion (23%), nausea (22%), and asthenia (20%). Grade ≥3 TEAEs occurring in >5% of patients included neutropenia (22%), thrombocytopenia (7%), and anemia (5.8%). At the time of this presentation, 32 patients in the expansion cohort including 16 with mCRPC were evaluable for response. Four of 16 (25%) patients with mCRPC experienced a response per RECIST v1.1, and 10 experienced reductions in target lesion sums from baseline. Twenty-one of 39 (53.8%) evaluable mCRPC patients exhibited a PSA reduction ≥50%. Twenty-four of 39 (61.5%) patients remained on treatment. These data suggest safety and preliminary efficacy for MGC018 in multiple solid tumor types including mCRPC, non-small cell lung cancer, and melanoma. Future studies plan to test alternative starting doses and identify the optimal total number of doses and treatment duration.

14.3 | Advances in T-cell redirecting immunotherapies

Oliver Sartor (Tulane University) discussed the landscape of novel T-cell redirecting agents under investigation in prostate cancer. This class of agents work by simultaneously binding to tumor cells and T cells, and includes bi-specific and tri-specific strategies. Prostate

cancer-associated proteins under investigation as targets for T-cell redirecting agents include DLL3 (discussed below), PSMA, STEAP1, KLK2, and TMEFF2.

AMG 212 is a PSMAxCD3 BiTE with potent in vitro and in vivo cytotoxic activity in preclinical prostate cancer models. AMG 212 is a canonical BiTE with a short serum half-life, requiring it to be administered by continual IV infusion. In a Phase 1 study testing AMG 212 in mCRPC, 16 patients were treated at one of five dose levels. Promising clinical activity was observed and no MTD was reached. Long-term PSA responses occurred in two patients (>14 and 19 months) and stable disease by RECIST 1.1 criteria occurred in three patients. Cytokine release syndrome (CRS) was observed in 3 of 16 patients (19%; two Grade 2, one Grade 3). However, the need for continual IV administration led to the discontinuation of AMG 212 development in favor of the extended serum half-life PSMAxCD3 BiTE, AMG 160, which can be administered bi-weekly.

A Phase 1 study of the PSMAxCD3 BiTE AMG 160 was performed to evaluate the safety and determine the R2PD or MTD in mCRPC.[74] Thirty-five patients were treated at one of six dose levels. Twenty-four of 35 (68.6%) patients experienced PSA reductions and 34.3% experienced PSA ≥ 50% responses. Three partial responses (1 unconfirmed) occurred in 15 patients with measurable disease. Ninety percent of patients experienced CRS events (60.5% Grades 1–2, 25.6% Grade 3), which tended to be manageable, reversible, most severe in Cycle 1, and associated with fever, hypotension, transient transaminitis, nausea/vomiting, and diarrhea. Reversible atrial fibrillation in the setting of CRS and/or tachycardia occurred in four (9.3%) patients. There were no Grade 4 or 5 CRS events. A prophylactic mitigation strategy that included dose priming, dexamethasone premedication, and prophylactic IV hydration eliminated Grade 3 CRS in a test cohort of five patients. As a comparison, two of four patients who received the same dose of AMG 160 without prophylactic mitigation experienced Grade 3 CRS events. This CRS mitigation strategy will be used with AMG 160 going forward. Ongoing trials are evaluating AMG 160 in combination with pembrolizumab, enzalutamide, abiraterone, or the anti-PD1 antibody AMG 404.

HPN424 is a PSMA-targeted T-cell redirecting agent engineered as a small globular protein (~50 kDa) with three domains that target PSMA, CD3, and albumin for serum half-life extension.[75] These features are designed to increase the therapeutic index compared to earlier generations of T-cell engagers by minimizing off-target toxicities. HPN424 exhibited efficient solid tumor penetration, long half-life, and excellent stability in preclinical studies. In a Phase 1 study to evaluate the safety and determine the R2PD or MTD of HPN424 in mCRPC, no MTD was determined and no Grade 4 CRS events or Grade 5 events occurred in 89 treated patients. Promising antitumor activity was observed, including PSA reductions in 15 of 74 (20%) evaluable patients, and PSA ≥ 50% responses in 4 of 74 patients. Of 34 evaluable patients with measurable disease at baseline, 19 (56%) exhibited stable disease or showed reduction, including one with a confirmed partial response per RECIST. Reductions in CTCs were observed in 36 of 64 (56%) evaluable patients, including 14 with CTC0 responses. Based on the moderate activity and challenging toxicity profile, Harpoon Therapeutics recently announced the HPN424 dose-escalation study has been discontinued.[76]

TNB-585 is a CD3xPSMA bi-specific antibody developed using a next-generation approach that employs multispecific antibodies developed from humanized Ig transgenic rats. The anti-CD3 used in this approach binds a unique epitope at low affinity, resulting in similar efficacy with reduced CRS. In preclinical studies, incubation of LNCaP tumor cells with resting primary T cells and TNB-585 resulted in moderate T-cell activation and tumor lysis compared with the positive control, minimal production of CRS-related cytokines (IFNγ, TNF-α, IL-2), and reduced Treg activation. A Phase 1 first-in-human study evaluating TNB-585 in mCRPC is underway.

AMG 509 is a STEAP1-targeted bispecific XmAb® 2 + 1 immune therapy consisting of two humanized anti-STEAP1 Fab domains, an anti-CD3 single-chain variable fragment domain, and an effectorless Fc domain to extend serum half-life.[77] A Phase 1 study to evaluate AMG 509 in patients with mCRPC has been initiated.

At least five additional prostate cancer-targeted T-cell redirecting agents targeting PSMA, KLK2, and TMEFF2, are in clinical trials. Many more are in preclinical development. As the sequence and structural complexity of these multispecific/multifunctional antibodies increases, of increasing concern is the emergence of antidrug antibodies. It will be critical to develop methods for early assessment of antidrug antibody liabilities and to conduct antidrug antibody de-risking studies during the lead selection process.

Rahul Aggarwal (University of California, San Francisco) discussed AMG 757 (tarlatamab), a Delta-like ligand 3 (DLL3)-targeted bi-specific T-cell engager (BiTE®), and a novel treatment candidate for NEPC. DLL3 is an atypical Notch pathway ligand that is overexpressed on the surface of neuroendocrine tumor types, including small cell lung cancer (SCLC) and NEPC. A study by Beltran and colleagues in 423 patients with prostate cancer (735 samples) found DLL3 was expressed in 77% of NEPC tumors, on 64% of their tumor cells on average. Another study found that DLL3 expression is inversely correlated with expression of PSMA and STEAP1, and is associated with significantly shorter OS than patients with DLL3-negative prostate cancer.

AMG 757 is a half-life extended BiTE® designed to redirect cytotoxic T cells to tumor cells by binding to DLL3 on cancer cells and CD3 on T cells. AMG 757 was demonstrated to induce T-cell-dependent lysis of DLL3-expressing neuroendocrine tumor cell lines, including NEPC cells, and to suppress tumor growth and extend survival in a DLL3-high PDX murine model of NEPC. AMG 757 also inhibited tumor growth in NEPC PDX models with heterogenous levels of DLL3; however, some late relapses occurred with relapsing tumors expressing lower levels of DLL3.

A first-in-human dose exploration study of AMG 757 in patients with relapsed/refractory SCLC has been initiated to evaluate safety and tolerability and determine the maximum tolerated dose (MTD) or RP2D. Preliminary results from 64 patients treated suggest safety and antitumor activity across a range of AMG 757 doses. The

observed disease control rate was 47% (30 of 64 patients) and objective response rate was 20% (13 of 64 patients).

A Phase 1b study (NCT04702737) evaluating AMG 757 in patients with de novo or treatment-emergent metastatic NEPC has recently opened to accrual. The two-part study includes a dose exploration phase and dose expansion phase. Enrollment criteria include a histological diagnosis of small cell NEPC, histologic evidence of prostate cancer with neuroendocrine differentiation, and/or ≥2 alterations in TP53, RB1, and/or PTEN by IHC or genomic analyses of baseline tumor tissue or ctDNA. The primary objectives are to evaluate the safety and tolerability of AMG 757 monotherapy and to determine the MTD or RP2D in patients with NEPC. Secondary objectives include evaluating antitumor activity (including objective response, duration of response, progression-free survival, overall response), and characterizing pharmacokinetics.

John Desjarlais (Xencor) discussed a bispecific antibody approach for solid tumors, which aims to optimize T-cell activation. Optimal T-cell activation requires multiple signals, including TCR/CD3 stimulation, costimulation by CD28 or other pathways, and activation by cytokines such as IL-15, IL-12, and IL-2. Combining bispecific antibodies that supply different activation signals, and/or block negative regulatory checkpoints, are being tested as strategies to optimize antitumor immunity.

XmAb717 (vudalimab) is a bispecific antibody under development for solid tumors, which co-targets the immune inhibitory checkpoints PD1 and CTLA4. In a Phase 1 trial with XmAb717, responses were observed in multiple tumor types, including patients with prior checkpoint immunotherapy. There were nine CPRC patients in this trial, four of whom experienced responses (one >50% PSA reduction, two >30% PSA reductions, one PR by RECIST). A Phase 2 study has been initiated in CRPC.

XmAb808 is B7H3 x CD28 bispecific antibody, under development for pan-tumor indications, including prostate cancer. This antibody may be combined with TAA x CD3 (TAA; tumor-associated antigen) bispecifics, or PD1 blockade, to optimize T-cell activation. In preclinical studies, the combination of B7H3 x CD28 and PSMA x CD3 bispecifics resulted in increased prostate cancer cell killing and increased T-cell proliferation and cytokine production, compared with PSMA x CD3 bispecific alone. No activity was seen against PSMA-negative cells, demonstrating PSMA-positive cell-specific killing and suggesting the safety of the tumor-targeted CD28 costimulation. In breast cancer xenograft models, treatment with B7H3 x CD28 + TAA x CD3 significantly inhibited tumor growth and increased T-cell proliferation, while TAA x CD3 had little effect alone.

XmAb306 is cytokine-Fc fusion consisting of IL15 x IL15Rα, with mutations to reduce potency, as a strategy to improve exposure and more safely enhance T-cell activation. XmAb306 was ~100-fold less potent than WT IL-15 at activating T-cell proliferation in vitro but was significantly more sustained in serum in cynomolgus monkeys, and induced more prolonged activation of T cells and NK cells. A Phase 1 dose-escalation trial testing XmAb306 monotherapy and in combination with atezolizumab has been initiated.

XmAb662 is a 100×-reduced potency form of IL-12. XmAb662 exhibited single -gent antitumor activity in murine xenograft models and significant synergy in combination with anti-PD1. In cynomolgus monkeys, XmAb662 was well tolerated with superior pharmacokinetics and was pharmacologically active as measured by induction of an IFNγ response. These products offer multiple therapeutic combinatorial strategies for inducing optimized antitumor immune responses.

14.4 | Novel chimeric antigen receptor (CAR) T-cell approaches

Gus Zeiner (Chimera Bioengineering) discussed "GOLD-CAR" T cells, a novel platform designed to deliver a payload only upon tumor cell interaction, as a strategy to increase potency, reduce toxicities, and overcome the immune-suppressive TME. In proof-of-concept studies, anti-CD19 GOLD-CAR T cells delivering a luciferase payload only produced luciferase at tumor sites in a mouse lymphoma model. In contrast, systemic luciferase delivery was seen with anti-CD19 CAR T cells with conventional (constitutive) luciferase expression. The immune activation cytokine IL-12 can be highly toxic when delivered systemically. The safety and efficacy of tumor-targeted delivery of IL-12 using GOLD-CARs were investigated. In mouse lymphoma models, anti-CD19 GOLD-CAR T cells delivering IL-12 demonstrated similar antitumor efficacy but significantly reduced circulating IL-12, compared with anti-CD19 GOLD-CAR T cells that constitutively express IL-12.

As discussed above, DLL3 is expressed on the surface of neuroendocrine cancers including small cell lung cancer, neuroblastoma, IDH-mutant gliomas, and NEPC, and has potential as a therapeutic target. A GOLD-CAR T cell targeting DLL3 and delivering an IL-12 payload (αDLL3 (IL12) GOLD-CAR) was developed and is being tested in NE tumor models.

An IL-12 delivering GOLD-CAR targeting the tumor-associated hypoglycosylated form of Muc1 (TnMuc1) has been developed (αTnMuc1 (IL12) GOLD-CAR). TnMuc1 is expressed in a number of adenocarcinomas, including the five with the highest mortality rates (lung, colon, pancreas, breast, and prostate). αTnMuc1 (IL12) GOLD-CAR had higher antitumor activity against pancreatic adenocarcinoma and metastatic prostate cancer cells in vitro and in mouse models, relative to unarmed αTnMuc1 CARs. Additional development of GOLD-CAR T cells is underway.

14.5 | New technologies to overcome the suppressive TME

Peter Fan (Teon Therapeutics) discussed the potential for adenosine pathway inhibitors as monotherapy or in combination

with immunotherapy agents in prostate cancer. Hypoxia in the TME drives upregulation of the adenosine metabolism enzyme CD73 and the low-affinity adenosine receptor $A_{2B}R$. Thus, high adenosine signaling is a common feature in tumors and promotes immune suppression, cancer cell proliferation, tumor angiogenesis, and metastasis. Blocking adenosine signaling may have therapeutic benefits. TT-702 is a novel $A_{2B}R$-inhibitor. In vitro treatment with TT-702 reverted adenosine-mediated suppression of dendritic cell proliferation, and of IFNγ production by CD4 T cells in mixed lymphocyte reactions. In contrast, the $A_{2A}R$-inhibitor preladenant was ineffective. TT-702 treatment was cytotoxic to LNCaP and PC3 cells in vitro, while preladenant had no effect. TT-702 also exhibited synergy with enzalutamide in killing LNCaP and PC3 cells in vitro. Treatment with TT-702 slowed the growth of colon cancer and melanoma tumors in mice models, and strongly synergized with anti-PD1. Evaluation of tumors from these mice found that TT-702 significantly increased the number of tumor-infiltrating CD4+ T cells, CD8+ T cells, and dendritic cells, and reduced tumor infiltration with myeloid-derived suppressor cells and regulatory T cells. Histologic evaluation of these tumors found that TT-702 also inhibited tumor angiogenesis and fibrosis. These studies provide preclinical evidence that $A_{2B}R$ antagonism can reverse adenosine-mediated immune suppression, and may have potential as a therapeutic alone or in combination with immunotherapy or other treatments. A Phase 1 trial, led by Johann de Bono, has been initiated to evaluate TT-702 in multiple tumor types, as monotherapy and in combination with anti-PD1 or hormonal therapy.

Maithreyan Srinivasan (Scribe Biosciences) discussed the development of a flexible droplet-microfluidic platform, "Micro-environment on Demand" (MOD), which enables interrogation of interactions between single T cells and target cells.[78] The platform is able to sort different cells from various sources into single-cell-containing droplets. Droplets can be studied alone or combined to study cell−cell interactions, for instance between a tumor cell and a T cell. Reagents can be added in droplets to cell-containing droplets to perform assays including phenotypic and functional analyses and scRNA-seq. In a proof-of-concept study testing the ability to combine single-cell droplets with a reagent to measure IFNγ production in 122,000 individual T cells, 82% of droplets contained the correct or extra combination. A study testing the ability to perform scRNA-seq in single anti-CD19 CAR T cells cocultured with single RAJI cells found 55% of sorted droplets contained the correct combination of cells, and only 3% of waste droplets contained IFNγ-producing CAR T cells. These studies indicate that the majority of desired droplets are being handled properly by the instrument. This platform is being further optimized for flexibility and performance of additional single-cell assays that will allow the study of TME interactions, such as the ability to perform single-cell TCR sequencing followed by matching of TCR to cognate antigen. Feedback from the research community on functionality and performance desires was sought.

15 | REAL-WORLD EVIDENCE AND SYNTHETIC/VIRTUAL CONTROL ARMS: LESSONS FROM THE VA AND PHARMA

Julie Lynch (VINCI Precision Medicine, Salt Lake City VA and University of Utah) discussed the opportunities and pitfalls of conducting prostate cancer research using big data in the Veterans Administration (VA) Healthcare System. The national VA electronic medical records portal, VINCI, contains data from over 8.76 million Veterans from 153 medical centers and 990 outpatient clinics. Since 2000, over 22.6 million patients have been seen at the VA, with collectively over 7.2 billion labs, 4.3 billion orders, 3.0 billion procedures, 2.8 billion clinical notes, 2.1 billion medication fills, 2.2 billion outpatient visits, and 14.7 million inpatient visits. These data are maintained as both structured and unstructured data fields in the VA Computerized Patient Record System (CPRS). VINCI has implemented standardization of the VA electronic health records data to enable use in studies and contribution to multinational efforts and patient outcomes registries, some of which have been published. Nevertheless, care must be taken in the use and interpretation of these data, due to some poor quality or incomplete data entry. For instance, some prostate cancer cohort studies have included patients who underwent biopsies but were not diagnosed with prostate cancer.

To create a prostate cancer core data set from patients in VINCI, Lynch and colleagues developed a machine-learning algorithm that uses diagnosis codes and natural-language processing of clinical notes for mentions of Gleason score or metastatic prostate cancer indicators.[1,79] This process was able to exclude patients with premalignant lesions or atypical prostate features without a prostate cancer diagnosis and to exclude false positives from notes that contain documentation of references or rule-out/negation phrases. Natural-language processing tools identified 685,847 veterans with prostate cancer. Additional natural-language processing tools are being developed to identify and classify biorepository samples, and to identify the highest Gleason score, castration status, HRR genetic testing, TNM stage, number of cores positive, and other characteristics from clinical notes and pathology reports.

Additional efforts underway in the VA include the development of a database of structured genetic and somatic test results. Over 20,000 veterans have undergone genomic sequencing in the VA. LEAP (Leveraging Electronic Health Information to Advance Precision Medicine) is a study on the ability to use real-world VA data to emulate clinic trials. A national cohort of veterans has been created for the LEAP study, with curated, longitudinal data on glycemic status, to mimic the design of a clinical trial testing metformin. These curated and standardized VA Prostate Cancer Data Cores will be a valuable resource for real-world evidence research and synthetic clinical trials.

Tito Fojo (Columbia University and the James J. Peters VAMC) discussed a method to estimate tumor growth rates that in prostate cancer is an excellent biomarker of OS and has potential as a clinical trial endpoint. Currently, prostate cancer clinical trial endpoints

accepted by the FDA include OS and radiographic progression-free survival (rPFS). PSA responses are often used as endpoints in trials but do not always correlate with OS and are not considered valid for FDA determinations. Biomarkers that correlate with OS but can be measured earlier or with fewer patients would greatly speed trials and clinical development of new treatments.

Fojo and colleagues developed population kinetics-based equations that calculate separate tumor growth (***g***) and regression (***d***) rate constants to estimate the overall change in tumor burden over time, "***g***," estimated using serum PSA measurements. This has been shown to be strongly predictive of OS in a data set containing over 12,000 patients with CRPC, from the VA, Project Data Sphere and abiraterone registration data.

g was also evaluated in a cohort of >5000 veterans with CRPC treated with abiraterone or enzalutamide, and after switching from one to the other.[80] ***g*** was similar in patients receiving first-line treatment with abiraterone or enzalutamide, and found both abiraterone and enzalutamide to be less effective when used in second-line compared to their use in first-line. Among patients switching from abiraterone to enzalutamide, ***g*** slowed in ~33%, but accelerated in ~66%, demonstrating that about 2/3 of patients may have done better if they had remained on abiraterone. This suggests that ***g*** can serve as a patient's own internal control and may help to determine if and when they should switch treatments.

In a separate study, estimates of ***g*** are being used to assess the benefit from olaparib in patients with mCRPC, by comparing ***g*** values estimated during olaparib administration and comparing these values to the ***g*** values on the therapy before olaparib (abiraterone, enzalutamide, docetaxel, or cabazitaxel). Recognizing successive therapies are invariably less effective, the metric for success is a ***g*** value (or the estimated tumor doubling time) that is better on olaparib than the previous therapy.

An FDA-led study evaluated the correlation between OS and ***g*** calculated from radiologic tumor measurements, using retrospective pooled data from nearly 10,000 metastatic non-small cell lung cancer patients from 24 randomized clinical trials. ***g*** was shown to inversely correlate with OS. Collectively, these data have prompted the FDA to request prospective studies evaluating ***g*** as a surrogate endpoint for OS.

Fojo and colleagues have also demonstrated the value of ***g*** as a biomarker of OS when ***g*** is estimated from radiologic tumor measurements in patients with NSCLC, breast cancer, colorectal cancer, pancreatic cancer, and other solid tumors. The potential value of this approach in reducing the size of clinical trials was demonstrated using data from a trial comparing FOLFIRI ± aflibercept in patients with colorectal cancer.[81] Simulations performed using data from the VELOUR trial found that only 23 patients would have been needed to predict superiority with 80% power.

These studies demonstrate that ***g*** is a highly promising surrogate biomarker for OS, can discriminate between two trial arms, may help to inform go/no-go decisions in small cohorts, and that ***g*** determinations using existing data may enable the reduction in size or even elimination of control arms. The VA patient data cores discussed by Lynch (above) offer an excellent opportunity to study ***g*** and develop virtual control arms for clinical trials.

Michael Spencer (Janssen Oncology) discussed the use of real-world evidence in driving stakeholder decisions in oncology. Real-world data are often variable, as the types of data and time points collected may not be standardized. However, understanding the real-world impact of treatments is critical for guiding decisions by policymakers, regulators, health technology assessment (HTA) bodies and payers, and patients.

Political rhetoric and policies on health care are often not supported by the data. For instance, there is an assumption that oncology is highly expensive; however, data show that oncology healthcare spending when compared to DALYs lost is lower than for other diseases such as cardiovascular disease and diabetes. Ensuring availability and appropriate communication of relevant data will help to improve policymaker decisions and accountability.

The FDA and other regulators have used real-world evidence to inform regulatory strategies, in surveillance of safety and efficacy of treatments following approval, and for guiding approval and pre-approval decisions. Real-world evidence is used by HTA bodies and payers to determine the relative efficacy, value, impacted population size and description, and unmet need of a new treatment, and inform decisions on reimbursement. For example, data on the prevalence and clinical outcomes of patients with mCRPC with DNA repair defects could inform decisions about reimbursement for recently approved PARP inhibitors. As regulators increasingly accept single-arm trials for determinations about new treatments (such as CD19-CAR T cells), HTA bodies and payers will increasingly rely on real-world evidence as the external standard of care controls. HTA bodies and payers often model the economic impact of a treatment (such as cost or quality-adjusted-life-year metrics), based on trial data and external evidence. However, the curve-fitting assumptions used can produce models with high uncertainty, that could be improved by careful use of real-world data. Real-world evidence can also be used to assess the relevance of clinical trial endpoints by evaluating their associations with other meaningful and longer-term outcomes in patients.

Multistakeholder consortia that include regulators, HTA bodies and payers, and patient groups brought together in pre-competitive settings are opportunities for developing evidence frameworks and reference models for assessing treatments and technologies, determining unmet needs, and creating alignment for collecting, analyzing, interpreting, and using real-world data in healthcare decision making. For example, PIONEER was a consortium created to assess new prostate cancer technologies in early-line settings, utilization of emerging prognostic/predictive endpoints and tools, adoption of technologies with co-diagnostics, and the value and flexibility of new technologies. Successful use of real-world data depends on data quality, the source population, methods of data collection and analysis, and requires consistency. It is hoped that lessons learned from the use of real-world data during the COVID-19 pandemic will provide a roadmap for improving and increasing the use of real-world data in other diseases by various stakeholders, and result in a new

paradigm of using real-world evidence to guide and support critical real-time decision making around the world.

16 | ONCOLOGY: A STORIED PAST AND PORTENTOUS FUTURE

Anna Barker (Lawrence J. Ellison Institute for Transformative Medicine of the University of Southern California) discussed the history, current status, and future outlook of oncology research. The history of cancer research can be divided into eras, based on the major research foci and information and technologies available at the time.

The earliest era focused on oncogene and tumor suppressor gene discovery work that was spurred by the discovery of the Rous Sarcoma virus by Peyton Rous and colleagues (1909–1911), and advances in cellular and molecular biology methodologies. Landmark discoveries during this era included those of v-SRC as the first oncogene (1950s), early retrovirus research (1960s), the reverse transcriptase gene (1970s), the ability of retroviruses to integrate into the host genome and produce oncogenes (1976), of p53 (1979) and its function as tumor suppressor (1989), and of the RAS oncogene (1982).

The National Cancer Act (1971) heralded the next era of cancer research, which focused on somatic alterations. Chemotherapy became the standard of care treatment for many cancers and hormone therapy was introduced (1970s). Many more oncogenes and their mechanisms were identified, including HER in breast cancer and HPV genes (1980s). In addition, targeted therapies such as Gleevec (FDA-approved in 2002) became a focus of research and development.

The Human Genome Project (1990) initiated the third era of cancer research. The first complete human genome was sequenced by ~1999, and published in 2004. In 2005, the Cancer Genome Atlas (TCGA) project was launched, co-led by Barker (NCI) and Francis Collins (NHGRI). TCGA resulted in the sequencing of genomes from over 30 cancer types, including rare cancers, and the creation of an open-access database that remains one of the richest cancer genomics databases. In 2008, TCGA published its first paper, on the genomic landscape of glioblastoma multiforme.[82] Major findings from this paper included the ability to group tumors into molecular subclasses, and genomic confirmation of the importance of oncogenes and tumor suppressor genes in cancer, as alterations in *RAS*, *TP53*, and *RB* pathways occurred in most glioblastoma multiforme cases. Moreover, this study made the seminal discovery that every cancer case has a unique set of genomic alterations.

In present-day cancer research, there is a wealth of data, with up to a TB of data generated per patient, and ~1 Exabyte of genomics data generated per year. Cancer is a complex adaptive system, consisting of many dynamic, interacting, and self-organizing agents with both dependent and independent behaviors, that drive emergent properties and co-evolution between tumor cells and their environments. Unifying theories and strategies are needed to leverage these data, to better understand cancer and develop improved interventions which avoid unintended consequences. Information Theory, founded by Claude Shannon in the 1940s, is the study of how to mathematically define information and distinguish it from entropy, how to process and transmit it, and how to use context to resolve uncertainty and make accurate predictions that outperform chance. Based on Shannon Information Theory, cancer can be understood as a disease of dysregulated communications. Barker predicts that the next era of cancer research will be information-informed oncology, in which integrating and applying methods including Shannon Information Theory, AI, and physics, mathematics, and engineering approaches to the vast amounts and types of cancer data, will enable the development of strategies and unifying theories for new cancer research solutions. Complex information-rich fields that are likely to benefit from this approach include cancer immunology and immunotherapy, molecular imaging, and digital pathology. Such approaches will enable improvements in cancer diagnostics, precision medicine, real-time therapeutic response measurements, and improved survivorship care. For example, self-monitoring smart devices will enable real-time reporting and improve predictions of the timing of recurrences and other events.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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