5500 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

TheraP: A randomised phase II trial of ^{177}Lu-PSMA-617 (LuPSMA) theranostic versus cabazitaxel in metastatic castration resistant prostate cancer (mCRPC) progressing after docetaxel: Initial results (ANZUP protocol 1603).

Michael S Hofman, Louise Emmett, Shahneen Kaur Sandhu, Amir Iravani, Anthony M. Joshua, Jeffrey C. Goh, David A. Pattison, Thean Hsiang Tan, Ian D. Kirkwood, Siobhan Ng, Roslyn J. Francis, Craig Gedye, Natalie K. Rutherford, Alison Yan Zhang, Margaret Mary McJannett, Martin R. Stockler, John A. Violet, Scott Williams, Andrew James Martin, Ian D. Davis; Peter MacCallum Cancer Centre, Melbourne, Australia; Department of Theranostics and Nuclear Medicine, St. Vincent's Hospital, Sydney, Australia; St Vincent's Hospital, Sydney, Australia; Royal Brisbane and Women's Hospital, Herston, Australia; Royal Brisbane and Women's Hospital, Brisbane, Australia; Royal Adelaide Hospital, Adelaide, Australia; Sir Charles Gairdner Hospital, Perth, Australia; Calvary Mater Newcastle, Waratah, Australia; Calvary Mater Newcastle, Newcastle, Australia; NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia; Australian and New Zealand Urogenital and Prostate Cancer Trials Group, Camperdown, NSW, Australia; Monash University Eastern Health Clinical School, Victoria, Australia

Background: LuPSMA is a radiolabeled small molecule that delivers therapeutic β-radiation to PSMA-expressing tumors. Encouraging efficacy and safety has been shown in non-randomized studies of mCRPC. TheraP is a randomized phase II trial comparing LuPSMA vs cabazitaxel in men with mCRPC progressing after docetaxel. **Methods:** Men with mCRPC, and imaging with ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT that confirmed high PSMA-expression and no sites of FDG-positive/PSMA-negative disease, were randomly assigned (1:1) to LuPSMA (6-8GBq q6weeks up to 6 cycles) vs cabazitaxel (20mg/m^2 q3weeks up to 10 cycles); stratified by disease burden ($>$20 vs $\leq$20 sites), prior novel antiandrogens (NAA; abiraterone or enzalutamide), and study site. The primary endpoint was PSA response rate (PSA50-RR) defined by $\geq$50% reduction. Secondary efficacy endpoints included PSA-progression-free survival (PSA-PFS) and overall survival (OS). Data cut-off was 31DEC19 at this first pre-specified analysis. **Results:** 200 (median age 72 y, prior NAA 91%, $>$20 lesions 78%) of 291 PET screened men were randomised to LuPSMA (N=99) or cabazitaxel (N=101). 17 patients withdrew or died before receiving study treatment (1 LuPSMA vs 16 cabazitaxel). The PSA50-RR was higher in those assigned LuPSMA than cabazitaxel (65/99 [66%; 95%CI 56-75] vs 37/101 [37%; 95%CI 27-46]; P$<$0.001). At a median follow-up of 11.3 months, LuPSMA significantly improved PSA-PFS (HR 0.63, 95%CI 0.45-0.88, P=0.007; 143 events with next pre-specified analysis planned after 170 events). Efficacy results were similar when analyses were restricted to per-protocol treated men. OS data remains immature (57 deaths). Grade III-IV adverse events (AEs) occurred in 31/98 (32%) LuPSMA-treated men vs 42/85 (49%) in cabazitaxel-treated men. Discontinuations for toxicity occurred in 1/98 (1%) LuPSMA vs 3/85 (4%) cabazitaxel-treated. There were no treatment-related deaths. **Conclusions:** In men with docetaxel-treated mCRPC, LuPSMA was more active (PSA50-RR) than cabazitaxel with relatively fewer G3-4 AEs and PSA-PFS favoring LuPSMA. Clinical trial information: NCT03392428. Research Sponsor: None.

5501 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

Impact of PSMA-targeted imaging with 18F-DCFPyL-PET/CT on clinical management of patients (pts) with biochemically recurrent (BCR) prostate cancer (PCa): Results from a phase III, prospective, multicenter study (CONDOR).

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Background: Current imaging modalities are inadequate for localizing and characterizing occult disease in men with BCR PCa, particularly in pts with low PSAs ($<$2 ng/mL). There is a need for improved diagnostic imaging to better inform treatment planning. ^{18}F-DCFPyL (PyL) is a novel PET imaging agent that binds selectively with high affinity to PSMA, which is overexpressed in PCa cells. **Methods:** Men $\geq$18 years- with rising PSA after definitive therapy and negative or equivocal standard of care imaging (e.g., CT/MRI, bone scintigraphy) were enrolled. A single 9 mCi (333 MBq) $\pm$ 20% dose of PyL was injected, followed by PET/CT 1-2 hours later. Primary endpoint was correct localization rate (CLR), defined as percentage of pts with a 1:1 correspondence between at least one lesion identified by PyL-PET/CT and the composite standard of truth: pathology, correlative imaging, or PSA response. The trial was successful if the lower bound of the 95% confidence interval (LLCI) for CLR exceeded 20% for two of three independent, blinded central PyL-PET/CT reviewers. The secondary endpoint, impact of PyL-PET/CT on clinical management of pts was based on the treating physician's documented clinical plans before and after PyL-PET/CT. **Results:** 208 men (median PSA 0.8 [0.2 - 98.4] ng/mL) underwent PyL PET/CT. The study achieved its primary endpoint: CLR of 84.8% to 87.0% among the three PyL-PET/CT readers; the LLCI for CLR by all three reviewers was $>$77%. Here we report the clinical impact. Based on local radiology assessment, PSMA-avid lesion(s) were identified in 69.3% (142/208) of pts. 63.9% (131/205) had a change in intended management after PyL-PET/CT, of which 78.6% (103/131) were attributable to positive PyL finding(s) and 21.4% (28/131) to negative PyL scans. Changes included: salvage local therapy to systemic therapy (n=58); observation before initiating therapy (n=49); noncurative systemic therapy to salvage local therapy (n=43); and planned treatment to observation (n=9). PyL was well tolerated with one drug-related SAE (hypersensitivity) and the most common AE being headache (n=4; 1.9%). **Conclusions:** PSMA-targeted PyL-PET/CT detected and localized occult disease in most men with BCR presenting with negative or equivocal conventional imaging. PyL-PET/CT led to changed management plans in the majority of pts, thus providing evidence that clinicians find PSMA PET imaging useful in men with recurrent or suspected metastatic PCa. Clinical trial information: NCT03739684. Research Sponsor: Progenics Pharmaceuticals, Inc.

5502 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

Accuracy of 68Ga-PSMA-11 for pelvic nodal metastasis detection prior to radical prostatectomy and pelvic lymph node dissection: A multicenter prospective phase III imaging study.

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Background: To determine the accuracy of 68Ga-PSMA-11 PET for the detection of pelvic nodal metastases (N1) compared to histopathology at time of radical prostatectomy (RP). **Methods:** This is a prospective multicenter single-arm open-label phase 3 imaging trial. Patients with intermediate to high risk prostate cancer (PCa) considered for RP with lymph node dissection (PLND) were enrolled at the University of California, Los Angeles (UCLA) and at the San Francisco (UCSF) (NCT03368547, NCT02611882, NCT02919111), and underwent one 68Ga-PSMA-11 PET. The primary endpoint was the sensitivity (Se) and specificity (Sp) of 68Ga-PSMA-11 PET for the N1 detection compared to PLND histopathology (reference-standard) on a per patient basis using nodal region-based correlation. Each scan was read by three blinded independent central readers (BICR). Consensus was based on majority rule. **Results:** From December 2015 to August 2019, 633 patients underwent one 68Ga-PSMA-11 PET for primary staging, and 277/633 (44%) subsequently underwent RP and PLND. The median initial PSA was 11.1 [0.04-147]. 75/277 patients (27%) had N1 disease per histopathology. Using a regional based analysis, Se, Sp, positive predictive value (PPV) and negative predictive value (NPV) for N1 detection was 0.40 [0.34, 0.46], 0.95 [0.92, 0.97], 0.75 [0.70, 0.80], 0.81 [0.76, 0.85], respectively. Se was higher for patients with higher PSA: 0.29 [0.24, 0.35] for PSA $<$ 11 ng/ml versus 0.48 [0.42, 0.54] for PSA $>$ 11. Se was higher when the nodes were larger: 0.30 [0.25, 0.36] for nodes $<$ 10 mm versus 0.68 [0.63, 0.74] for nodes $>$ 10. The average node size in true positive patients was 10 mm versus 4 mm in false negative patients. **Conclusions:** In intermediate to high risk PCa patients who underwent RP and PLND, 68Ga-PSMA-11 PET detected pelvic nodal metastases with a sensitivity of 0.40 and a specificity of 0.95. Higher PSAs and larger node size correlated with increased sensitivity. Clinical trial information: NCT03368547, NCT02611882, NCT02919111. Research Sponsor: Prostate Cancer Foundation.

5503 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Results of a phase II trial of intense androgen deprivation therapy prior to radical prostatectomy (RP) in men with high-risk localized prostate cancer (PC).

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Background: Patients with high-risk localized PC have an increased risk of recurrence and death despite treatment. Abiraterone acetate (AA), a potent CYP17 inhibitor, and apalutamide, a next generation anti-androgen, have each demonstrated improved overall survival in metastatic PC. In this multicenter randomized phase II trial we investigate the impact of intense androgen deprivation on RP pathologic response (NCT02903368). **Methods:** Eligible patients had a Gleason score ≥4+3=7, PSA >20 ng/mL or T3 disease (by prostate MRI) and lymph node <20 mm. During Part 1 of the study, patients were randomized 1:1 to AA + prednisone + apalutamide + leuprolide (APAL) or AA + prednisone + leuprolide (APL) for 6 cycles (1 cycle=28 days) followed by RP. All RPs underwent central pathology review. The primary endpoint was the rate of a pathologic complete response (pCR) or minimum residual disease (MRD, tumor ≤5 mm). Secondary endpoints include PSA response, surgical staging at RP, positive margin rate, and safety. **Results:** 118 patients were enrolled at four sites. Median age was 61 (range 46-72) years. The majority of patients had NCCN high-risk disease [n=111, 94%; T3 n=73 (62%), Gleason 8-10 n=84 (71%), PSA >20 ng/mL n=28 (24%)]. 114 (97%) patients completed 6 therapy cycles followed by RP. Median PSA nadir was <0.01 versus 0.02 ng/mL and time to nadir was 4.2 versus 4.6 months in the APAL and APL arms, respectively. RP outcomes are displayed in Table. The combined pCR or MRD rate was 21.8% in the APAL arm and 20.3% in the APL arm (p=0.85). 13 (11%) patients (8 in APAL; 5 in APL) experienced grade 3 treatment-related adverse events (TrAEs). The most common grade 3 TrAEs were hypertension (5%), elevated ALT (3%) and elevated AST (3%). No grade 4 or 5 TrAE was reported. **Conclusions:** Intense neoadjuvant hormone therapy followed by RP in men with high-risk PC resulted in favorable pathologic responses (<5 mm residual tumor) in 21% of patients. Pathologic responses were similar between the treatment arms. Follow-up is necessary to evaluate the significance of a pathologic response on recurrence rates. Part 2 of this trial will investigate the impact of an additional 12 months of APAL post-RP on biochemical recurrence. A phase 3 trial investigating neoadjuvant apalutamide + leuprolide prior to RP is ongoing. Clinical trial information: NCT02903368. Research Sponsor: Janssen.

Pathologic outcomes at RP.

	APAL (N=55)	APL (N=59)
ypT2	21 (38%)	19 (32%)
ypT3	27 (49%)	34 (58%)
Positive Margins	4 (7%)	7 (12%)
Positive Seminal Vesicles	15 (27%)	16 (27%)
Positive Lymph Nodes	4 (7%)	10 (17%)
pCR	7 (13%)	6 (10%)
MRD	5 (9%)	6 (10%)

5504 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

Neoadjuvant apalutamide (APA) plus leuprolide (LHRHa) with or without abiraterone (AA) in localized high-risk prostate cancer (LHRPC).

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Background: Novel androgen signaling inhibitors (ASI) with medical castration may improve outcomes in LHRPC. We previously reported relapse free survival association with pathologic measures of tumor regression. However a wide range of persistent cancers was recorded. To build on our findings and test candidate predictors of outcome, we conducted a study examining APA effect in LHRPC. **Methods:** This is a phase II neoadjuvant study of 6 months APA+LHRHa +/- AA (randomized 1:1) in LHRPC ($\geq$ cT2 + Gleason Score $\geq$ 8 or $\geq$ cT2b + Gleason $\geq$ 7 + PSA $>$ 10 ng/mL) followed by radical prostatectomy (RP). We studied treatment effect by pathology measures [path. stage, tumor volume (TV), tumor cellularity % (TC), tumor epithelial volume (TEV: TC x TV)]. Tumor expression of candidate markers of outcome was assessed in the diagnostic biopsy by IHC [AR signaling (AR-N, ARC19, ARV7, PSA), PTEN, glucocorticoid receptor (GR), Ki67, p53, RB] and DNA/RNA seq. A previously identified candidate predictive molecular signature (AR-N overexpression, nARV7 absence, no GR overexpression, Ki67 $\leq$10%) was tested. Univariate (Fisher's exact, Wilcoxon) and multivariate (logistic, linear models) analyses employed. **Results:** Sixty three -of 65 pts enrolled- had RP. PS-ECOG 0, median age 65 (43-77). Treatment was well tolerated with Grade 3 hypertension in 7 (2 APA + LHRHa). Presurgical PSA was $\leq$0.1 in 62/63 (98%). Organ confined disease ($\leq$ypT2N0) found in 13/32(41%) APA+LHRHa vs. 12/31 (39%) APA+AA+LHRHa treated. 2 (3%) had pathologic complete remission (APA+AA+LHRHa), 6 (10%) minimal residual disease (5 on APA +LHRHa). Despite uniformity in PSA response, we recorded heterogeneity in measures of tumor viability: TV (0-11.5cc), TC (1-80%), TEV (0-6.1cc). $\leq$ypT2N0 associates with diagnostic biopsy positivity for the prespecified molecular signature ($p < 0.0001$), PTEN expression (p: 0.004), absence of cribriform/ intraductal spread (p 0.002) but not with Gleason Score. On multivariate analysis only the prespecified biopsy signature associates with outcome (p 0.003). Findings were replicated when analyzed by TV, TC and TEV measures. **Conclusions:** Neoadjuvant Apalutamide plus LHRHa is tolerable and results in tumor regression in a subset of LHRPC patients. Dual ASI treatment does not further improve outcomes. Biopsy positive for a prespecified molecular signature, associated with response. Study results emphasize the need to consider biologic heterogeneity and pursue validation of predictors of response in order to improve therapeutic outcomes in LHRPC. Clinical trial information: NCT03279250. Research Sponsor: Prostate Cancer Foundation, Pharmaceutical/Biotech Company, U.S. National Institutes of Health.

5505 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

Phase II randomized study of abiraterone acetate plus prednisone (AAP) added to ADT versus apalutamide alone (APA) versus AAP+APA in patients with advanced prostate cancer with noncastrate testosterone levels: (LACOG 0415).

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Background: ADT combined with AAP, APA, enzalutamide or docetaxel are among the standard treatment options to patients (pts) with hormone sensitive advanced/metastatic prostate cancer (PC). However, treatment-related adverse events (TRAEs) due to ADT impact negatively on the quality of life of these patients. Effective options with fewer TRAEs are required. **Methods:** LACOG 0415 is a phase II, randomized trial (1:1:1) evaluating the use of AA 1000mg po + prednisone 5mg po BID + ADT versus APA 240mg po alone versus AA 1000mg po + prednisone 5mg po BID + APA 240mg po in patients with advanced PC with non-castrate testosterone levels and indication of ADT (N+ or M+ or biochemical relapse combined with PSA $\geq$ 20 ng/ml or with PSA$\geq$4 ng/ml and PSA doubling-time $<$ 10 months). Stratification factors: metastatic disease (+/-). Primary endpoint was the percentage of pts who achieved PSA $\leq$ 0.2 ng/mL at Week 25, we estimated a PSA response rate of 65% in each of the three arms with a null hypothesis of 45%, power of 80% and alfa 5%, using Fleming one-stage method. Secondary endpoints were percentage of pts with $\geq$ 80% and $\geq$ 50% decline in PSA at week 25, radiographic progression-free survival (rPFS) and safety. **Results:** 128 patients were randomized between Oct 2017 and Apr 2019, and 122 pts were evaluable for PSA response. Median age was 69y (range, 53-88); most pts had ECOG PS0-1(99%). 17% of pts had biochemical relapse only, 9% N+ and 74% M+ disease. At week 25 the PSA was $\leq$ 0.2 ng/mL in 76% of pts in AAP+ADT arm, 59% in APA, and 80% in APA+AAP. All pts had a decline of $\geq$ 50% in PSA at week 25. 97% had a decline of $\geq$ 80% in PSA at week 25: 100% of pts in AAP+ADT arm, 95% in APA and 98% in APA+AAP. A total of 3 pts had clinical progressive disease, one in each arm. Two of them also had radiological progression at week 25, 1 pt in AAP+ADT arm and 1 pt in APA. TRAEs rates of any grade were 71% in AAP+ADT arm, 64% in APA, and 65% in APA+AAP. TRAEs rates of Grade$\geq$3 were 12% in AAP+ADT arm, 9% in APA and 16% in APA+AAP. 9 pts (7%) discontinued the treatment before the week 25, 5(4%) of them due to toxicity: 1 pt from AAP+ADT, 2 pts from APA, and 6 pts from APA+AAP. **Conclusions:** The AAP+ADT and APA+AAP groups showed high effectiveness in terms of PSA response. Radiologic disease control and the decline of $\geq$ 80% in PSA at week 25 were similar among all treatment arms. APA alone had less toxicity. APA+AAP and APA alone are promising regimens in this setting. No new safety signal was detected in the study. Clinical trial information: NCT02867020. Research Sponsor: Janssen.

5506 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Baseline circulating tumor cell (CTC) count as a prognostic marker of PSA response and progression in metastatic castrate sensitive prostate cancer (mCSPC): Results from SWOG S1216, a phase III randomized trial of androgen deprivation plus orteronel (cyp17 inhibitor) or bicalutamide.

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Background: In mCSPC, androgen deprivation therapy (ADT) combined with chemotherapy or androgen receptor signaling inhibition (ARSI) is the new standard of care. Biomarkers that predict clinical outcomes with these therapies are needed. We hypothesized that CellSearch CTC count, an FDA-cleared biomarker in metastatic castrate resistant PC (mCRPC), may be a valuable biomarker in mCSPC. **Methods:** In S1216, peripheral blood was drawn with informed consent at registration (baseline), and CTCs were enumerated on the FDA-cleared CellSearch platform (Menarini) per standard manufacturer protocol. CTC counts were analyzed centrally for associations with 2 pre-specified trial intermediate endpoints: 7-month PSA (7mPSA) $\leq$ 0.2 ng/ml vs. 0.2–4.0 vs. $>$ 4.0, (intermediate endpoint for overall survival, OS); and progression-free survival (PFS) $<$ vs. $>$ 2 years. Because OS data have not matured, analysis was pooled and equal numbers of samples were analyzed from each treatment arm and outcome measure (7mPSA and PFS) as stipulated by the Data Safety Monitoring Committee. **Results:** From 2014 to 2017, 523 baseline samples were collected. In the 7mPSA analysis (n = 264), CTCs were detected in 38% of men, with a median of 4 CTCs in those with detectable CTCs. In the PFS analysis (n = 336), CTCs were detected in 37% of men, with a median of 3 CTCs in those with detectable CTCs. Adjusting for disease burden (minimal vs. extensive) and ADT status (already initiated or not) at the time of CTC measurement, men with undetectable CTCs were 6.1-fold more likely to attain 7mPSA $\leq$ 0.2 (OR 6.1, 95% CI 2.1-17.2, $p < 0.001$) and 3.7-fold more likely to achieve $>$ 2 years PFS (OR 3.7, 95% CI 1.7-8.1, $p < 0.001$) compared to men with baseline CTCs $\geq$ 5. Other cutpoints previously validated in mCRPC studies (CTC $<$ 5 vs. $\geq$5 and CTCs 0 vs. $\geq$1) also strongly discriminated 7mPSA and PFS with statistical significance in this mCSPC cohort. **Conclusions:** CTC count at the start of treatment for mCSPC was highly prognostic of 7-month PSA response (intermediate endpoint for OS) and of PFS at 2 years. To our knowledge, this is the first such strong evidence from a prospective phase 3 trial of this magnitude. Additional analyses are planned when the trial is fully reported. Baseline CTC count may serve as a valuable prognostic marker to discriminate men likely to respond favorably to hormonal therapies from those who may benefit from early alternate interventions. Research Sponsor: U.S. National Institutes of Health.

5507 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

The comprehensive methylation landscape of metastatic castration-resistant prostate cancer (mCRPC) identifies new phenotypic subtypes: Results from the West Coast Prostate Cancer Dream Team (WCDT).

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Background: While recent studies have delineated the genomic landscape of mCRPC, its epigenomic landscape has not been as well characterized. The goal of this study was to define the comprehensive methylation landscape of mCRPC. **Methods:** mCRPC patients (pts) underwent a metastasis biopsy as part of a multi-institutional study (NCT02432001). Deep whole-genome bisulfite sequencing (mean depth 46x) was performed on fresh frozen tissue from 100 mCRPC patients; data was paired with deep whole-genome and transcriptome sequencing from the same samples. Unbiased hierarchical clustering of the mCRPC methylome was undertaken, and the survival of patients in each cluster was calculated using the Kaplan Meier method. **Results:** Unbiased hierarchical clustering revealed several distinct subtypes. 22% of mCRPC samples exhibited a novel epigenomic subtype associated with hyper-methylation. This hypermethylated (HM) cluster was significantly associated with somatic mutations in genes known to be involved in methylation, eg *TET2* and *DNMT3B*, as well as in genes in which mutations have been associated with hyper-methylation in other cancer types (*IDH1* in glioblastoma and *BRAF* in colon cancer). mCRPC survival was 56.1 mos in pts with HM cancers compared to 35.6 mos in non-HM ($p = .055$). Methylome clustering also identified a unique cluster comprised of all patients with treatment-induced small cell/neuroendocrine cancer, a subtype previously associated with poor survival. **Conclusions:** This integrated study of whole-genome, whole methylome and whole-transcriptome sequencing provides the first comprehensive overview of the important regulatory role of methylation in metastatic castration-resistant prostate cancer, and has identified at least two distinct subtypes. The clinical and therapeutic implications of methylation subtypes should be explored in future studies. Clinical trial information: NCT02432001. Research Sponsor: Prostate Cancer Foundation; Stand Up to Cancer.

5508 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

Circulating tumor DNA (ctDNA) dynamics associate with treatment response and radiological progression-free survival (rPFS): Analyses from a randomized phase II trial in metastatic castration-resistant prostate cancer (mCRPC).

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Background: ctDNA can inform on prognosis, treatment response and survival. We evaluated ctDNA in serial plasma samples from patients enrolled in A.MARTIN (NCT01485861), a randomized phase II study of abiraterone with or without ipatasertib in patients with mCRPC. **Methods:** Blood was collected in cell-free DNA Streck tubes from 216 patients at 3 time points; baseline, C3D1 and end of treatment. Cell-free DNA (cfDNA) was extracted from plasma using a Circulating DNA Kit (Qiagen) on a QIASymphony machine (Qiagen). 25ng of extracted cfDNA was used in library preparation, constructed with a custom designed, 58 gene, QIAseq Targeted DNA panel (Qiagen) enriched for PI3K/AR pathway genes. Samples were sequenced to mean depth of 3394x on a NextSeq500 machine. Unless otherwise noted, all analyses combine patients across the 3 study arms, and reported p-values are unadjusted. **Results:** Baseline (BL) ctDNA positivity correlated with radiological progression-free survival (rPFS; HR: 1.8 [95% CI 1.3-2.6], $p < 0.01$); this association with rPFS was maintained in a multivariate cox model with > 5 baseline clinical variables (HR: 1.6 [95% CI 1.1-2.4]; $p = 0.011$). Patients with a C3D1 reduction in ctDNA had superior rPFS compared to patients with a C3D1 increase in ctDNA (HR: 2 [95% CI 1.3-3.2], $p < 0.01$). The rate of ctDNA clearance at C3D1 was higher in the Ipatasertib 400mg arm compared to placebo (56.3% versus 24.4%, $p < 0.01$). We find that changes in ctDNA associated with best confirmed overall response ($p = 0.024$); CR patients had the greatest reduction in ctDNA (mean of -23.4%), followed by PR (-16.3%), then SD (-4.1%), and lastly PD patients (-1.3%). Changes in ctDNA levels correlated with SLD changes ($rs = 0.289$, $p = 0.05$), and also PSA changes ($rs = 0.33$, $p < 0.01$). Changes in ctDNA were associated with rPFS in a multivariate cox analysis that included PSA change ($p < 0.01$), as well as in a separate multivariate analysis that included SLD change ($p < 0.01$). Lastly, we explored CNVs and observed emerging resistance mutations in progression samples, including alterations in *TP53*, *AR*, *FOXA, PTEN*, and *PI3K/AKT* pathway genes. **Conclusions:** ctDNA analyses may help (i) identify poorer prognosis disease at baseline, (ii) inform on treatment response (CR/PR/SD/PD) and radiological progression free survival (rPFS) in on-treatment (C3D1) samples, and (iii) can elucidate emerging resistance mechanisms at disease progression. Clinical trial information: NCT01485861. Research Sponsor: Roche.

5509 Poster Discussion Session; Displayed in Poster Session (Board #90), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Prostate cancer relative survival by stage and race/ethnicity, United States, 2001 to 2015.

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Background: Prostate cancer is the most common cancer diagnosed and the second leading cause of cancer-related deaths among U.S. men. Incidence rates for distant stage cancer increased during 2010–2014, and survival at all stages was lower for black men than white men. We examined temporal changes in survival by race/ethnicity. **Methods:** Five-year relative survival (RS) (cancer survival in the absence of other causes of death) was calculated for men with prostate cancer aged ≥40 years using National Program of Cancer Registries data (93% U.S. population coverage). Cancers were diagnosed during 2001–2015 with follow-up through 2015. RS was estimated by race/ethnicity (non-Hispanic white, non-Hispanic black, and Hispanic), stage, and year (2001–2007 and 2008–2015). Differences were determined by non-overlapping 95% confidence intervals (CI). **Results:** During 2001–2015, 2,234,233 cases were recorded. Five-year RS was 100% for localized disease in all race/ethnicities and time periods. Overall, RS improved from 29.0% (95% CI, 28.5–29.5) to 31.3% (30.8–31.9) for distant stage and 83.4% (83.0–83.8) to 84.7% (84.2–85.1) for unknown stage. For regional stage, RS improved for white men (table). For distant stage, RS was highest for black and Hispanic men. For unknown stage, RS was highest for white and Hispanic men. **Conclusions:** RS improved for regional, distant, and unknown stage, but disparities by race/ethnicity persist. The disparity between black and white men for distant stage reversed compared to past studies. Further investigation of diagnosis patterns and clinical characteristics of men with distant and unknown stage cancer could inform interventions to address disparities in outcomes. Research Sponsor: None.

Stage	Race/ ethnicity	No., 2001–2007	RS (95% CI), 2001–2007	No., 2008–2015	RS (95% CI), 2008–2015
Regional	White	100,214	97.9 (97.7–98.2)	132,175	99.4 (99.1–99.6)
	Black	15,966	98.4 (97.6–98.9)	23,094	99.1 (98.2–99.5)
	Hispanic	7,544	96.8 (95.9–97.5)	11,547	98.1 (97.2–98.7)
Distant	White	36,398	27.5 (27.0–28.1)	53,859	29.4 (28.8–30.1)
	Black	10,784	29.9 (28.9–30.9)	14,774	32.2 (31.1–33.4)
	Hispanic	3,835	35.4 (33.7–37.1)	6,310	38.7 (36.9–40.5)
Unknown	White	83,667	83.2 (82.7–83.6)	61,482	81.1 (80.5–81.7)
	Black	15,645	78.3 (77.2–79.3)	14,914	77.9 (76.7–79.0)
	Hispanic	7,758	81.8 (80.4–83.0)	9,762	86.0 (84.7–87.3)

5510 Poster Discussion Session; Displayed in Poster Session (Board #91), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Assessment and management of cardiovascular risk factors among U.S. Veterans with newly diagnosed prostate cancer.

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Background: Cardiovascular disease (CVD) is a leading cause of death in men with prostate cancer (PC). Androgen deprivation therapy (ADT) is associated with increased CVD risk, and American Heart Association guidelines recommend CVD risk factor assessment and management in PC patients starting ADT. We characterized rates of guideline-concordant assessment and management of CVD risk factors for US Veterans with newly diagnosed PC, according to ADT use and prior atherosclerotic CVD diagnosis. **Methods:** We used cross-sectional data from VA Corporate Data Warehouse to identify Veterans with an incident diagnosis of PC from 2001-2017. Primary outcomes were guideline-concordant baseline CVD risk factor assessment (defined as $\geq$1 blood pressure, cholesterol, and HbA1c or fasting glucose measurement within 1 year prior to 6 months after ADT start or PC diagnosis), CVD risk factor control, and CVD risk-reducing medication use. Risk difference multivariable regression analyses adjusting for age, race, poverty, PC risk category, and year were used to evaluate the effect of ADT on study outcomes. **Results:** Of 191,829 Veterans with newly diagnosed PC, 27% (n = 51,419) were treated with ADT within 1 year of diagnosis, and 18% (n = 34,110) had a pre-existing diagnosis of atherosclerotic CVD. From 2001-2017, annual rates of guideline-concordant CVD risk factor assessment increased from 26% to 77%. In adjusted analyses, pre-existing atherosclerotic CVD diagnosis was associated with higher CVD risk factor assessment rate (64% vs 53%), better control of baseline LDL (94 vs 108 mg/dL), and higher rates of anti-hypertensive (90% vs 66%), lipid-lowering (83% vs 49%), and glucose-lowering (32% vs 20%) medication use. Treatment with ADT was associated with similar to minimally higher rates of CVD risk factor assessment (58% vs 54%), LDL control (104 vs 105 mg/dL), and anti-hypertensive (73% vs 69%), lipid-lowering (55% vs 55%), and glucose-lowering (25% vs 21%) medication use. Sixty percent of men starting ADT had at least one sub-optimally controlled CVD risk factor, and 1 in 4 of these men were not receiving a corresponding risk-reducing medication. One third of men starting ADT had BMI $>$ 30 kg/m2. **Conclusions:** CVD risk factor assessment in Veterans with PC has increased over time. However, ADT does not appear to meaningfully impact CVD assessment or management, despite its known association with CVD risk. Over half of patients initiating ADT had elevated CVD risk factor(s). Multi-disciplinary efforts to improve CVD risk mitigation are needed among men initiating ADT. Research Sponsor: U.S. National Institutes of Health, VA Center for Health Equity Research and Promotion.

5511 Poster Discussion Session; Displayed in Poster Session (Board #92), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

PROREPAIR-A: Clinical and molecular characterization study of prostate cancer (PC) patients with and without previously known germline *BRCA1/2* mutations.

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Background: Germline *BRCA1/2* (g*BRCA1/2*) mutations are associated with poor clinical outcomes in PC. Previous studies showed that g*BRCA2* carriers present more CNV in several genes associated with more aggressive disease. These aberrations may explain the poor clinical outcomes of these patients, but larger studies are needed to confirm these findings. **Methods:** PROREPAIR-A is a multicenter case-control study in which g*BRCA2* carriers with available diagnostic timor-tissue were matched 1:2 by Gleason and stage at diagnosis (M0 vs M1) with known non-carriers (NC). A minimum of 120 controls-60 cases were required to prove a 5yr Cause Specific Survival (CSS)-rate of 85% vs 60%. The primary endpoint was to confirm the independent prognostic value of g*BRCA2* in PC CSS. In addition, we explored the prognostic role of g*BRCA1* and somatic events in *BRCA2*, *RB1*, *MYC*, *PTEN* and *TMPRSS2-ERG* by FISH. X^2, Kaplan-Meier, log-rank and cox-regression models were carried out to identify associations with baseline characteristics and outcomes: Metastases Free Survival (MFS), Time to Castration-Resistance (TTCR) and CSS. **Results:** A total of 80:160 matched cases-controls were initially included, but tumor tissue and clinical data were only available in 73 g*BRCA2* and 127 NC. 14 g*BRCA1* were also included. At diagnosis, g*BRCA2* were younger (median 62.6 vs 64.5, $p = 0.02$) and had cT3-4 disease more often than NC (31.5% vs 9.4%, $p < 0.01$), but no other significant differences were found. Somatic *BRCA2-RB1* codeletion (40.8% vs 11.8%, $p < 0.01$) and *MYC* amplification (51.4% vs 22.8%, $p < 0.01$) were more frequent in g*BRCA2* compared to NC, but no significant differences in *PTEN* and *TMPRSS2-ERG* were observed. g*BRCA2* mutations as well as somatic *BRCA2-RB1* codel and *MYC* amplif were significantly associated with shorter CSS, MFS and TTCR (Table). MVA model confirmed the independent prognostic value of g*BRCA2* (HR 1.94, $p = 0.03$), *BRCA2-RB1* codel (HR 3.16, $p < 0.01$), *MYC* amplif (HR 2.36, $p < 0.01$), Gleason ≥8 ($p < 0.01$) and M1 at diagnosis ($p < 0.01$) for CSS. **Conclusions:** PROREPAIR-A confirmed the independent prognostic value of g*BRCA2* for CSS. Somatic *BRCA2*, *RB1* and *MYC* aberrations were more frequent in g*BRCA2* carriers. Those alterations are associated with shorter CSS, MFS and TTCR, and may contribute to poor clinical outcomes in g*BRCA2* and NC. Research Sponsor: Prostate Cancer Foundation.

	CSS	MFS	TTCR
g*BRCA2* vs NC	110 vs 211 m $p < 0.01$	105 vs NR m $p < 0.01$	105 vs NR m $p < 0.01$
BRCA2-RB1 codel vs No	76 vs 203 m $p < 0.01$	112 vs NR m $p < 0.01$	60 vs NR m $p < 0.01$
MYC amplif vs No	75 vs 211 m $p < 0.01$	114 vs NR m $p < 0.01$	45 vs NR $p < 0.01$

5512 Poster Discussion Session; Displayed in Poster Session (Board #93), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Late toxicities and recurrences in patients with clinical stage I nonseminomatous germ cell tumor after one cycle of adjuvant BEP versus primary retroperitoneal lymph node dissection: A 13-years follow-up analysis of a phase III trial cohort.

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Background: One cycle of adjuvant BEP has shown superiority in recurrence free survival over RPLND in patients (pts) with clinical stage (CS) I nonseminomatous germ cell tumor of the testis (NSGCT) (JCO 2008). We report recurrences and late toxicities of this randomized trial after 13 yrs of follow-up (FU). **Methods:** Questionnaires of 382 unselected pts with CS I NSGCT treated within a phase III trial comparing recurrence rate after 1 cycle of adjuvant BEP (arm A) vs. RPLND (arm B) were evaluated regarding recurrences and late toxicity. Overall (OS) and progression free survival (PFS) was calculated by Kaplan-Meier and arms were compared using logrank test. Categorial data were analyzed by chi-square test (PRISM v8). **Results:** In each arm 191 pts were analyzed as intention-to-treat with a median FU of 13.75 yrs (0-22.9 yrs); 3/191 pts (1.6 %) in arm A and 16/191 pts (8.4 %) in arm B had a recurrence. 20-yrs PFS in arm A / B was 97 % (CI 96-99 %) / 92 % (CI 90-95 %), ($p = .0049$). 20-yrs OS in arm A / B was 90 % (CI 86-94 %) / 88 % (CI 86-94 %), ($p = .83$). 23/382 (6 %) pts have died, 22/23 not related to testis cancer, 1/23 died of a recurrence in arm B. 8/191 pts (4.2 %) in arm A and 4/191 pts (2.1 %) in arm B showed metachronous secondary testis cancer ($p = .26$). 5/191 pts (2.6 %) in arm A and 4/191 pts (2.1 %) in arm B developed other malignancies. 170/382 questionnaires were evaluable (arm A: 95; arm B: 75). 45 pts were lost to FU. There were no significant differences comparing both treatment arms regarding potentially treatment-related late toxicities. However, excluding pre-existing complaints, ototoxicity (9/95 (9 %) vs. 4/75 (5 %) pts, $p = .31$) was reported more frequently in arm A. Excluding pre-existing neurological conditions, peripheral neuropathy of all grades was more frequently reported in arm A (15/95 pts; 16 % vs. 9/75 pts; 12 % pts; $p = .48$). Retrograde ejaculation occurred more frequently after RPLND (9/95 pts; 9% vs. 18/75 pts; 24 %, $p = .01$). **Conclusions:** After more than 13 yrs of FU, recurrences in non-risk factor selected pts with CS I NSGCT remain to be significantly more frequent with RPLND. No excess mortality due to secondary malignancies was observed. Late toxicities did not differ between 1 cycle of BEP and RPLND. Only retrograde ejaculation was observed significantly more frequent after RPLND. With long-term observation, 1 cycle of BEP has not only a high efficacy to prevent recurrence but also seems to be tolerated without clinically relevant long-term toxicity. Research Sponsor: None.

5513 Poster Discussion Session; Displayed in Poster Session (Board #94), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Population-based prostate cancer screening using a prospective, blinded, paired screen-positive comparison of PSA and fast MRI: The IP1-PROSTAGRAM study.

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Background: The prostate-specific antigen (PSA) test can lead to under- and over-diagnosis of prostate cancer and has not been recommended for population screening. A fast MRI scan might overcome the limitations of PSA. IP1-PROSTAGRAM is the first study to evaluate the performance of a 15-minute non-contrast MRI for prostate cancer screening in comparison to PSA. **Methods:** IP1-PROSTAGRAM was a prospective, population-based, screen-positive paired-cohort study. Men aged 50-69 years in the UK were invited for prostate cancer screening through seven primary care practices or community-based recruitment. Participants underwent a PSA and MRI scan (T2-weighted and diffusion). MRI was scored using PIRADS version 2.0 without knowledge of PSA; screen-positive MRI (defined as either PIRADS score 3-5 or 4-5) were compared against a screen-positive PSA defined as $\geq$3ng/ml. If any test was screen-positive, a systematic 12-core biopsy was performed with MRI-ultrasound image-fusion targeted biopsy to MRI suspicious areas, as appropriate. Clinically-significant cancer was defined as any Gleason score $\geq$3+4. The primary outcome was the proportion of screen-positive MRI at different scores; important secondary outcomes were the number of clinically-significant and insignificant cancers detected. **Results:** 2034 men were invited to participate of whom 408 consented and 406 were screened by both PSA and MRI (10/Oct/2018-15/May/2019). The proportion with a screen-positive MRI (score 3-5) was higher than the proportion with a screen-positive PSA (17.7% [95%CI 14.3-21.8] vs. 9.9% [95%CI 7.3-13.2]; $p < 0.001$). A screen-positive MRI (score 4-5) was similar to a screen-positive PSA (10.6% [95%CI 7.9-14.0] vs. 9.9% [95%CI 7.3-13.2], $p = 0.71$). An MRI score 3-5 or 4-5 used to denote a screen-positive MRI, compared to PSA alone, detected 14, 11 and 7 clinically-significant cancers, respectively. There were 7, 5 and 6 clinically-insignificant cancers detected, respectively. No serious adverse events occurred. **Conclusions:** When screening the general population for prostate cancer, MRI using a score of 4-5 to define a screen-positive test, compared to PSA alone at $\geq$3ng/ml, could lead to more men diagnosed with clinically-significant cancer without increasing the number of men biopsied or diagnosed with clinically-insignificant cancer. Clinical trial information: NCT03702439. Research Sponsor: Wellcome Trust, Other Foundation, The Urology Foundation.

5514 Poster Discussion Session; Displayed in Poster Session (Board #95), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Overall survival (OS) results of phase III ARAMIS study of darolutamide (DARO) added to androgen deprivation therapy (ADT) for nonmetastatic castration-resistant prostate cancer (nmCRPC).

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Background: DARO is a structurally distinct androgen receptor inhibitor with a favorable safety profile, approved for treating men with nmCRPC after demonstrating significantly prolonged metastasis-free survival, compared with placebo (PBO), in the phase III ARAMIS trial: median 40.4 vs 18.4 months, respectively (HR 0.41; 95% CI 0.34–0.50; $P<0.0001$). We report final analyses of OS and prospectively collected, patient-relevant secondary endpoints, and updated safety results. **Methods:** 1509 patients (pts) with nmCRPC were randomized 2:1 to DARO 600 mg twice daily (n=955) or PBO (n=554) while continuing ADT. Secondary endpoints included OS, and times to pain progression, first cytotoxic chemotherapy, and first symptomatic skeletal event. The OS analysis was planned to occur after approximately 240 deaths. Secondary endpoints were evaluated in a hierarchical order. **Results:** Final analysis was conducted after 254 deaths were observed (15.5% of DARO and 19.1% of PBO patients). After unblinding at the primary analysis, 170 pts crossed over from PBO to DARO. DARO showed a statistically significant OS benefit corresponding to a 31% reduction in the risk of death compared with placebo. All other secondary endpoints were significantly prolonged by DARO (Table), regardless of the effect of crossover and subsequent therapies on survival benefit. Incidences of treatment-emergent adverse events (AEs) with ≥5% frequency were generally comparable between DARO and PBO, similar to the safety profile observed at the primary analysis. Incidences of AEs of interest (including falls, CNS effects, and hypertension) were not increased with DARO compared with PBO when adjusted for treatment exposure. AEs in the crossover group were consistent with those for the DARO treatment arm. **Conclusions:** DARO showed a statistically significant OS benefit for men with nmCRPC. In addition, DARO delayed onset of cancer-related symptoms and subsequent chemotherapy, compared with PBO. With extended follow-up, safety and tolerability were favorable and consistent with the primary ARAMIS analysis (Fizazi et al, *N Engl J Med* 2019;380:1235-46). Clinical trial information: NCT02200614.Research Sponsor: Bayer AG and Orion Pharma.

Endpoint (median, months)	DARO + ADT (n=955)	PBO + ADT (n=554)	HR (95% CI)	P-value
OS	NR	NR	0.69 (0.53–0.88)	0.003
Time to				
Pain progression	40.3	25.4	0.65 (0.53–0.79)	<0.001
First cytotoxic chemotherapy	NR	NR	0.58 (0.44–0.76)	<0.001
First SSE	NR	NR	0.48 (0.29–0.82)	0.005

5515 Poster Discussion Session; Displayed in Poster Session (Board #96), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Final overall survival (OS) from PROSPER: A phase III, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) in men with nonmetastatic castration-resistant prostate cancer (nmCRPC).

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Background: PROSPER previously demonstrated a statistically significant and clinically meaningful improvement in metastasis-free survival (MFS) (hazard ratio [HR] 0.29; 95% CI 0.24-0.35; $P < .001$) in men with nmCRPC and rapidly rising prostate-specific antigen (PSA) who received ENZA. When first reported, OS was immature with only 165 of 596 (28%) prespecified deaths. Here we report results from the final OS analysis. **Methods:** Men with nmCRPC, PSA doubling time $\leq$ 10 mo, and PSA $\geq$ 2 ng/mL at screening continued androgen deprivation therapy (ADT) and were randomized 2:1 to ENZA 160 mg or PBO. OS treatment effect was assessed using a group sequential testing procedure with O'Brien-Fleming-type alpha spending function ($P \leq .021$ required for statistical significance). Medians were estimated using the Kaplan-Meier method; 95% CIs using a stratified Cox regression model. **Results:** As of Oct 15, 2019 (median follow-up $\approx$ 48 mo), there were 466 deaths (288 [30.9%] and 178 [38.0%] in the ENZA and PBO arms, respectively). ENZA significantly prolonged OS compared with PBO (HR 0.73; 95% CI 0.61-0.89; $P = .0011$). Median OS was 67.0 mo (95% CI 64.0-not reached) in the ENZA arm and 56.3 mo (95% CI 54.4-63.0) in the PBO arm. Subsequent antineoplastic therapies were initiated after treatment discontinuation by 310 (33%) men in the ENZA arm vs 303 (65%) in the PBO arm. Median duration of treatment was 33.9 mo vs 14.2 mo with ENZA vs PBO, respectively. Grade $\geq$ 3 adverse events (AEs) were reported by 48% of men in the ENZA arm vs 27% in the PBO arm (16% vs 6% were drug related, respectively). AEs with event rates per 100 patient-yr that were $\geq$ 2 points higher with ENZA vs PBO were falls (9 vs 4), fatigue (14 vs 12), and hypertension (7 vs 5). **Conclusions:** ENZA treatment resulted in a statistically significant 27% reduced risk of death compared with PBO, demonstrating that initiation of ENZA + ADT before the onset of detectable metastasis improves OS in men with CRPC and rapidly rising PSA. This OS benefit ensues despite crossover from the PBO arm to ENZA and higher rates of subsequent antineoplastic therapies in men from the PBO arm. Safety was consistent with previous clinical trials. This final OS analysis from PROSPER provides prospective validation of MFS as a potential surrogate endpoint for OS in nmCRPC and supports the continued use of ENZA + ADT as a standard of care in men with nmCRPC and rapidly rising PSA. Clinical trial information: NCT02003924. Research Sponsor: Pfizer Inc. and Astellas Pharma, Inc.

5516 Poster Discussion Session; Displayed in Poster Session (Board #97), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Final survival results from SPARTAN, a phase III study of apalutamide (APA) versus placebo (PBO) in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC).

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Background: SPARTAN evaluated APA vs PBO in pts with nmCRPC and a prostate-specific antigen doubling time of $\leq$ 10 mo receiving androgen deprivation therapy (ADT). At primary end point analysis of metastasis-free survival (MFS), APA significantly improved median MFS by 2 yrs, as well as time to metastasis, progression-free survival, and time to symptomatic progression vs PBO (Smith, et al. *NEJM* 2018); overall survival (OS) results were immature. SPARTAN was unblinded upon meeting the primary end point; pts still on PBO were allowed to cross over to APA. Final survival results are reported herein. **Methods:** 1207 nmCRPC pts were randomized 2:1 to APA (240 mg QD) or PBO plus ongoing ADT. At progression, pts could receive open-label sponsor-provided abiraterone acetate + prednisone. After the primary efficacy end point (MFS) was met, 76 PBO pts (19%) crossed over to APA. OS and time to cytotoxic chemotherapy (TTCx) were tested by group sequential testing procedure with O'Brien-Fleming (OBF)-type alpha spending function. Time-to-event end points were analyzed by Kaplan-Meier method and Cox model. A sensitivity analysis for OS, accounting for crossover using a naïve censoring approach, was conducted. **Results:** With follow-up of 52.0 mo, 428 (of 427 required) OS events had occurred. Median treatment duration: APA, 32.9 mo; PBO, 11.5 mo. Median OS was significantly longer with APA + ADT vs PBO + ADT (73.9 vs 59.9 mo), (hazard ratio [HR], 0.784, Table). APA significantly lengthened TTCx (HR, 0.629). Discontinuation rates (APA vs PBO) due to progressive disease were 42.7% vs 73.9%, and due to adverse events (AE) 15.2% vs 8.4%. Safety was consistent with previous reports; grade 3/4 treatment-emergent (TE) AEs of special interest were rash 5.2%, fractures 4.9%, falls 2.7%, ischemic heart disease 2.6%, hypothyroidism 0%, and seizures 0%. 1 TEAE leading to death (myocardial infarction) was considered potentially APA related. **Conclusions:** In pts with nmCRPC, APA + ADT significantly improved OS compared with PBO + ADT, with median OS $>$ 6 yr in the APA + ADT group and 14 mo improvement over PBO + ADT. Benefit from APA was observed despite a 19% crossover from PBO. The safety profile of APA was consistent with prior interim analyses. Clinical trial information: NCT01946204. Research Sponsor: Janssen Research & Development.

End point, median mo	APA + ADT (n = 806)	PBO + ADT (n = 401)	HR	p Value[a]
OS	73.9	59.9	0.784	0.0161[b]
OS (naïve censoring crossover)	73.9	52.8	0.685	0.0002
TTCx	NR	NR	0.629	0.0002

[a]p value from stratified log-rank test.
[b]OBF required p value $\leq$ 0.046 to be considered statistically significant.
NR, not reached.

5517 Poster Discussion Session; Displayed in Poster Session (Board #98), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

TRANSFORMER: Bipolar androgen therapy (BAT) versus enzalutamide (E) for castration-resistant metastatic prostate cancer (mCRPC).

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Background: Rapid cycling between high and low testosterone (T) (i.e BAT) produces tumor response in mCRPC, and may overcome resistance to newer AR therapies. Here we report a randomized study comparing BAT to E in men with mCRPC progressing on abiraterone (A). **Methods:** In this phase 2 trial, men received either T cypionate 400mg IM (BAT) once every 28 days or daily oral E 160mg. Primary endpoint was clinical/radiographic PFS; crossover was permitted at progression. Secondary endpoints were OS, PSA progression to primary and crossover therapy, PSA and objective responses (OR), time to PSA progression from randomization through crossover (PFS2), quality of life (QoL), and AEs. **Results:** 195 men were randomized (94 to BAT, 101 to E). Results are presented in table. Although diametrically opposed therapies, median PFS and PSA response in the intent-to-treat (ITT) population was not significantly different between BAT and E. OR and OS favored BAT. For those who received BAT and then crossed over to E the PSA50 response was 77.8% and time to PSA progression was 10.9 mo compared to 25.3% and 3.8 mo for those receiving E immediately after A. The sequence of treatment had a significant effect on median PSF2 which was 28.2 mo for men receiving BAT→E vs. 19.6 m for E→BAT. For men who crossed over from BAT to E, OS was 37.3 mo vs. 28.6 months for those receiving E without crossover. AEs were primarily grade 1-2 in the BAT arm and included fatigue, generalized pain, and lower extremity edema. BAT improved QoL (fatigue, physical functioning, sexual function) vs. E. **Conclusions:** BAT could be safely administered to asymptomatic men with mCRPC. BAT produced a comparable PFS to E in A-refractory mCRPC pts. However, PSA50 and OR after crossover, as well as PFS2, were significantly improved in men who received BAT→E versus E→BAT. OS in men receiving BAT→E was 37.3 mo, exceeding historical expectations. These results support the hypothesis that treatment with BAT is safe, has efficacy and can restore sensitivity to antiandrogens. Clinical trial information: NCT02286921. Research Sponsor: Department of Defense Prostate Cancer Research Program.

Prespecified end points (ITT population).

Initial	N =	BAT	N =	E	HR	P Value
Time to clin/radio prog-mo	94	5.7	101	5.7	1.14	0.42
Time to PSA prog.- mo	91	2.8	98	3.8	1.51	0.02
PSA50-no. (%)	85	23 (27.1)	91	23 (25.3)		0.70
OR- no. (%)	33	8 (24.2)	24	1 (4.2)		0.07
OS-mo	94	32.9	101	29.0	0.93	0.74
Crossover		BAT to E		E to BAT		
OS (BAT-Enza vs Enza-BAT)-mo	34	37.3	46	30.2	0.63	0.17
OS (BAT-Enza vs Enza only)-mo	34	37.3	55	28.6	0.50	0.03
Time to PSA prog.- mo	36	10.8	47	1.1	0.26	0.0001
PSA50-no. (%)	36	28 (77.8)	47	11 (23.4)		
OR- no. (%)	35	10 (28.6)	41	3 (7.3)		0.03
PFS2-mo	94	28.2	101	19.6	0.44	0.02

5518 Poster Discussion Session; Displayed in Poster Session (Board #99), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

A phase I, open-label, multicenter study to assess the safety, pharmacokinetics, and preliminary antitumor activity of AZD4635 both as monotherapy and in combination in patients with advanced solid malignancies: Results from prostate cancer patients (NCT02740985).

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Background: AZD4635 inhibits adenosine 2a receptor (A2aR) signaling and improves immune activation and anti-tumor activity in preclinical models. This phase I study assessed the safety, pharmacokinetics, pharmacodynamics and efficacy of AZD4635 monotherapy (mono) and in combination (combo) with durvalumab (durva) in patients (pts) with refractory solid tumors. Here we present data for immune checkpoint-naïve pts with metastatic castrate-resistant prostate cancer (mCRPC). **Methods:** Pts with refractory mCRPC received AZD4635 mono (75 mg or 100 mg QD oral nanosuspension [(RP2D]) or in combination (75 mg or 100mg QD) with durva 1.5g IV q4wk. **Results:** Between 30Aug16 and 20Jun19 (data cutoff [DCO]) 94 mCRPC pts were treated with mono (n = 49) or combo (n = 45): median age 70.5 yrs; ECOG 0-1 = 99%. The median number of prior treatment regimens was 5 (range = 1-10); 61% of pts (57/94) had prior chemotherapy, 90% had prior new hormonal therapy. PK data suggest AZD4635 concentrations at 75-100 mg QD are above the *in vitro* IC_{50} for A2aR inhibition throughout the dosing interval. Modeling predicts 80-90% A2aR occupancy at steady state for doses at $\geq$75 mg QD. Most common treatment-related AEs ($>$ 10%) were nausea, vomiting, fatigue, decreased appetite, dizziness, and diarrhea. At the DCO in this ongoing study, 70 pts were evaluable for response by RECIST v1.1 (mono = 33, combo = 37). Confirmed response occurred in 8 pts: mono = ORR 6.1% (2PRs) and combo = 16.2% (2CRs, 4PRs). The duration of response across cohorts ranged from 1-18.5 mo (5 pts ongoing). PSA response (defined as $\geq$50% decrease from baseline of $\geq$1ng/ml) was observed in 6.4% (3/47 pts; 95% CI, 1.3-17.5) of mono-treated patients and 20% (9/45 pts; 95% CI, 9.6-34.6) of combo-treated patients. Patients with high adenosine (ADO) gene expression signature (N = 46) in peripheral blood, showed a median PFS of 21 weeks v. 8.7 weeks in ADO signature low patients (N = 46) (HR 0.5, CI 0.3-0.9) (DCO 20Jun19). In addition, baseline TCR clonality and diversity were linked with response. **Conclusions:** In mCRPC pts, AZD4635 alone or in combination with durva was tolerable and associated with clinical benefit. A mCRPC phase II trial is ongoing with continued exploration of predictors of response to treatment. Clinical trial information: NCT02740985. Research Sponsor: Astra Zeneca.

5520 Poster Discussion Session; Displayed in Poster Session (Board #101), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

ProCAID: A randomized double-blind phase II clinical trial of capivasertib (C) in combination with docetaxel and prednisolone chemotherapy (DP) in metastatic castration-resistant prostate cancer (mCRPC).

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Background: DP extends survival in mCRPC, but clinical benefit is modest. PI3K/AKT/PTEN pathway activation is common in mCRPC contributing to disease progression and DP resistance. C is a pan-AKT inhibitor. Pre-clinical data indicate activity in prostate cancer and synergism with DP. This phase II trial combined C with DP in mCRPC. **Methods:** Key eligibility criteria: histologically or cytologically proven measurable or evaluable mCRPC, suitable for treatment with DP for PSA and/or radiographic disease progression, ECOG performance status 0-1, no prior chemotherapy for mCRPC, not requiring insulin or $>$ 2 oral hypoglycaemic drugs for diabetes mellitus. Treatment: up to 10 cycles of DP (D: 75 mg/m^2 IV, day 1; P: 5 mg bd oral, day 1 – 21) and random assignment (1:1, double blind) to oral C (320 mg twice daily, 4 days on/3 days off, from cycle 1, day 2) or matched placebo to disease progression. Primary endpoint: progression free survival (PFS; comprising PSA, radiographic or clinical progression, new cancer therapy or death; PCWG2 criteria) in the intent to treat (ITT) population. Secondary endpoints included overall survival (OS) and safety. PFS and OS were also assessed by composite biomarker (B) subgroup for PI3K/AKT/PTEN pathway activation status (NGS/IHC on archival tumour, contemporaneous ctDNA). Statistics: designed to detect a 50% increase in median PFS (6 to 9 months (mo)) between the placebo and C arms (90% power, 20% 1-sided alpha) by Cox proportional hazards model. Registration: ISRCTN 69139368. **Results:** 150 patients were randomised to 01/2019. Median follow up 16.77 months (IQR 12.0-26.5). PFS and OS by ITT and B status, are shown in the table (NR, not reached; CI confidence interval). Grade 3–4 adverse events (AE) were equally common between arms (62.2%). The most common AEs were diarrhoea, fatigue and nausea. **Conclusions:** Adding C to DP did not extend PFS. The OS secondary endpoint was significantly increased. PFS and OS results were consistent irrespective of PI3K/AKT/PTEN pathway activation status. Clinical trial information: 69139368. Research Sponsor: Cancer Research UK, Pharmaceutical/Biotech Company.

	C, mo (95% CI)	Placebo, mo (95% CI)	Hazard ratio (95% CI)	p-value
PFS, ITT	7.03 (6.28-8.25)	6.7 (5.52-7.36)	0.92 (0.65-1.31)	0.32
PFS, B +ve (n = 44)	7.75(6.44-9.63)	7.98(5.09-9.82)	1.17(0.61-2.23)	
PFS, B -ve (n = 92)	7.03(4.21-8.25)	6.34(4.76-7.13)	0.89(0.57-1.37)	
OS, ITT	31.15 (20.07-NR)	20.27 (17.51-24.18)	0.54 (0.34-0.88)	0.01
OS, B +ve	26.87(14.59-NR)	20.27(12.91-35.71)	0.62(0.26-1.47)	
OS, B -ve	32.43(18.5-NR)	20.30(16.82-24.18)	0.54(0.30-0.99)	

5521 **Poster Session (Board #102), Fri, 8:00 AM-11:00 AM**

Molecular determinants of prostate specific antigen (PSA) kinetics and clinical response to apalutamide (APA) in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC) in SPARTAN.

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Background: In SPARTAN, APA + androgen deprivation therapy (ADT) prolonged metastasis-free survival (MFS) and improved PSA kinetics over placebo (PBO) + ADT in high-risk nmCRPC. All molecular subtypes derived benefit in MFS from APA (Feng FY, et al. ASCO GU 2019; abstract 42). We evaluated the association of PSA decline and efficacy outcomes in SPARTAN pts with different molecular subtypes. **Methods:** Gene expression from archival primary tumors (biomarker population) was assessed with the DECIPHER platform (Decipher Biosciences, Inc.) and stratified into genomic classifier (GC) high- and low-to-average risk using GC score > 0.6 and ≤ 0.6, respectively, and ADT-resistant or -sensitive basal or luminal A/B (PAM50 classifier) subtypes. PSA nadir and confirmed PSA decline (Table) were assessed in APA pts overall and at 3, 6, and 12 mo. Associations between molecular subtypes and outcomes were assessed. **Results:** Of 233 available samples, 154 were from APA pts; 49% of APA pts had high GC score and 66% had basal subtype. PSA levels at baseline were similar across all subtypes. Regardless of GC score or basal/luminal subtype, $>$ 50% of patients achieved $\geq$ 90% reduction in PSA with APA. PSA declined faster and PSA reduction was deeper at 6 mo (Table) in GC low to average vs GC high risk and luminal vs basal subtypes. Overall, only luminal vs basal subtypes had a significantly higher % of pts with $\geq$ 90% PSA decline (Chi square $p = 0.037$). In luminal pts, deeper PSA decline with APA was consistent with improved MFS vs basal pts. In GC high pts, MFS benefit with APA was similar to that in GC low to average pts despite lower PSA decline. Although GC low to average and luminal pts had more rapid and deeper PSA responses than GC high or basal pts, respectively, all pts derived MFS benefit. Association of long-term outcomes with PSA decline in these molecular subtypes will be presented. **Conclusions:** In SPARTAN, all molecular subtypes of pts with nmCRPC treated with APA + ADT had MFS benefit and rapid and sustained PSA decline. PSA responses were deepest and most rapid in GC low to average and luminal subtypes. Clinical trial information: NCT01946204. Research Sponsor: Janssen Research & Development.

PSA kinetics in APA pts at 6 mo.

n (%)	GC high n = 76	GC low to average n = 78	Basal n = 102	Luminal n = 52
PSA decline:				
≥ 50%	71 (93.4)	73 (93.6)	94 (92.2)	50 (96.2)
≥ 90%	39 (51.3)	50 (64.1)	52 (51.0)	37 (71.2)
PSA ≤ 0.2 ng/mL	25 (32.9)	29 (37.2)	31 (30.4)	23 (44.2)
Depth of PSA decline:				
< 50%	5 (6.6)	5 (6.4)	8 (7.8)	2 (3.8)
50%-< 90%	32 (42.1)	23 (29.5)	42 (41.2)	13 (25.0)
≥ 90%	39 (51.3)	50 (64.1)	52 (51.0)	37 (71.2)

5522 **Poster Session (Board #103), Fri, 8:00 AM-11:00 AM**

A urine exosomal circRNA classifier for detection of high-grade prostate cancer at initial biopsy: A multicenter, retrospective study.

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Background: The low specificity of prostate-specific antigen (PSA) has resulted in the overdiagnosis and overtreatment of clinically indolent prostate cancer (PCa). We aimed to identify a urine exosomal circular RNA (circRNA) classifier that could detect high-grade (Gleason score [GS]7 or greater) PCa. **Methods:** We did a three-stage study that enrolled eligible participants, including PCa-free men, 45 years or older, scheduled for an initial prostate biopsy due to suspicious digital rectal examination findings and/or PSA levels (limit range, 2.0-20.0 ng/mL), from four hospitals in China. We used RNA sequencing and digital droplet polymerase chain reaction to identify 18 candidate urine exosomal circRNAs that were increased in 11 patients with high-grade PCa compared with 11 case-matched patients with benign prostatic hyperplasia. Using a training cohort of eligible participants, we built a urine exosomal circRNA classifier (Ccirc) to detect high-grade PCa. We then evaluated the classifier in discrimination of GS7 or greater from GS6 and benign disease on initial biopsy in two independent cohorts. We used the sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) to evaluate diagnostic performance, and compared Ccirc with standard of care (SOC) (ie, PSA level, age, race, and family history). **Results:** Between June 1, 2016, and July 31, 2019, we recruited 356 participants to the training cohort, and 442 and 325 participants to the two independent validation cohorts. We identified a Ccirc containing five differentially expressed circRNAs (circ_0049335, circ_0056536, circ_0004028, circ_0008475, and circ_0126027) that could detect high-grade PCa. Ccirc showed higher accuracy than SOC to distinguish individuals with high-grade PCa from controls in both the training cohort and the validation cohorts. (AUC 0.831 [95% CI 0.765-0.883] *vs* 0.724 [0.705-0.852], P = 0.032 in the training cohort; 0.823 [0.762-0.871] *vs* 0.706 [0.649-0.762], P = 0.007 in validation cohort 1; and 0.878 [0.802-0.943] *vs* 0.785 [0.701-0.890], P = 0.021 for validation cohort 2). In all three cohorts, Ccirc had higher sensitivity (range 71.6-87.2%) and specificity (82.3-90.7%) than did SOC (sensitivity, 42.3-68.2%; specificity, 40.1-62.3%) to detect high-grade PCa. Using a predefined cut point, 202 of 767 (26.3%) biopsies would have been avoided, missing only 6% of patients with dominant pattern 4 high-risk GS 7 disease. **Conclusions:** Ccirc is a potential biomarker for high-grade PCa among suspicious men. Research Sponsor: National Natural Science Foundation of China.

5523 **Poster Session (Board #104), Fri, 8:00 AM-11:00 AM**

Bone metabolism biomarkers (BMB) and progression-free survival (PFS) in men with metastatic hormone-sensitive prostate cancer (HSPC): SWOG S1216, a phase III trial of androgen deprivation therapy (ADT) with or without orteronel.

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Background: We previously reported that baseline BMB are independently prognostic for overall survival (OS) in men with castration resistant prostate cancer. We correlated BMB with outcomes in mHSPC as part of S1216, a phase III trial of ADT +/- the novel CYP17 inhibitor orteronel. **Methods:** Blood was obtained at study entry for bone resorption [C-telopeptide(CTx) & Pyridinoline(PYD)] & formation markers [C-terminal collagen propeptide(CICP) & bone alkaline phosphatase(BAP)]. With prior DSMC approval, patients were sampled to mask potential treatment effect. Logistic regression was used to assess if BMB elevation above median was prognostic for a PFS event w/in 2 years across pooled study treatment arms, adjusting for baseline variables (including disease extent, PSA, age, pre-randomization ADT, & presence of bone mets). An additional interaction term between BMB elevation & presence of bone mets was included; if significant, separate models were developed for men +/- bone mets. **Results:** Of 1,313 men, 656 were included in this analysis. All 4 BMB levels were higher in men with a PFS event w/in 2 years vs. those with no PFS event. The odds ratio (OR) for a PFS event was significantly higher in men w/ elevated baseline BMB (see table). For BAP, a significant interaction between marker elevation and bone mets was seen ($p = 0.003$); men w/ bone mets and BAP elevation had an OR of 1.83 for a PFS event in 2 years. **Conclusions:** In men with newly diagnosed HSPC, elevated baseline levels of BMB were significantly associated with PFS, with about a two-fold increased risk of a progression event w/in 2 years. For CICP, CTx, & PYD, this association was independent of the presence of bone metastases. Baseline BMB levels have strong prognostic value in the mHSPC context. Correlative analysis of BMB & OS is planned. Clinical trial information: NCT01809691. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Bone metabolism biomarker	Population	Odds Ratio (95% CI)	p-value	Bone marker X presence of bone mets interaction p-value
CICP	Full cohort	1.73 (1.21, 2.47)	0.003	0.73
CTx	Full cohort	1.90 (1.35, 2.69)	0.0003	0.66
PYD	Full cohort	2.22 (1.56, 3.14)	< 0.0001	0.34
BAP	Full cohort	---	---	0.003
	Men with bone mets	1.83 (1.23, 2.73)	0.003	---
	Men without bone mets	0.47 (0.22,1.02)	0.06	---

Ability of cell-cycle progression score to predict risk for progression to metastatic disease and disease-specific mortality in prostate cancer patients after prostatectomy.

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Background: Prostate cancer treatment aims to prevent metastatic disease (METS) and disease-specific mortality (DSM). A major challenge is to identify those at highest risk so additional intervention can be initiated earlier when it has a better chance of success. Pathologic parameters alone have limited ability to predict METS and DSM, but data suggests biomarkers can improve risk discrimination. **Methods:** Eligible patients had: (1) prostate cancer treated with radical prostatectomy (RP; 1988-1995); (2) available tissue for cell-cycle progression (CCP) testing that resulted in a valid score; (3) preoperative prostate-specific antigen (PSA); (4) no neoadjuvant therapy; and (5) clinical follow-up (N = 360). Cancer of the prostate risk assessment post-surgical (CAPRA-S) was combined with CCP into a combined cell-cycle risk score (CCR = 0.38 $\times$ CAPRA-S + 0.57 $\times$ CCP). **Results:** Median follow-up was 23.5 years for patients alive at last follow-up. Overall, 11% (41/360) developed METS and 9% (33/360) had DSM. CCP score added significant information to CAPRA-S when predicting METS (p = 0.001) and DSM (p = 0.001). CCR score was also a significant predictor of METS and DSM (p-values $< 1\times10^{-8}$). CCP and CCR scores were prognostic of METS in patients with rising post-RP PSA. Of patients with biochemical recurrence (BCR), 25% (41/163) developed METS. CAPRA-S alone was predictive of these events (p = 0.01) but was significantly improved with the addition of CCP (Hazard Ratio [HR] = 1.69 [95% Confidence Interval (CI) 1.13, 2.52], p = 0.014). CCR was also highly prognostic (HR = 1.56 [95% CI 1.20, 2.03], p = 0.001). CCR score discriminated risk of METS both post-RP and after post-RP BCR (Table). **Conclusions:** Overall, the CCR score significantly predicted METS and DSM in prostate cancer post-RP and was also highly prognostic in those with a post-RP rising PSA. It is therefore a useful tool for determining who is at greatest risk of treatment failure and may benefit from earlier intervention. Research Sponsor: Myriad Genetics.

Kaplan-Meier estimates (95% CI) of 15-year risk of METS or DSM post-RP or after post-RP BCR.

CCR	Risk of METS Post-RP (%)	Risk of DSM post-RP (%)	CCR	Risk of METS post-BCR (%)	Risk of DSM post-BCR (%)
(-1, 1] n = 156	4.7 (0.9, 8.3)	2.5 (0, 5.2)	(-1, 1] n = 39	24.9 (7.9, 38.8)	16.1 (1.7, 28.4)
(1, 2] n = 109	6.6 (0.8, 12.1)	4.4 (0, 9.2)	(1, 2] n = 48	15.1 (1.5, 26.9)	9.9 (0, 20.2)
(2, 3] n = 60	26.9 (11.8, 39.3)	17.3 (4.6, 28.4)	(2, 3] n = 47	34.3 (15.4, 48.9)	27.9 (9, 42.9)
(3, 6] n = 35	35.7 (16, 50.8)	30% (11.2, 44.8)	(3, 6] n = 29	46.2 (22.5, 62.6)	34.8 (13.2, 51)

5525 **Poster Session (Board #106), Fri, 8:00 AM-11:00 AM**

HSD3B1 (1245A>C) polymorphism and clinical outcomes in metastatic castration-resistant prostate cancer (mCRPC) patients treated with abiraterone acetate (AA) and enzalutamide (ENZA): Results from two prospective studies.

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Background: The common HSD3B1 (1245A > C) germline variant is associated with increased *de-novo* synthesis of androgens and worse outcomes in men treated with androgen-deprivation therapy in metastatic hormone sensitive prostate cancer. The aim of this study is to determine the role of this polymorphism on treatment outcomes for AA and ENZA in patients with mCRPC. **Methods:** A total of 547 patients treated with AA or ENZA for mCRPC from two prospective cohorts; cohort 1 included 202 from British Columbia (Canada) and cohort 2 enrolled 345 patients from the Spanish study PROREPAIR-B. HSD3B1 genotype was determined by targeted sequencing in cohort 1 and by Taqman SNP genotyping assay in cohort 2. Associations between HSD3B1 genotypes and (TTPP), time to progression (TTP) and overall survival (OS) were evaluated via univariate COX regression. Multivariate analysis was performed to determine the independent association of each covariate. **Results:** The proportions of patients with a homozygous wild-type HSD3B1 (AA), heterozygous (AC) and homozygous variant (CC) genotype were respectively 45.6%, 39.4% and 15%. As expected, known prognostic factors for mCRPC such as hemoglobin, alkaline phosphatase (ALP), LDH, PSA at baseline as well as site of metastasis were significantly associated with TTPP and TPP. In the combined cohort, HSD3B1 (CC) genotype was associated with worse TTP (HR 1.31, 95%CI 1.02-1.67, p = 0.032) and PSA response rates (48% for CC vs 62% and 65% for AA and AC, respectively ($p = 0.019$, χ^2)). Similar trend was observed for TTPP (HR 1.28, 95%CI 0.99-1.66, p = 0.064). OS was not different among genotypes, but was significantly shorter for patients with CC genotype in cohort 1 (HR 1.97, 95%CI 1.14-3.40, p = 0.016). There was no association between HSD3B1 genotype and time to castration-resistance in either of the two cohorts. Multivariable analysis showed that LDH, ALP, hemoglobin and use of AA or ENZA as first-line therapy for mCRPC were independent prognostic factors for TTP and TTPP; non-significant association was observed for genotype and TTP. **Conclusions:** HSD3B1 homozygous variant genotype (CC) was associated with shorter TTP and lower PSA response rate in mCRPC patients treated with AA or ENZA. However, the CC genotype did not provide prognostic information beyond that conferred by standard clinical variables, suggesting that it may not be a suitable stand-alone biomarker in mCRPC. Research Sponsor: BC Cancer Foundation, Other Foundation, Other Government Agency.

5526 **Poster Session (Board #107), Fri, 8:00 AM-11:00 AM**

Biomarker analysis from the KEYNOTE-199 trial of pembrolizumab in patients (pts) with docetaxel-refractory metastatic castration-resistant prostate cancer (mCRPC).

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Background: In the phase II KEYNOTE-199 study (NCT02787005), pembrolizumab monotherapy demonstrated antitumor activity in pts with docetaxel-refractory mCRPC (n = 258). Here we evaluated the association between prespecified molecular biomarkers and clinical outcomes. **Methods:** Cohorts 1 (C1) and 2 (C2) enrolled pts with RECIST-measurable PD-L1–positive (combined positive score [CPS] $\geq$1 using immunohistochemistry) and PD-L1–negative (CPS $<$1) disease, respectively. C3 enrolled pts with nonmeasurable, bone-predominant disease, irrespective of PD-L1 status. Biomarkers evaluated in this analysis were tumor mutational burden ([TMB; mutations/exome] n = 155), PD-L1 CPS (n = 255), tumor microenvironment–based 18-gene RNA expression profile ([GEP] n = 196), and microsatellite instability ([MSI] as determined by Promega PCR analysis; n = 147). Outcomes evaluated for C1 and C2 (n = 200) were ORR, disease control rate (DCR), and radiographic PFS (rPFS) per blinded, independent central review per PCWG-modified RECIST v1.1. Outcomes evaluated for C1-C3 (n = 258) were prostate-specific antigen (PSA) response, time to PSA progression, and OS. Significance of continuous biomarkers (CPS; TMB; GEP) was prespecified at 0.05 for one-sided *P* values from logistic (ORR; DCR; PSA response) and Cox proportional hazard regression (rPFS; OS; PSA progression) adjusted for Eastern Cooperative Oncology Group performance status. Binary biomarkers (MSI) were analyzed using Fisher's exact test (ORR; DCR; PSA response). Clinical data cutoff date: Jun 24, 2019. **Results:** Median TMB was 53.0 (interquartile range [IQR], 40.5 to 78.0), median CPS was 1 (IQR, 0 to 5), and median GEP was –0.64 (IQR, –0.88 to –0.46); 6 pts (2.3%) had MSI-high tumors. In C1-C3, TMB was associated with PSA response (one-sided nominal $P = 0.0016$) and time to PSA progression (one-sided nominal $P = 0.00092$). In C1-C3, PD-L1 CPS was associated with PSA response (one-sided nominal $P = 0.046$) and time to PSA progression (one-sided nominal $P = 0.021$). In C1-C3, GEP was not significantly associated with response. In C1-C3, MSI was associated with PSA response (one-sided nominal $P = 0.019$). **Conclusions:** In this biomarker analysis from KEYNOTE-199 C1-C3, TMB and PD-L1 CPS were associated with better PSA response; however, small pt numbers limit definitive conclusions on ORR, DCR, and OS. Further evaluation of molecular biomarkers in pts with mCRPC treated with pembrolizumab is warranted. Clinical trial information: NCT02787005. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

5527 **Poster Session (Board #108), Fri, 8:00 AM-11:00 AM**

Association of BRCA alteration (alt) type with real-world (RW) outcomes to PARP inhibitors (PARPi) in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC).

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Background: Inactivating alts in *BRCA1/2* result in homologous recombination deficiency and are predictive of PARPi response in mCRPC. *BRCA* reversion mutations, which restore the protein function, are frequently observed in acquired resistance to PARPi. In tumors harboring homozygous gene deletions (*BRCA*del) reversions cannot develop; thus, we hypothesize that *BRCA*del pts may have prolonged benefit from PARPi compared to pts harboring other BRCA alterations. **Methods:** Pts were included from the Flatiron Health (FH)-Foundation Medicine (FMI) de-identified clinico-genomic database (CGDB). Inclusion criteria were diagnosis of mCRPC, treatment in the FH network and an FMI comprehensive genomic profiling result between 1/1/2011 - 9/30/2019. Time to therapy discontinuation (TTD) and overall survival (OS) from start of PARPi were estimated with Kaplan-Meier analysis and unadjusted/adjusted (age at PARPi initiation, line number, practice type) hazard ratios (HR/aHR) from Cox proportional hazards models adjusted for survival bias. **Results:** Out of 829 mCRPC cases, *BRCA1/2* alts were detected in 15 (1.8%) and 71 (8.6%) respectively, with 2 cases included in both groups. 26% of *BRCA*alts were *BRCA*del, 67% were coding mutations, and 7% were genomic rearrangements. 25 (28%) *BRCA*alt pts were treated with PARPi, 11/25 in the 1st or 2nd line setting including 43% of *BRCA*del and 44% of other *BRCA*alt cohorts. Median age at PARPi initiation was 70 yrs and 88% were treated in community practices. TTD was significantly longer in the *BRCA*del (n = 7) cohort vs. other *BRCA*alt cohort (n = 18) (22.7 vs. 9.2 months; HR: 0.16 [0.03-0.74]; aHR: 0.13 [0.02 – 0.92]) while a statistically nonsignificant difference in median OS was observed (31.5 vs. 11.9 months; HR: 0.20 [0.02-1.58]; aHR: 0.24 [0.02-3.15]). In comparison, no statistically significant difference in TTD was observed for *BRCA*del (n= 7) vs. other BRCAalts (n=19) pts treated with 1st line hormonal therapies (abiraterone or enzalutamide) (3.4 vs. 5.7 months; HR: 1.16 [0.45-2.98]; aHR: 0.72 [0.25-2.10]). Follow up analysis with more pts and somatic/germline status and zygosity of *BRCA*alts will be presented. **Conclusions:** These data suggest a differential benefit from PARPi therapy across *BRCA*alt subgroups. This observation may in part be explained by the inability to develop reversion mutations to restore BRCA function in tumors with *BRCA*del. Further studies are warranted to fully assess the association of *BRCA*alt type with outcomes to PARPi-based treatments. Research Sponsor: Foundation Medicine, Inc.

5528 **Poster Session (Board #109), Fri, 8:00 AM-11:00 AM**

Association of polymorphisms in androgen production, uptake, and conversion chain (APUC) genes with mortality of prostate cancer patients.

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Background: Genes involved in APUC may affect prognosis in PC. We tested the association of four SNPs involved in the APUC pathway: hydroxy-delta-5-steroid dehydrogenase, 3 beta-and steroid delta-isomerase 1 (*HSD3B1*), 5α reductase enzyme (*SRD5A*), and solute carrier organic ion (*SLCO2B1*) with all-cause and PC mortality 596 in the Atherosclerosis Risk in Communities (ARIC) study. **Methods:** Between 1987 & 2015 596 men were diagnosed with PC. Median age at diagnosis was 70 (range 53-86) years; 21% of all PC patients were African American. After diagnosis, follow-up was median 8.4 years (max 26.7 years) until PrC death (N = 60), death from any cause (N = 253), or end of 2015. SNPs were genotyped using the Affymetrix Genome-Wide Human SNP Array 6.0 and imputed to the 1000 Genomes Phase 3 reference panel. To examine survival, we used Kaplan-Meier curves and Cox proportional hazards regression. Hazard ratios (HR) and 95% confidence intervals (CI) were adjusted for age, field center, stage and grade at diagnosis. We also controlled for confounding by ancestry by adjusting for genetic principal components. The analyses were conducted in all PrCa patients and in Whites PrCa patients only. Polymorphisms tested included rs1047303 (A = > C, also called 1245C); rs523349 (C = > G); and rs1789693 (A = > T) and rs12422149 (G = > A), located in the aforementioned genes. **Results:** The A allele for *SLCO2B1* rs1789693 (A = > T) was significantly associated with an increased risk of PC mortality (versus T): multivariable-adjusted HRs (95%CI) were (2.06, 1.14-3.74; p = 0.02) and all-cause mortality (1.29, 1.00-1.66; p = 0.05) among Whites. The associations were similar when Whites and African-Americans were combined and when accounting for ancestry. The C allele for *HSD3B1* rs1047303 (C = > A) was not statistically significantly associated with either PC or all-cause mortality in the whole cohort (which included localized disease), although HRs were increased for men diagnosed with stage 4 disease (n = 35) in both additive and dominant models. For carriers of the C allele (gain of function) versus AA, HRs were 5.32 (1.16-24.33; p = 0.03) and 6.13 (1.51-24.86; p = 0.01) for PC and all-cause mortality, respectively. All associations with *SRDA2* (rs12422149) and *SLCO2B1* (rs12422149) were not significant. **Conclusions:** The gain of function allele in *HSD3B1* rs1047303 (1245C) was associated with increased PC and all-cause mortality in men diagnosed with metastatic PC, paralleling prior findings. Associations with *SLCO2B1* SNP rs1789693 require validation in larger studies. Research Sponsor: None.

5529 **Poster Session (Board #110), Fri, 8:00 AM-11:00 AM**

AR enhancer and locus genomic alterations as cell-free DNA biomarkers of primary resistance to AR-directed treatment of metastatic prostate cancer.

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Background: Predicting primary resistance to androgen receptor (AR)-directed therapies is critical for personalizing treatment of metastatic prostate cancer (mPCa). Analyses of liquid biopsies are potential tools but remained underutilized due to limited sensitivity. We developed a cell-free DNA (cfDNA) assay (EnhanceAR-Seq) to monitor genomic alterations in mPCa including *AR* enhancer duplication, a resistance marker recently discovered in ~81% of mPCa patients. Here we show that applying EnhanceAR-Seq to plasma cfDNA to monitor alterations of *AR* gene and enhancer (*AR*/enhancer) predicted primary resistance with high sensitivity and outperformed the clinically validated CTC AR-V7 assay. **Methods:** Forty mPCa patients were prospectively enrolled at the Washington University School of Medicine Siteman Cancer Center with plasma cfDNA analyzed by EnhanceAR-Seq. Twenty-five of them also had the Oncotype DX AR-V7 Nucleus Detect CTC assay performed at a similar timepoint at the discretion of the treating oncologist. All patients received AR-directed therapy (eg. abiraterone, enzalutamide) and underwent standard-of-care clinical and laboratory follow-up. Primary resistance was defined as PSA progression, change of treatment or death within 4 months of treatment initiation, or radiographic progression within 6 months. **Results:** Median clinical follow up after diagnosis was 50 months. EnhanceAR-Seq detected alterations targeting *AR*/enhancer in 18 patients (45%), *TP53* in 8 patients (20%), and *PTEN* in 6 patients (15%). We found that *AR*/enhancer alterations (copy gain, tandem duplication, and point mutation) in cfDNA were strongly predictive of primary resistance to AR-directed therapy (PPV = 100%, Sens. = 89%). Our assay outperformed the CTC AR-V7 assay, which was positive in only two patients (PPV = 50%, Sens. = 6%). Furthermore, patients with *AR*/enhancer alterations had significantly worse progression-free survival (P = 0.0015; HR = 11.5) and overall survival (P = 0.0002; HR = 6.8). Finally, serial cell-free DNA analysis of 10 patients showed that *AR*/enhancer copy number gain was maintained or acquired in 5 of 6 AR-resistant cases, and neutrality maintained in 4 of 4 AR-sensitive cases. **Conclusions:** cfDNA-based *AR*/enhancer locus genomic alterations could potentially be used to predict primary resistance to AR-directed therapy with higher sensitivity than the clinically validated CTC AR-V7 assay, be used for serial timepoint monitoring and guiding personalized clinical decision-making. Research Sponsor: American Cancer Society and Siteman Cancer Center.

5530 **Poster Session (Board #111), Fri, 8:00 AM-11:00 AM**

Clinical analysis of the extracellular vesicle-fingerprint score blood test to refine the prediction of clinically significant prostate cancer and avoid prostate biopsy.

Adrian S. Fairey, Robert J Paproski, Desmond Pink, Deborah L Sosnowski, Catalina Vasquez, Bryan Donnelly, M. Eric Hyndman, Armen G. Aprikian, Perrin Beatty, John D Lewis; University of Alberta, Edmonton, AB, Canada; Nanostics Inc., Edmonton, AB, Canada; Department of Surgical Oncology, University of Calgary, Calgary, AB, Canada; University of Calgary, Calgary, AB, Canada; Division of Urology, Department of Surgery, McGill University, Montreal, QC, Canada; University of Alberta, Edmonton,, AB, Canada

Background: The accuracy of the extracellular vesicle-fingerprint score (EV-FPS) test to predict clinically significant prostate cancer (PCa; Gleason grade (GG) $\geq$ 3) from indolent disease (GG $\leq$ 2) and avoid unnecessary prostate biopsies was determined at the point of prostate biopsy decision. **Methods:** Clinical data, health information, and blood samples were collected from a prospective validation cohort of 415 men, without prior PCa diagnosis, referred to urology clinics for prostate biopsy or transurethral prostate surgery (June 2014-Dec 2016). The patient's EV-FPS risk score was calculated by combining machine learning model-analyzed microflow cytometry data from EV biomarkers with logistic regression-analyzed patient-centric clinical features. The plasma-derived EV biomarkers were prostate-specific membrane antigen, polysialic acid and ghrelin-growth hormone receptor. The patient clinical features were; age, ethnicity, PCa family history, PSA levels, abnormal digital rectal examination (DRE) and prior negative prostate biopsy. Together, the biomarkers and clinical features provided specificity for clinically significant PCa. **Results:** The EV-FPS test identified clinically significant PCa patients with high accuracy (0.81 area under curve) at 95% sensitivity and 97% negative predictive value. Using a 7.85% probability cut-off after test validation; 95% of the patients with GG $\geq$ 3 would have been found before biopsy, 35% biopsies would have been avoided and diagnosis of GG $\geq$ 3 PCa would have been missed in only 5% of the cohort. **Conclusions:** This minimally invasive EV-FPS test accurately predicted clinically significant PCa in men with high EV-FPS risk scores, high PSA level and/or abnormal DRE. Therefore, men with low EV-FPS risk scores could potentially avoid unnecessary prostate biopsies. Clinical care cut-offs to calculate the number of biopsies that could have been avoided, and the percentage of GG $\geq$ 1 to GG $\geq$ 3 PCa that could have had a delayed diagnosis. Research Sponsor: Alberta Cancer Foundation, Other Foundation.

	Biopsies		GG ≥ 1 PCa		GG ≥ 2 PCa		GG ≥ 3 PCa	
PCPTRC + EV-FPS cut-off	Performed (%)	Avoided (%)	Found (%)	Missed (%)	Found (%)	Missed (%)	Found (%)	Missed (%)
0%	415 (100%)	0 (0%)	258 (100%)	0 (0%)	168 (100%)	0 (0%)	73 (100%)	0 (0%)
≥ 5%	384 (93%)	31 (7%)	248 (96%)	10 (4%)	164 (98%)	4 (2%)	73 (100%)	0 (0%)
≥ 7.5%	294 (71%)	121 (29%)	203 (79%)	55 (21%)	143 (85%)	25 (15%)	69 (95%)	4 (5%)
≥ 7.847%	271 (65%)	144 (35%)	190 (74%)	68 (26%)	139 (83%)	29 (17%)	69 (95%)	4 (5%)
≥ 10%	200 (48%)	215 (52%)	143 (55%)	115 (45%)	106 (63%)	62 (37%)	61 (84%)	12 (16%)

5531 **Poster Session (Board #112), Fri, 8:00 AM-11:00 AM**

Prevalence and tissue concordance of BRCA2 copy number loss evaluated by single-cell, shallow whole genome sequencing of circulating tumor cells (CTCs) in castration-resistant prostate cancer (CRPC).

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Background: Genomic studies have shown that up to 25% of prostate cancer tissue specimens harbor alterations in DNA Damage Repair (DDR) genes, which may sensitize the tumor to poly ADP-ribose polymerase inhibitors (PARPi). Trials evaluating PARPi in patients with DDR deficiencies have shown varied response rates and differences regarding which genomic alterations predict for sensitivity to these agents, with the majority of objective responses seen in BRCA2-altered tumors. These results highlight the need to develop biomarker assays which can predict benefit from PARPi therapy. Tissue and cell-free DNA (cfDNA) have been the most utilized sources of tumor material for analysis in this setting, but success rates of obtaining sufficient tumor for analysis from bone are low and detecting tumor-derived copy number variants (CNVs) in cfDNA is challenging. Circulating tumor cells (CTCs) represent an alternate source of genetic information, for which assays are available to isolate and sequence individual cells in a manner that eliminates background noise from stroma and healthy cells, while capturing inter-cellular heterogeneity. **Methods:** Blood samples, collected from 138 progressing metastatic CRPC patients within 30 days of a pre-treatment biopsy intended for sequencing using MSK-IMPACT, were sent to EPIC Sciences for CTC analysis. Detected CTCs underwent single cell, low pass whole genome sequencing. Prevalence and concordance of BRCA2 copy-loss, regardless of whether single copy or homozygous, was compared in matched tissue and CTC samples. **Results:** BRCA2 copy-loss was identified in 21% (23/108) and 50% (58/115) of successfully sequenced tissue and CTC samples, respectively. In the 58 patients with CTC-detected BRCA2 loss, BRCA2 loss was detected in 36% (220/565) of the sequenced CTCs, representing a median of 46% (range 4-100%) of CTCs found in each individual sample. When both sequencing assays were successful, BRCA2 loss was detected in CTCs in 84% (16/19) of the tissue-positive cases, whereas tissue sequencing detected BRCA2 loss in 35% (16/46) of CTC-positive cases. **Conclusions:** Data from this study supports the notion that single-cell CTC sequencing can detect BRCA2 copy-loss at a high frequency, including cases that were negative in tissue, while also characterizing inter-cellular heterogeneity. Further studies will investigate whether CTC BRCA2 copy-loss can predict the likelihood of response to PARPi. Research Sponsor: EPIC Sciences.

5532 Poster Session (Board #113), Fri, 8:00 AM-11:00 AM

Comparative effectiveness of systemic treatments for metastatic castration-sensitive prostate cancer: A parametric survival network meta-analysis of randomized controlled trials.

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Background: Treatment decision-making for metastatic castration-sensitive prostate cancer (mCSPC) is complicated by the unclear comparative effectiveness and widely varying costs of competing strategies. Objective: To compare the effectiveness and safety of systemic treatments for mCSPC. **Methods:** We searched bibliographic databases, regulatory documents, and trial registries for randomized controlled trials testing active drugs added to androgen deprivation therapy (ADT) for mCSPC. We used Cochrane risk-of-bias tool (version 2) to assess trial quality and Bayesian network meta-analysis (NMA) to estimate the relative effects of competing treatments. In addition to combing published time-invariant hazard ratios (HRs), we reconstructed survival data from Kaplan Meier curves to enable parametric survival NMA that allows time-varying HR. **Results:** Seven trials with 7,236 patients were included comparing six treatments (Table). Risk of bias is a concern for trials with open label (N=4), missing data (N=3), or unprespecified analysis (N=3). Ordered from the most to the least effective, treatments significantly improving overall survival (OS) include abiraterone acetate, apalutamide, and docetaxel; treatments significantly improving radiographic progression-free survival (rPFS) include enzalutamide, abiraterone, apalutamide, and docetaxel. (see HRs in Table) Allowing time-varying HR produced similar treatment rankings. Serious adverse events (SAE) were substantially increased for docetaxel (odds ratio [OR] 104.17, 95% credible interval [CI] 24.85-1012.32) and slightly increased for abiraterone (OR 1.42, 95% CI 1.11-1.83). **Conclusions:** Abiraterone provided the largest OS benefit with slightly increased risk of SAE. Apalutamide offered comparable OS benefit with abiraterone without increasing SAE risk. Although enzalutamide delayed rPFS to the greatest extent, longer follow-up is needed to examine its OS benefit. Research Sponsor: None.

Treatment rankings based on overall survival and radiographic progression-free survival.

Treatment strategy (plus ADT)	HR of OS vs ADT (95% CI)	Median rank for OS	HR of rPFS vs ADT (95% CI)	Median rank for rPFS
Abiraterone acetate	0.62 (0.54-0.71)	1	0.45 (0.40-0.51)	2
Apalutamide	0.67 (0.51-0.88)	2	0.48 (0.39-0.59)	3
Docetaxel	0.80 (0.71-0.89)	3	0.68 (0.61-0.75)	4
Enzalutamide	0.81 (0.53-1.23)	4	0.39 (0.30-0.51)	1
Standard non-steroid antiandrogen (bicalutamide, nilutamide, or flutamide)	1.21 (0.74-1.97)	5	0.97 (0.70-1.35)	5

5533 **Poster Session (Board #114), Fri, 8:00 AM-11:00 AM**

Phase I study of a novel S1P inhibitor, NOX66, in combination with radiotherapy in patients with metastatic castration-resistant prostate cancer.

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Background: NOX66 is a new formulation of the small molecule, idronoxil. The primary mechanism of action of idronoxil stems from its binding to the transmembrane enzyme ENOX2 expressed on cancer cells, resulting in reduced S1P and increased ceramide levels, thereby promoting apoptosis. Additional intracellular effects include the inhibition of DNA repair mechanisms. There is growing evidence that S1P is a promotor of tumour resistance to immune cell infiltration, highlighting NOX66's potential to modulate the immune response against cancer. **Methods:** This two-part phase 1b open-label study enrolled patients with late-stage progressive mCRPC. Part 1 was a dose-escalation safety assessment of three doses of NOX66 (400 mg, n = 4; 800 mg, n = 6 and 1200 mg, n = 15) administered daily for 14 days with radiation therapy (20 Gy) delivered in 5 fractionated doses to one or more symptomatic lesion/s. Part 2 was an expansion cohort with NOX66 at 1200 mg in conjunction with radiation therapy. The primary endpoint of safety was assessed by the frequency and grade of treatment-emergent adverse events (TEAEs). At 6 weeks, 3- and 6-month follow up, treatment response was assessed radiographically by RECIST1.1 and by PSA >50% reduction. **Results:** 25 patients received and completed treatment. TEAEs considered related to NOX66 alone were mild (Grade 1) cases of dry mouth and oral mucositis; mild (Grade 1) fatigue was considered related to both NOX66 and radiation. None of the 21 Grade ≥3 TEAEs were considered related to NOX66. At 6 months, of the 15 evaluable patients by RECIST1.1, 9 had SD and 1 had PR and these same patients had maintained this response from 3 months. Five of the 16 PSA-evaluable patients achieved a PSA response (61-98% PSA reduction) at 6 months, which again was maintained from 3 months. **Conclusions:** NOX66 in combination with low-dose radiation therapy was found to be safe and well tolerated with promising signals of durable efficacy in patients with late-stage mCRPC. Responses of lesions outside the radiation field are being reviewed. Clinical trial information: NCT03307629. Research Sponsor: Noxopharm Limited.

5534 **Poster Session (Board #115), Fri, 8:00 AM-11:00 AM**

Contrasting genomic profiles in post-systemic treatment metastatic sites (MET), pre-treatment primary tumors (PT), and liquid biopsies (LB) of clinically advanced prostate cancer (PC).

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Background: Comprehensive genomic profiling (CGP) was done on pre-systemic treatment (pre) PT, post-treatment (post) MET sites and LB in PC to uncover differences in genomic alterations (GA) and potential impact on therapy selection. **Methods:** 1,294 PC tissues and 782 LB underwent hybrid-capture based CGP. PT biopsies and resections were compared with post-treatment MET biopsies from bone (BO), liver (LIV), lung (LU), brain (BN), lymph node (LN) and soft tissue (ST) sites and LB. TMB was determined on up to 1.1 Mbp of sequenced DNA for tumor samples. Tumor cell PD-L1 IHC was measured (Dako 22C3). **Results:** Differences in alteration frequencies between PT, MET and LB for selected genes are shown in the Table. *TMPRSS2:ERG* fusion frequencies were similar between PT and MET (35% vs 33%) but varied between MET sites (27% in BO and ST to 40% in LN). GA in *AR* were lowest in pre PT (2%) and highest in MET (24% in LU to 50% in LIV). BN had the highest GA/tumor (8) and the most *PTEN* GA. *BRCA2* GA frequency varied from 0% in BN to 15% in LI. Potential predictors of IO response included *CDK12* GA (16% in LU) and MSI high status (29% in BN). High PD-L1 expression was found in only two cases (LN) and low PD-L1 expression was relatively uncommon. *ERBB2* amplifications were increased in MET compared with PT. *RB1* GA were increased in LIV cases. LB GA had a similar increase in *AR* and *TP53* GA to MET and appeared to be a blend of MET site biopsies across alteration frequencies. **Conclusions:** CGP of PT, MET and LB in PC demonstrates differences most likely associated with exposure to systemic therapies. Differences identified in the MET GA landscape suggest that liquid biopsies may capture a broader range of therapeutic opportunities for PC patients. Research Sponsor: Foundation Medicine Inc.

	Pre	Post						
	PT	BO	LIV	LU	BN	LN	ST	LB
Cases	770	127	34	25	7	205	126	782
Median age (range)	64 (39-89+)	68 (44-89+)	69 (48-84)	70 (50-86)	75 (58-84)	68 (39-89+)	68 (44-89+)	71 (45-89+)
GA/sample	3.8	5.0	5.1	4.2	8.0	4.8	5.0	-
TMPRSS2:ERG	35%	27%	32%	32%	29%	40%	27%	-
AR	2%	31%	50%	24%	43%	33%	31%	32% (n = 290)
TP53	37%	41%	56%	28%	57%	50%	41%	50%
PTEN Copy Number Alterations	16%	25%	24%	28%	57%	33%	25%	-
PTEN Short Variants	6%	10%	15%	4%	29%	7%	10%	7%
BRCA2	9%	8%	15%	8%	0%	7%	8%	8%
ATM	6%	6%	0%	24%	0%	5%	6%	15% (n = 290)
PIK3CA	7%	6%	3%	8%	14%	6%	6%	5%
RB1	4%	9%	30%	0%	0%	5%	9%	5% (n-290)
CDK12	5%	10%	0%	16%	0%	5%	10%	4% (n = 290)
BRAF	4%	3%	6%	0%	0%	3%	3%	3%
ERBB2	0.6%	5%	3%	8%	0%	2%	5%	1%
MSI-High	2%	5%	7%	0%	29%	2%	5%	1% (n = 290)
Median TMB	1.3	2.5	2.5	2.5	7.5	2.5	2.5	-
TMB > 10 mut/Mb	5%	7%	9%	0%	43%	4%	7%	-
TMB > 20 mut/Mb	3%	4%	3%	0%	29%	2%	4%	-
PD-L1 IHC Low (> 1%) Positive	8%	3%	15%	13%	0%	4%	3%	-

5535 **Poster Session (Board #116), Fri, 8:00 AM-11:00 AM**

Molecular determinants of outcome for metastatic castration-sensitive prostate cancer (mCSPC) with addition of apalutamide (APA) or placebo (PBO) to androgen deprivation therapy (ADT) in TITAN.

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Background: In TITAN, addition of APA to ADT improved radiographic progression-free survival (rPFS) and overall survival (OS) versus PBO plus ADT in patients (pts) with mCSPC. In this post hoc analysis, we performed transcriptome-wide profiling of tumor samples and assessed association of molecular subtypes with rPFS. **Methods:** The DECIPHER platform (Decipher Biosciences, Inc.) was used to assess gene expression in archival primary prostate tumors from TITAN. Samples were classified into high versus low to average risk of metastases (DECIPHER genomic classifier [GC] $>$ 0.6 and $\leq$ 0.6, respectively), basal and luminal A/B (PAM50 classifier), and androgen receptor activity (AR-A) signature high and low. Associations between subtypes with rPFS were assessed with Cox proportional hazards model. **Results:** The biomarker population included 222 pts (APA, 110; PBO, 112). Benefit in rPFS from APA in the biomarker population (HR [95% CI]; p value; 0.49 [0.31-0.78]; 0.002) resembled that in the overall study population (0.49 [0.40-0.61]; $<$ 0.0001). The majority of TITAN pts had GC high scores (n = 166, 75%). GC high risk subtype in the PBO group had poorer prognosis for rPFS than GC low to average risk subtype (median rPFS 18.2 mos for GC high vs not reached [NR] for GC low to average, 0.28 [0.11-0.69]; 0.006), but there was no difference in prognosis between high and low to average GC risk subtypes in the APA group (GC high NR vs GC low to average NR; 0.81 [0.35-1.89]; 0.625). Pts were further stratified based on basal/luminal and AR-A signatures. Basal (n = 112, 50%) and AR-A low (n = 96, 43%) subtypes, known to be nonresponsive to ADT, both showed significant benefit from APA vs PBO (0.30 [0.16-0.57]; $<$ 0.001 and 0.25 [0.12-0.52]; $<$ 0.001, respectively). The majority of AR-A low subtype (74%, 71/96) overlapped with basal subtype. Further conclusions for risk of rPFS in GC low, luminal, and AR-A high subtypes and OS across all subtypes will be assessed as more events occur. **Conclusions:** In TITAN, addition of APA to ADT improved rPFS for all subtypes of pts with mCSPC. APA overcame the poor prognosis of GC high risk subtype and prolonged rPFS in ADT-resistant AR-A low and basal molecular subtypes, suggesting APA is beneficial especially for the highest risk molecular subtypes. Clinical trial information: NCT02489318. Research Sponsor: Janssen Research & Development.

5536 **Poster Session (Board #117), Fri, 8:00 AM-11:00 AM**

Clinical, genetic, and pathologic determinants of prostate cancer brain metastasis.

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Background: Prostate cancer (PCa) brain metastasis (BM) is a rare event occurring in 0.16-0.63% of PCa patients. Current clinical data on this phenomenon is limited to small retrospective cohorts and our understanding of it is incomplete. We sought to identify clinical and molecular predictors of PCa BM in a large retrospective cohort treated at our institution. **Methods:** Men diagnosed with Pca from 1995-2017 with ≥6 months of follow-up were included. Data was collected on clinical and tumor characteristics at diagnosis, PCa treatment, brain and bone metastasis, and tumor genetic profile based on Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT) analysis. Results were examined using Kyoto Encyclopedia of Genes and Genome (KEGG) pathway. Genes altered in ≥5% of patients were included. Time to brain metastasis (TTBM) and overall survival (OS) were analyzed with univariable (UVA) Fine-Gray competing risks regression and Cox proportional hazards. TTBM and OS were landmarked at 6 months after PCa diagnosis. False discovery rate (FDR) adjustment accounted for multiple comparisons. **Results:** 27,887 men met inclusion criteria; 74 developed BM. Clinical variables associated with increased hazard of TTBM in UVA were high-clinical and pathologic-* ($p<.001$) T stage, node-positive disease* ($p<.001$), primary* and total* Gleason ($p<.001$), receipt of abiraterone* (HR 52.51 (95% CI 7.1-389.8), $p<.001$), and receipt of leuprolide* (HR 3.0 (95% CI 1.7-5.4), $p<.001$). Tumor alterations associated with BM include mutations in BRCA2 (HR 2.94 (95% CI 1.1-8.0), p=.04), MYC (HR 3.41 (95% CI 1.2-9.5), p=.02), PTEN (HR 2.90 (95% CI 1.2-6.9), p=.02), RB1 (HR 3.09 (95% CI 1.2-8.0), p=.02), and pathways involving homologous recombination (HR 2.70 (95% CI 1.1-6.4), p=.02), Fanconi anemia* (HR 4.22 (95% CI 1.8-10.0), $p<.001$), Ras signaling* (HR 4.6 (95% CI 1.5-13.9), p=.006), mTOR signaling (HR 2.88 (95% CI 1.1-7.9), p=.04), VEGF signaling* (HR 3.60 (95% CI 1.5-8.8), p=.005), and GnRH signaling* genes (HR 3.93 (95% CI 1.6-9.6), p0.003). Variables associated with increased hazard of BM after FDR adjustment are denoted with an asterisk. Variables associated with reduced OS after FDR adjustment were neuroendocrine or blastoma histology, node-positive disease, high-T stage, high initial PSA, receipt of leuprolide, and alterations in AR, TP53, and CDK12 genes. **Conclusions:** PCa BM is significantly associated with high-stage and grade disease, receipt of androgen deprivation agents such as abiraterone and leuprolide, and alterations in the Fanconi anemia, Ras, VEGF, and GnRH pathways. Research Sponsor: None.

5537 **Poster Session (Board #118), Fri, 8:00 AM-11:00 AM**

Overall survival (OS) with docetaxel (D) vs novel hormonal therapy (NHT) with abiraterone (A) or enzalutamide (E) after a prior NHT in patients (Pts) with metastatic prostate cancer (mPC): Results from a real-world dataset.

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Background: NHT (A and E) are approved first-line (1L) treatment (Rx) for mPC. After progression on NHT, Rx include either alternate NHT or D. However, OS from a randomized trial comparing NHT vs D after progression on 1L NHT has not been reported. **Methods:** Pts data were extracted from the Flatiron Health EHR-derived de-identified database. Inclusion: diagnosis of mPC; 1L Rx with single agent A or E only, single-agent Rx with alternate NHT (E or A) or D in second line (2L). Exclusion: $>$ 180 days between date of diagnosis of mPC and date of next visit to ensure Pts were actively engaged in care at data-providing site; Rx with NHT in non-metastatic setting, any prior exposure to D. OS was compared using Cox proportional hazards model stratified by Rx propensity score. Each Pts' probability of receiving D (rather than NHT) was modeled via a random forest based on Pts and disease characteristics which may drive treatment selection. These included pre-2L Rx ECOG scores, PSA, LDH, ALPH, Hb, age, ICD codes for liver metastasis, diabetes, neuropathy, and heart failure; insurance payer, year of start of 2L Rx, time on 1 L NHT, Gleason score, PSA at the original diagnosis of mPC. Subgroup analyses included 1L Rx duration $<$ 12 mos. **Results:** 1165 Pts between 2/5/2013 to 9/27/2019 were eligible. Median follow up 8 mos (range 0.1-64.5). Median OS after 1L A was higher with E as compared to D (15.7 vs. 9.4 mos). Median OS after 1L E was higher with A as compared to D (13.3 vs. 9.7 mos) (table). Propensity distributions were overlapping among Rx arms and showed only modest imbalance. In 2L, D had a worse adjusted hazard ratio of 1.29 and 1.35 as compared to E and A respectively ($p < 0.05$). Similar results were seen with 1L Rx duration of $<$ 12 mos ($p < 0.05$). **Conclusions:** These hypothesis-generating data provide real-world OS estimates with 2L D & NHT in mPC. In propensity-stratified analyses, mPC Pts who progressed on NHT had a worse OS with 2L D as compared to alternate NHT. Results were consistent in unadjusted analysis & subgroup analyses of 1L Rx $<$ 12 mos. Results are subject to residual confounding and missingness. After prospective validation these data may aid in Rx sequencing, Pts counselling, and design of future clinical trials in this setting. Research Sponsor: None.

Propensity score adjusted OS analyses.

	A-->D vs E	E-->D vs A
Overall no. of Pts	206 vs 514	137 vs 308
HR; 95% CI, p-value	1.29; 1.04-1.60, 0.02	1.35; 1.03, 1.77, 0.03
No. of Pts with 1L <12 mos	172 vs 344	108 vs 192
HR; 95% CI, p-value	1.33; 1.07-1.65, 0.01	1.36; 1.01-1.82, 0.04

5538 **Poster Session (Board #119), Fri, 8:00 AM-11:00 AM**

Impact of olaparib vs physician's choice of new hormonal agent (pcNHA) on burden of pain in metastatic castration-resistant prostate cancer (mCRPC): PROfound.

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Background: In the Phase III PROfound study (NCT02987543) olaparib significantly improved radiographic progression-free survival (primary endpoint) vs pcNHA (enzalutamide or abiraterone) in patients (pts) with mCRPC and homologous recombination repair (HRR) gene alterations. In pts with alterations in *BRCA1*, *BRCA2* and/or *ATM* (cohort A), time to pain progression was also significantly improved by olaparib vs pcNHA. We report additional pain analyses evaluated in the overall study population (cohort A and B). **Methods:** Pts were randomized to olaparib tablets (300 mg bid; n=256) or pcNHA (n=131). Pts completed the Brief Pain Inventory-Short Form (BPI–SF) questionnaire (electronic administration) every 4 weeks up to 6 months after progression or treatment crossover. Responses were analysed to determine time to progression to worst pain, pain severity and first opiate use for cancer-related pain (Kaplan-Meier), and also pain interference in daily activity (mixed model for repeated measures). **Results:** 85% and 76% of olaparib pts were free of pain progression (worst pain item) compared with 75% and 51% in the pcNHA arm, respectively at 6 and 12 months. The proportion of pts without pain progression (overall pain severity) also favoured olaparib (Table). Median time to first opiate use was significantly prolonged in olaparib arm compared with pcNHA arm; 18 months for olaparib vs 9 months for pcNHA (Table). BPI-SF pain interference scores were also more favourable for olaparib than pcNHA; difference in overall adjusted mean change from baseline score −0.75 (95% CI: −1.14, −0.36) *P*=0.0002. Further pain burden results for cohort A will also be presented. **Conclusions:** Olaparib reduced the burden of pain and time to first opiate use in pts with mCRPC and HRR gene alterations vs pcNHA, demonstrating a clinical and symptomatic patient benefit. Clinical trial information: NCT02987543. Research Sponsor: AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Time to pain progression and first opiate use (overall population).

	Endpoint	Events n (%)	6-month event free rate (%)	12-month event free rate (%)	Median (m)	HR (95% CI)	*P* value (nominal)
Time to progression in worst pain	olaparib (N=256)	32 (12.5)	85.2	76.3	NR	0.64 (0.35, 1.21)	0.149
	pcNHA (N=131)	16 (12.2)	74.7	50.5	NR		
Time to progression in pain severity	olaparib (N=256)	24 (9.4)	88.7	81.0	NR	0.71 (0.35, 1.54)	0.411
	pcNHA (N=131)	11 (8.4)	81.5	65.2	NR		
Time to first opiate use*	olaparib (n=175)	65 (37.1)	74.8	58.8	18.0	0.67 (0.46, 0.99)	0.023
	pcNHA (n=92)	44 (47.8)	61.0	47.7	9.0		

Overall questionnaire compliance rate: 92.6% olaparib; 93.1% pcNHA. *pts not on opiates at baseline

5539 **Poster Session (Board #120), Fri, 8:00 AM-11:00 AM**

Health-related quality of life (HRQoL) for olaparib versus enzalutamide or abiraterone in metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (HRR) gene alterations: PROfound.

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Background: In the randomized Phase III PROfound trial (NCT02987543), olaparib significantly prolonged radiographic progression-free survival compared with physician s choice of new hormonal agent (pcNHA, enzalutamide or abiraterone) in men with mCRPC and HRR gene alterations, whose disease had progressed on prior NHA. Olaparib significantly improved time to pain progression in Cohort A. We report additional patient reported outcome measures of HRQoL in the overall study population (Cohorts A+B). **Methods:** HRQoL was assessed in the overall study population using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, comprising 5 subscales: physical wellbeing (PWB), functional wellbeing (FWB), emotional wellbeing, social wellbeing, and prostate cancer subscale (PCS). The Trial Outcome Index (TOI; PWB+FWB+PCS) and FACT Advanced Prostate Symptom Index (FAPSI-6: derived from 6 FACT-P items) were also calculated. Adjusted mean change and time to deterioration in scores were statistically analyzed. **Results:** Baseline FACT-P total score was similar for both treatment arms. FACT-P total and subscale scores during treatment were all higher for olaparib vs pcNHA, with clinically meaningful differences between treatment arms in the adjusted least square (LS) mean changes from baseline in all but FWB and FAPSI-6 (Table). The time to deterioration in FACT-P total and TOI, FAPSI-6, PWB and PCS scores favored olaparib but were not statistically significant, with hazard ratios ranging from 0.68 to 0.94. Further HRQoL results for cohort A will also be presented. **Conclusions:** Olaparib delayed deterioration in HRQoL scores vs pcNHA and was associated with better HRQoL functioning over time compared with pcNHA in men with mCRPC and HRR gene alterations. Clinical trial information: NCT02987543. Research Sponsor: AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Comparison of change from baseline.

	LS means		
	Olaparib N = 162	pcNHA N = 74	Difference in LS means
FACT-P total	-8.01	-14.67	6.67
TOI	-5.05	-12.21	7.16
FAPSI-6	-0.54	-2.92	2.38
FWB*	-1.94	-3.53	1.59
PWB	-2.10	-4.30	2.20
PCS	-0.99	-4.32	3.33

*Olaparib n = 160. A clinically meaningful change was an increase (improvement) or decrease (deterioration) of ≥6 (FACT-P total), ≥5 (TOI), ≥3 (FAPSI-6, PCS), or ≥2 points (PWB, FWB)

Radium-223 (Rad) and niraparib (Nira) treatment (tx) in castrate-resistant prostate cancer (CRPC) patients (pts) with and without prior chemotherapy (chemo).

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Background: Despite multimodality txs such as surgery, radiotherapy, hormonal tx and chemo, metastatic CRPC (mCRPC) prognosis remains poor. Research suggests PARP-1 is a key regulator of androgen receptor (AR) signaling and transition to lethal CRPC. Nira is a safe, potent and selective PARP-1/2 inhibitor that has shown single agent clinical activity in CRPC, and Rad is an alpha particle emitter. Addition of PARP inhibition may further enhance the clinical benefit of Rad. Nira has a favorable safety profile however, data on safety, tolerability and efficacy of Nira plus radiotherapy is limited. We hypothesize that targeting the PARP-1/AR axis in combination with radiation is safe and will improve mCRPC management. **Methods:** This is a phase (ph) Ib dose finding study (NCT03076203) of pts with progressive mCRPC using Time-to-Event Continual Reassessment Method (TITE-CRM). The primary objective is to determine the optimum ph II dose of Nira plus Rad (55 kBq/kg of body weight) in pts with and without prior chemo. Secondary endpoints include PSA reduction at 12 weeks (wks) and radiographic progression-free survival at 6 months. Pts enrolled to one of three dose levels of Nira (100, 200, and 300 mg PO daily). After completing 6 cycles of Rad, pts continued on Nira alone until objective progression, tx intolerance or pt decision. TITE-CRM identifies the maximum tolerated dose (MTD) based on toxicities observed over 12 wks of tx. **Results:** Between Oct 2017 and Jan 2020, 30 pts were enrolled (15 per stratum). Median age was 70 years; ECOG performance status was 0. The MTD of Nira was 100 mg in the chemo-exposed arm and 200 mg in the chemo-naïve arm. 19 Grade $\geq$ 3 adverse events were possibly related to tx: lymphocyte count decrease (n = 4, 13%), neutrophil count decrease (n = 3, 10%), anemia (n = 3, 10%), hypertension (n = 3, 10%), platelet count decrease (n = 2, 7%), creatinine increase (n = 1, 3%), hydronephrosis (n = 1, 3%), nausea (n = 1, 3%), white blood cell count decrease (n = 1, 3%). Tx duration and PSA response are shown in the table. **Conclusions:** Nira plus Rad was determined to be safe and tolerable. The MTD of Nira was identified and is pending ph II investigation. Managed by: Prostate Cancer Clinical Trials Consortium; Funded by: Janssen Scientific Affairs and Bayer Healthcare Pharmaceuticals, Inc Clinical trial information: NCT03076203. Research Sponsor: Janssen Scientific Affairs, Pharmaceutical/Biotech Company.

Cohort		Median Tx Duration (wks)	Proportion of Pts with ≥50% PSA Decline at 12 wks (%)
100 mg	Chemo-naïve (n = 3)	21	33
	Chemo-exposed (n = 10)	18	0
200 mg	Chemo-naïve (n = 7)	25	14
	Chemo-exposed (n = 5)	15	0
300 mg	Chemo-naïve (n = 5)	24	20
All Pts (n = 30)		19	10

5541 **Poster Session (Board #122), Fri, 8:00 AM-11:00 AM**

Prostate-specific antigen (PSA) kinetics in patients (pts) with advanced prostate cancer treated with apalutamide: Results from the TITAN and SPARTAN studies.

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Background: The phase III TITAN and SPARTAN studies demonstrated improved outcomes with the addition of apalutamide (APA) to androgen deprivation therapy (ADT); outcomes included prolonging overall survival and radiographic progression-free survival (rPFS) in metastatic castration-sensitive prostate cancer (mCSPC) in TITAN, and metastasis-free survival (MFS) in nonmetastatic castration-resistant PC (nmCRPC) in SPARTAN. A post hoc analysis of PSA kinetics in pts from both studies is reported. **Methods:** Baseline PSA at randomization, time to PSA nadir, and proportion of pts achieving a PSA decline of $\geq$ 90% (PSA90) and of pts achieving a PSA $\leq$ 0.2 ng/mL at 3 and 12 months and at any time after treatment in the APA arms of the TITAN and SPARTAN studies were evaluated. Within each study, rPFS/MFS were compared between pts achieving a PSA90 or PSA $\leq$ 0.2 ng/mL response vs not. **Results:** 525 TITAN pts and 806 SPARTAN pts treated with APA were included in the analysis. Median baseline PSA, time to PSA nadir, median PSA nadir, and maximum percentage changes from baseline PSA are shown in the table. PSA90 and confirmed PSA $\leq$ 0.2 ng/mL were evident as early as 3 months in both TITAN and SPARTAN, and percentage of confirmed response continued to increase at 12 months. Pts treated with APA who achieved PSA90 were at lower risk of rPFS events in TITAN and of MFS events in SPARTAN, with a hazard ratio (95% confidence interval) of 0.46 (0.321-0.653) and 0.36 (0.271-0.489) in each respective study (both $p < 0.0001$), compared with APA pts who did not achieve PSA90. Pts with confirmed PSA $\leq$ 0.2 ng/mL had similar rPFS and MFS benefits. **Conclusions:** Pts with advanced PC, whether mCSPC or nmCRPC, treated with APA + ADT demonstrated rapid PSA declines that continued over time. There was a high rate of pts with PSA90 and with PSA $\leq$ 0.2 ng/mL responses, with a majority of pts reaching PSA90 by 12 months. Pts achieving PSA90 and/or PSA nadir of $\leq$ 0.2 ng/mL had a prolonged rPFS and MFS in TITAN and SPARTAN, respectively. Clinical trial information: NCT02489318; NCT01946204. Research Sponsor: Janssen Research and Development.

	TITAN (mCSPC) N = 525	SPARTAN (nmCRPC) N = 806
Median baseline PSA, ng/mL	5.97	7.78
Time to PSA nadir (median), mo	5.55	7.36
Median PSA nadir, ng/mL	0.03	0.37
Maximum decrease from baseline (median), %	98	94
90% PSA rate, %		
3 mo	58	46
12 mo	71	61
Overall	72	62
Confirmed PSA ≤ 0.2 ng/mL, %		
3 mo	51	21
12 mo	64	35
Overall	67	38

5542 **Poster Session (Board #123), Fri, 8:00 AM-11:00 AM**

Safety and overall survival (OS) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with radium-223 (Ra-223) plus subsequent taxane therapy.

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Background: Ra-223, a targeted alpha therapy, showed a survival benefit and favorable safety profile over 3 years' (yrs) follow-up in mCRPC pts (ALSYMPCA trial). REASSURE (NCT02141438) is a global, prospective, single-arm, observational study of long-term Ra-223 safety in routine clinical practice in mCRPC pts (planned 7-yr follow-up). **Methods:** This analysis, based on the second prespecified interim analysis (data cutoff 3-20-2019) of REASSURE (N = 1465), evaluated safety/OS in the pt subset that was chemotherapy-naïve at Ra-223 administration but received subsequent taxane therapy any time after Ra-223 completion. **Results:** 182 pts received taxane therapy after Ra-223. Most (58%) had unresected primary tumors, 69% had ≥6 metastases, 99% received prior systemic anticancer therapy (Table). 143 (79%) completed 5 or 6 Ra-223 injections. Subsequent anticancer therapies included docetaxel (95%), enzalutamide (25%), cabazitaxel (24%), abiraterone (12%), lutetium-177-prostate-specific membrane antigen (4%), and sipuleucel-T (1%). During/up to 30 days after taxane therapy, 15 pts (8%) had grade 3/4 hematologic adverse events: anemia (erythropenia) (n = 11, 6%), neutropenia (n = 3, 2%), and thrombocytopenia (n = 2, 1%). Median OS was 24.3 (95% CI: 20.9–27.5) months from Ra-223 initiation and 11.8 (95% CI: 10.6–14.1) months from subsequent taxane initiation. **Conclusions:** In this cohort where Ra-223 was integrated prior to taxane therapy, most pts received multiple subsequent anticancer therapies. It appears that sequencing of multiple treatment modalities with different mechanisms of action may contribute to improved OS. Taxane therapy in routine clinical practice in pts previously treated with Ra-223 had acceptable hematologic safety/tolerability profiles. Clinical trial information: NCT02141438. Research Sponsor: Bayer.

	N = 182
Median age, yrs	70
Eastern Cooperative Oncology Group performance status 0–1, n (%)	160 (88)
Median time, months, from:	
Initial diagnosis to CRPC (n = 85)	36
CRPC to study entry (n = 104)	11
Diagnosis of bone metastases to study entry (n = 133)	22
Extent of disease, n (%)	
< 6 lesions	43 (25)
6–20 lesions	85 (50)
> 20 lesions	26 (15)
Superscan	6 (4)
Median laboratory values	
Prostate-specific antigen, ng/mL	33
Alkaline phosphatase, U/L	106
Lactate dehydrogenase, U/L	228
Hemoglobin, g/dL	13
Prior anticancer therapies, n (%)	
Abiraterone acetate	95 (52)
Enzalutamide	66 (36)
Sipuleucel-T	22 (12)
Fractures, n (%)	11 (6)
OS from start of:	
Ra-223, months	24.3
Subsequent taxane, months	11.8

5543 Poster Session (Board #124), Fri, 8:00 AM-11:00 AM

KEYNOTE-199 cohorts (C) 4 and 5: Phase II study of pembrolizumab (pembro) plus enzalutamide (enza) for enza-resistant metastatic castration-resistant prostate cancer (mCRPC).

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Background: Initial evidence suggests activity of pembro + enza in patients (pts) resistant to enza. We present results from the multicohort phase II study KEYNOTE-199 (NCT02787005) in chemotherapy-naive pts with mCRPC treated with pembro + enza after progression with enza and who had RECIST-measurable (C4) or bone-predominant (C5) disease. **Methods:** Pts who did or did previously receive abiraterone and for whom enza treatment failed after clinically meaningful response received pembro 200 mg Q3W, with continuation of enza for up to 2 y or until progression, toxicity, or withdrawal. End point was ORR per RECIST v1.1 (C4) by blinded independent central review (primary); DOR (C4), time to PSA progression, rPFS, OS, and safety. **Results:** A total of126 pts (C4, 81; C5, 45) were treated. Median (range) PSA was 31 ng/mL (0.4-1667) in C4 and 19 ng/mL (1-1750) in C5.Median (range) time from enrollment to data cut off was 15 mo (7-21) in C4 and 19 mo (7-21) in C5. In C4, ORR (95% CI) was 12% (6-22; 2 CRs, 8 PRs) and median (range) DOR was 6 mo (3+ to 13); 60% of pts had DOR ≥6 mo. DCR (CR + PR + SD) was 51% in C4 and C5. Median (95% CI) time to PSA progression was 4 mo (4-4) in C4 and 4 mo (4-4) in C5. Median (95% CI) rPFS was 4 mo (3-6) for C4 and 4 mo (3-6) for C5; 12-mo rPFS rate was 17% in C4 and 23% in C5. Median (95% CI) OS was NR (16-NR) in C4 and 19 (14-NR) mo in C5; 12-mo OS rate was 70% in C4 and 75% in C5. Shorter median OS was more associated with prior enza treatment <6 mo than with prior enza treatment ≥6 mo. Liver metastasis was associated with shorter median OS however, median OS in visceral disease subgroups appeared longer than expected. Any-grade/grade ≥3 treatment-related AEs occurred in 75%/26% of pts in C4 and 69%/24% in C5. Two pts in C5 died of immune-related AEs (Miller Fisher syndrome and myasthenia gravis). Any-grade/grade 3/4 rash (regardless of relatedness) was higher than that in prior reports for individual agents (33%/6%). **Conclusions:** Pembro + enza after enza resistance had manageable safety and showed antitumor activity for RECIST-measurable and bone-predominant mCRPC. This combination is being evaluated in an ongoing phase III combination trial. Clinical trial information: NCT02787005. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

OS by Subgroup	C4+C5 (N=126)	
	Median OS, mo (95% CI)	OS at 12 mo, %
Visceral disease		
With liver	n=15 11 (6-NE)	40
Without liver	n=25 NR (6-NE)	59
None	n=86 NR (18-NE)	82
Prior enza use		
<6 mo	n=16 11 (5-16)	40
≥6 mo	n=110 NR (18-NE)	77

5544 **Poster Session (Board #125), Fri, 8:00 AM-11:00 AM**

Pembrolizumab (pembro) plus olaparib in patients (pts) with docetaxel-pretreated metastatic castration-resistant prostate cancer (mCRPC): KEYNOTE-365 cohort A efficacy, safety, and biomarker results.

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Background: Pembro + olaparib has shown antitumor activity and acceptable safety in docetaxel-pretreated pts with mCRPC enrolled in cohort A of the phase I/II KEYNOTE-365 study (NCT02861573). Updated results with new biomarker data are reported. **Methods:** Pts with docetaxel-pretreated mCRPC who progressed within 6 mo of screening received pembro 200 mg IV Q3W + olaparib 400-mg capsule or 300-mg tablet PO BID. Pts might have received 1 other chemotherapy and ≤2 second-generation androgen-receptor targeted therapies. Primary end points: PSA response rate (decrease ≥50% from baseline, confirmed by a second value ≥3 wks later), ORR per RECIST v1.1, and safety. Key secondary end points: DCR, DOR, rPFS, and OS. Biospecimens (eg, blood, tissue) were collected for biomarker analysis (tissue PD-L1 expression, androgen receptor variant 7 [AR-v7] expression in circulating tumor cells [CTCs], and a T-cell–inflamed gene expression profile [GEP]). ctDNA was analyzed by Guardant Health 360 (GH360) and Omni (GH Omni) assays. FFPE tissue was analyzed by FoundationOne CDx (F1CDx) assay. **Results:** 84 of 87 enrolled pts were treated; 48/84 (57.1%) had measurable disease. Median (range) time from enrollment to data cutoff was 3.6 mo (0.0-29.2) for all pts and 26.7 mo (21.2-29.2) for 41 pts with ≥27 wks' follow-up. Confirmed PSA response rate was 9% (95% CI, 3.5-16.8) in 82 pts with a baseline PSA assessment. Median time to PSA progression: 3.8 mo (95% CI, 2.9-4.4). In 24 pts with measurable disease and ≥27 wks' follow-up, ORR was 8.3% (95% CI, 1.0-27.0; 2 PRs) and DCR ≥6 mo was 20.8% (95% CI, 7.1-42.2). Median (range) DOR was NR (12.0+ to 21.4+ mo); 2 pts had DOR ≥12 mo. In all pts, median rPFS was 4.3 mo (95% CI, 3.4-7.7) and median OS was 14.4 mo (95% CI, 8.1-18.5). Grade ≥3 TRAEs occurred in 29 pts (35%); 2 pts died of TRAEs (1 myocardial infarction, 1 unknown). Overall, 26% had PD-L1$^+$ tumors (combined positive score ≥1). Of 31 pts with CTC data, 12.9% were AR-v7$^+$. No *BRCA1/2* mutation was detected by GH360 (n=42). Of 57 pts analyzed by GH Omni, 2 had *BRCA2* mutations, 1 had a *BRCA1* mutation, 4 had *ATM* mutations, 1 had a *CHEK1* mutation, and 6 had *CDK12* mutations. Of 49 pts analyzed by F1CDx, 4 had *BRCA* mutations; 1 pt had a copy number loss mutation not detected by ctDNA analysis. GEP was not associated with ORR or PSA response. **Conclusions:** Pembro + olaparib continued to show activity and acceptable safety in pts with docetaxel-pretreated mCRPC. A phase III study of this combination is ongoing (KEYLYNK-010, NCT03834519). Clinical trial information: NCT02861573. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

5545 **Poster Session (Board #126), Fri, 8:00 AM-11:00 AM**

Pembrolizumab (pembro) plus enzalutamide (enza) in patients (pts) with abiraterone acetate (abi)-pretreated metastatic castration-resistant prostate cancer (mCRPC): KEYNOTE-365 cohort C efficacy, safety, and biomarker results.

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Background: Pembro + enza (cohort C) has shown antitumor activity and acceptable safety in abi-pretreated pts with mCRPC in the phase I/II KEYNOTE-365 study (NCT02861573). Updated results with new biomarker data from cohort C are reported. **Methods:** Pts who became intolerant to or for whom ≥4 weeks of abi failed in the prechemotherapy mCRPC state and who progressed within 6 mo of screening were enrolled. Pts received pembro 200 mg IV Q3W + enza 160 mg/day orally. Primary end points were PSA response rate (PSA decrease ≥50%; confirmed by a second value ≥3 weeks later), ORR per RECIST v1.1 by blinded independent central review, and safety. Key secondary end points were DCR per RECIST v1.1 (CR+PR+SD or non-CR/non-PD ≥6 mo), DOR per RECIST v1.1, radiographic PFS (rPFS) per PCWG-modified RECIST v1.1, and OS. Biospecimens (eg, blood, tissue) were collected at baseline and during the study for biomarker analysis, including tissue PD-L1 expression, androgen receptor variant 7 (AR-v7) expression in circulating tumor cells (CTCs), and a T-cell-inflamed gene expression profile (GEP). **Results:** Of 103 enrolled pts, 102 were treated; 39% of treated pts had measurable disease. Median (range) time from enrollment to data cutoff was 19.1 mo (1.1-28.8) for all pts and 21.4 mo (15.1-28.8) for pts with ≥27 wks' follow-up (n=69). Confirmed PSA response rate was 22% in 101 pts with a baseline PSA assessment. Median time to PSA progression was 3.5 mo (95% CI, 2.9-4.0). In pts with measurable disease and ≥27 wks' follow-up (n=25), confirmed ORR was 12% (2 CRs, 1 PR) and DCR was 32%. Median DOR was not reached (range, 0.0+ to 24.4+ mo); 2 pts had a response for ≥6 mo. In all pts, median (95% CI) rPFS was 6.1 mo (4.4-6.5) and median OS was 20.4 mo (15.5-NR). At 6 mo, rPFS rate was 55.1% and OS rate was 88.2%. Treatment-related AEs occurred in 92 pts (90%); most frequent (≥20%) were fatigue (38%), nausea (22%), and rash (20%). Grade 3-5 treatment-related AEs occurred in 40 pts (39%). Three pts died of AEs (1 AE was treatment related [cause unknown]). Of all pts, 29% had PD-L1^{+} tumors (combined positive score ≥1). Of 51 pts with AR-v7 data, 13.7% were AR-v7^{+} and 86.3% were AR-v7^{-}. GEP was not significantly associated with ORR or PSA response. **Conclusions:** Pembro + enza continued to show activity in pts with abi-pretreated mCRPC. Safety of the combination was consistent with the known profiles of pembro and enza. A phase III study of this combination is ongoing (KEYNOTE-641, NCT03834493). Clinical trial information: NCT02861573. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

5546 **Poster Session (Board #127), Fri, 8:00 AM-11:00 AM**

Use of plasma androgen receptor (AR) testing to optimize docetaxel chemotherapy in castration-resistant prostate cancer (CRPC): A multicenter biomarker study.

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Background: Plasma *AR* status has been identified as a potential biomarker of response in CRPC patients receiving docetaxel or the *AR*-targeted therapies abiraterone or enzalutamide. However, the relevance of plasma *AR* in the overall management of CRPC patients (pts) receiving docetaxel at different dose due to the toxicity profiles and physician-patient preferences is unknown. **Methods:** This was a multi-institution study of associations between baseline plasma *AR*-copy-number status assessed by droplet digital PCR and outcome in 325 CRPC pts. Between September 2011 and July 2019 pts started treatment with docetaxel administered at standard regimen 75mg/m^2 every three weeks or adapted regimen (75-80% of standard recommended dose or 30mg/m^2 weekly administration) at the discretion of the treating physician. Patients were assigned randomly into 2 sets with a ratio 2:1 to either training (n=217) and internal validation (n=108) cohorts. **Results:** In our study, adapted regimen of docetaxel was administered in 68 (31.3%) and 35 (32.4%) of training and validation cohorts, respectively. Based on plasma *AR* status, 67 (30.9%) and 39 (36.1%) validation and training set pts were classified as *AR* gain, respectively. In men treated with standard docetaxel regimen, no difference in progression-free/overall survival (PFS/OS) was seen between plasma *AR* normal and gain in both cohorts. In patients treated with adapted docetaxel regimen, we observed a significantly shorter median PFS (3.9 vs. 6.4 months, HR 4.77, 95%CI 1.48-3.80, p=0.0003) and median OS (11.2 vs. 20.4 months, HR 2.87, 95%CI 1.73-2.13, p=0.0008) in the training cohort. This finding was confirmed in the validation cohort (median PFS: 4.8 vs. 7.4 months, HR 2.54, 95%CI 1.40-4.58, p=0.005, and median OS: 11.8 vs. 26.4 months, HR 5.00, 95%CI 2.59-9.65, p<0.0001). In addition, *AR*-gained patients were less likely than *AR* normal to have a PSA decline when receiving an adapted regimen in both cohorts (p=0.010 e p=0.003, respectively). **Conclusions:** This study suggests that plasma *AR* may improve clinical decision making in choosing not only between *AR*-directed therapies and taxanes, but also between adapted and standard regimen of docetaxel in first- and subsequent-therapy lines, providing promising clinical implications to select the proper timing and dose of docetaxel. Prospective trials to validate these findings are warranted. Research Sponsor: None.

5547 **Poster Session (Board #128), Fri, 8:00 AM-11:00 AM**

Efficacy of enzalutamide (ENZA) + androgen deprivation therapy (ADT) in metastatic hormone-sensitive prostate cancer (mHSPC) by pattern of metastatic spread: ARCHES *post hoc* analyses.

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Background: ENZA + ADT significantly reduced the risk of radiographic progression or death in men with mHSPC (NCT02677896). Here, we assess how pattern of metastatic spread impacts the efficacy of ENZA + ADT in patients enrolled in ARCHES. **Methods:** Patients with mHSPC were randomized 1:1 to ENZA (160 mg/day) + ADT or placebo (PBO) + ADT, stratified by disease volume and prior docetaxel treatment. The primary endpoint was radiographic progression-free survival (rPFS). Secondary endpoints included time to prostate-specific antigen (PSA) progression, time to first symptomatic skeletal event (SSE), time to castration resistance, and time to initiation of new antineoplastic therapy. *Post hoc* analyses were performed by pattern of metastatic spread at study entry. **Results:** Of the overall population with known metastases at screening (n=1146), the largest patient subgroups were those with bone metastases only (n=513) and those with bone and soft-tissue metastases only (n=351); there were fewer M0 patients or patients with soft-tissue metastases only (n=154) and patients with visceral ± bone metastases (n=128). ENZA + ADT reduced the risk of rPFS and other secondary endpoint measures versus PBO + ADT across all subgroups, with greater relative efficacy observed in patients without visceral metastases (Table). **Conclusions:** ENZA + ADT provides improvements in rPFS and other secondary endpoints versus PBO + ADT in patients with mHSPC regardless of pattern of metastatic spread, particularly in patients without visceral metastases. These results highlight the importance of patient/physician discussion regarding the use of ENZA in the treatment of mHSPC. Clinical trial information: NCT02677896. Research Sponsor: This study was funded by Astellas Pharma Inc. and Pfizer Inc., the co-developers of enzalutamide. Medical writing and editorial assistance were provided by Lianne Young, BSc (Hons), and Jane Beck from Complete HealthVizion, funded by the study sponsors.

Endpoint, HR (95% CI)	Bone only (n=268;[b] n=245[c])	Bone and soft tissue only (n=164;[b] n=187[c])	M0[a] or soft tissue only (n=74;[b] n=80[c])	Visceral ± bone (n=64;[b] n=64[c])
rPFS	0.33 (0.22, 0.49)	0.31 (0.21, 0.47)	0.43 (0.16, 1.20)	0.94 (0.51, 1.73)
Time to PSA progression	0.12 (0.07, 0.22)	0.24 (0.15, 0.39)	0.07 (0.01, 0.54)	0.39 (0.17, 0.90)
Time to first SSE	0.51 (0.27, 0.96)	0.45 (0.22, 0.92)	NE (0.00, NR)	0.45 (0.11, 1.81)
Time to castration resistance	0.25 (0.17, 0.36)	0.26 (0.18, 0.39)	0.33 (0.13, 0.82)	0.49 (0.26, 0.92)
Time to new antineoplastic therapy	0.31 (0.19, 0.49)	0.16 (0.08, 0.33)	0.31 (0.07, 1.52)	0.68 (0.28, 1.61)

[a]Assessed as M0 by independent central review after investigator assessment as M1 at study entry; [b]ENZA + ADT; [c]PBO + ADT NE, not estimable; NR, not reached

5548 **Poster Session (Board #129), Fri, 8:00 AM-11:00 AM**

Prognostic markers for overall survival and outcome to LuPSMA radionuclide treatment in patients with metastatic castration-resistant prostate cancer.

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Background: The aim of this international multicenter retrospective analysis was to identify prognostic markers for the clinical outcome in late-stage mCRPC patients treated with ^{177}Lutetium-prostate-specific membrane antigen (LuPSMA) radionuclide treatment. **Methods:** Patients with progressive mCRPC treated with LuPSMA at six centers in Germany, USA, and Australia were considered for inclusion. Eligible patients had 24 predefined, pretherapeutic covariates (demographics, prior mCRPC treatments, and PSMA PET/CT derived parameters) and survival data available. Endpoints included overall survival (OS) and PSA progression-free survival (PSA-PFS). Covariates were tested using univariate and mulitvariate proportional hazards regression Cox models. **Results:** 267/414 (64%) patients met inclusion criteria and were analyzed. 113 patients participated in clinical trials (ACTRN12615000912583, NCT03042312), while 154 were enrolled in compassionate-access programs. After a median follow-up of 22.5 months, median OS was 13.0 months (95%CI 11.6-14.4); 83% of the patients died. Median PSA-PFS was 4.0 months (95%CI 3.2-4.7). In the multivariate analysis, factors associated with shorter OS were: shorter time since diagnosis of prostate cancer (HR=2.04; p=0.002), lower number of prior systemic therapies ($\leq$3; HR=1.56; p=0.006), prior exposure to chemotherapy (HR=1.42; p=0.05), lower hemoglobin levels (HR=1.13; p=0.002), higher number of lesions ($\geq$20: HR=1.53; p=0.009), multiple sites of metastases (bone/LN only vs. bone + LN; HR=1.39; p=0.03) and visceral involvement (M1c) (HR=1.45; p=0.01). Factors associated with longer PSA-PFS were: longer time since diagnosis of prostate cancer (HR=0.44; $p<0.001$), higher hemoglobin levels (HR=0.32; p=0.03), presence of pelvic lymph nodes (LN) metastasis (N1) (HR=0.68; p=0.01), no distant lymph node metastases (M1a) (HR=0.66; p=0.01), no skeleton involvement (HR=0.44; p=0.01), no visceral metastases (M1c) (HR=0.51; $p<0.001$), higher PSMA-positive tumor volume (HR=0.87; p=0.04), and higher SUVmean (HR=0.94; p=0.002). **Conclusions:** This retrospective analysis identified prognostic factors for survival and treatment response to LuPSMA. Along with the conventional risk factors in mCRPC, PSMA PET/CT can be a useful tool for stratifying patients and guide patient's selection for LuPSMA radionuclide treatment. Research Sponsor: Prostate Cancer Foundation.

5549 **Poster Session (Board #130), Fri, 8:00 AM-11:00 AM**

Overall survival after ^{177}Lu-PSMA-617 molecular radiotherapy in patients with metastatic castrate-resistant prostate cancer: Post-hoc analysis of a prospective phase II trial.

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Background: This was an open-label randomized prospective bi-centric single-arm phase II clinical trial of ^{177}Lu-PSMA-617 molecular radiotherapy in patients with progressive metastatic castrate-resistant prostate cancer (mCRPC) conducted at University of California Los Angeles (USA) and Excel Diagnostics & Nuclear Oncology Center (Houston, TX, USA) (NCT03042312). The study was investigator-initiated under an investigational new drug approval protocol (IND#133661) with authorization of charging for investigational drug (cost-recovery, Title 21 CFR 312.8). We report here the post-hoc analysis of overall survival (OS) in a single-study site cohort (UCLA). **Methods:** Patients with progressive mCRPC (biochemical, radiographic, or clinical) after ≥1 novel androgen axis drug (NAAD), either chemotherapy (CTX) naïve or post-CTX, with sufficient bone marrow reserve, normal kidney function, and sufficient PSMA-target expression by PET were eligible. Patients received up to 4 cycles of ^{177}Lu-PSMA-617 every 8±1 weeks and were randomized into 2 treatment activities groups (6.0 or 7.4 GBq). Efficacy was defined as serum PSA decline of ≥50% from baseline and served as primary endpoint (hypothesis: ≥40% of responders after 2 cycles). **Results:** 43 patients were randomized to the 6.0 GBq (n= 14) and 7.4 GBq (n=29) treatment arms. 11/43 (26%) were CTX naïve while 10/43 (23%), 12/43 (28%), 5/43 (12%) and 5/43 (12%) had received 1, 2, 3 or 4 CTX regimens. Median baseline PSA was 29.2 ng/ml (mean 228.8, range 0.5-2082.6). 21/43 (49%) completed 4 cycles of ^{177}Lu-PSMA-617 whereas 4/43 (9%), 13/43 (30%) and 5/43 (12%) underwent 1, 2 and 3 cycles. PSA decline of ≥50% was observed in 11/43 of patients (26%) after 2 cycles and in 16/43 (37%) at any time (best PSA response). 9/43 (21%) had a PSA decline of ≥90% and 23/43 (53%) had any PSA decline (>0%). After a median follow-up of 19.5 months the median OS was 14.8, 15.7 and 13.5 months in the whole cohort, the 6.0 GBq and 7.4 GBq treatment arms, respectively (p=0.68). Patients showing a PSA decline of ≥50% after 2 cycles and at any time had a longer OS: median 20.1 months vs. 13.6 (p=0.091) and 20.1 vs. 11.6 (p=0.002), respectively. **Conclusions:** In this post-hoc analysis of a single-site cohort of 43 patients included in a prospective phase II trial the median OS after 177Lu-PSMA-617 molecular radiotherapy in patients with progressive mCRPC was 14.8 months. There was no difference of efficacy between the 6.0 GBq and 7.4 GBq treatment arms. Clinical trial information: NCT03042312. Research Sponsor: None.

5550 **Poster Session (Board #131), Fri, 8:00 AM-11:00 AM**

Pembrolizumab (pembro) plus docetaxel and prednisone in patients (pts) with abiraterone acetate (abi) or enzalutamide (enza)-pretreated metastatic castration-resistant prostate cancer (mCRPC): KEYNOTE-365 cohort B efficacy, safety and, biomarker results.

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Background: Pembro + docetaxel and prednisone (cohort B) has shown antitumor activity in pts with mCRPC in the phase I/II KEYNOTE-365 study (NCT02861573). Updated efficacy and safety and new biomarker data from cohort B are reported. **Methods:** Pts who received at least 4 wk of abi or enza in the prechemotherapy mCRPC setting and whose disease progressed within 6 mo of screening were eligible. Pts received pembro 200 mg IV + docetaxel 75 mg/m^2 IV Q3W and prednisone 5 mg orally twice daily. Primary end points were PSA response rate (PSA decrease ≥50%; confirmed by a second value ≥3 weeks later), ORR per RECIST v1.1 by blinded independent central review, and safety. Key secondary end points were DCR per RECIST v1.1 (CR+PR+SD or non-CR/non-PD ≥6 mo), DOR per RECIST v1.1, radiographic PFS (rPFS) per PCWG-modified RECIST, and OS. Biospecimens (blood, tissue) were collected for biomarker analysis, including tissue PD-L1 expression, androgen receptor variant 7 (AR-v7) expression in circulating tumor cells, and a T-cell-inflamed gene expression profile (GEP). **Results:** Of 105 enrolled pts, 104 were treated, and 50% had measurable disease. Median (range) time from enrollment to data cutoff was 19.9 mo (1.4-27.8) for all pts and 21.8 mo (17.9-27.8) for pts with ≥27 wks follow-up (n=72). Confirmed PSA response rate was 28% in 103 pts with a baseline PSA assessment. Median time to PSA progression was 6.2 mo (95% CI, 3.7-7.4). In pts with measurable disease and ≥27 wks follow-up (n=39), ORR was 18% (7/39, all PRs) and DCR was 51%. Median DOR was 6.7 mo (range, 3.4-9.0+ [+ indicates ongoing responder]); 5 pts had a response for ≥6 mo. In all pts, median rPFS was 8.3 mo (95% CI, 7.6-10.1) and OS was 20.4 mo (16.9-NR). At 6 mo, the rPFS rate was 72.8% and OS rate was 95.3%. Treatment-related AEs (TRAEs) occurred in 96% of all pts; most frequent were alopecia (39%), diarrhea (38%), and fatigue (38%). Grade 3-5 TRAEs occurred in 40% of pts; 2 pts died of TRAEs (pneumonitis). Overall, 24% of pts were PD-L1$^+$ (combined positive score ≥1). Of 57 pts with AR-v7 data, 17.5% were AR-v7$^+$, 77% were AR-v7$^-$, and 5% were undetermined. GEP was not significantly associated with ORR or PSA response. **Conclusions:** Pembro + docetaxel and prednisone showed activity in pts with abi or enza-pretreated mCRPC. Safety of the combination was consistent with the known profiles of the individual agents. A phase 3 study of this combination is ongoing (KEYNOTE-921, NCT03834506). Clinical trial information: NCT02861573. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

5551 **Poster Session (Board #132), Fri, 8:00 AM-11:00 AM**

Prostate cancer biomarker enrichment and treatment selection (PC-BETS) study: A Canadian cancer trials group phase II umbrella trial for metastatic castration-resistant prostate cancer (mCRPC).

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Background: Genomic characterization of mCRPC has identified commonly occurring alterations but also recurrently mutated genes at much lower frequencies. To efficiently evaluate anti-tumor activity of novel targeted therapies in mCRPC patients (pts) we initiated an umbrella trial using circulating tumour DNA (ctDNA) to enrich accrual for cancers with alterations that may predict response. **Methods:** mCRPC pts that have progressed after treatment with a next generation AR-pathway inhibitor (ARPI) were enrolled to this multi-center, multi-arm, 2-stage phase II trial. Plasma cell-free DNA was subjected to targeted sequencing and pts allocated to a treatment arm by a Tumor Board (TB) based on *a priori* criteria (biomarker positive, BM+) or by randomization if biomarker negative (BM-). Primary objective was to determine the clinical benefit rate (CBR: PSA decline ≥50% (PSA50), CR/PR, or stable disease ≥12 weeks). We report on 1st-stage activity of arms evaluating inhibitors of CDK4/6 (palbociclib), WEE1 kinase (adavosertib), cMET (savolitinib) and the AR inhibitor darolutamide. Additional planned arms include inhibitors of AKT (ipatasertib), Polo-like Kinase 4 (CFI-400945), immune checkpoints (durvalumab, tremelimumab) and carboplatin. **Results:** 250 pts were screened from two sequential trials over 29 months at 11 centers. Median time from blood draw to TB decision was 35 days. 169 pts (68%) had detectable ctDNA (≥1%) with a mean ctDNA fraction of 24% (range 1-95%). Commonly detected genomic alterations involved AR (49% gain, 24% mutation), TP53 (49%), PTEN/PI3K pathway (35%), DNA repair (23%: mismatch repair (5%), BRCA2 (8%), ATM (3%), CDK12 (5%), other (2%)) and CTNNB1/APC (14%). To date, 46 BM+ pts and 37 BM- patients were enrolled: median age 70 years (53-88), 100% had prior ARPI, 45% had prior docetaxel, 17% with visceral metastases. Accrual and CBR are presented in table. Adverse events were as expected. **Conclusions:** Prospective centralized screening of ctDNA to stratify mCRPC pts into a precision oncology trial is feasible. Activity was seen in 4 of 7 evaluable cohorts with darolutamide and adavosertib, meeting the threshold for expansion of these arms. Clinical trial information: NCT03385655, NCT02905318. Research Sponsor: Canadian Cancer Clinical Trials Network, Other Foundation, Pharmaceutical/Biotech Company, Canadian Cancer Society.

	Palbociclib		Adavosertib		Savolitinib		Darolutamide		
	BM+	BM-	BM+	BM-	BM+	BM-	BM+ AR gain	BM+ AR mut	BM-
Pts Enrolled (N)	6	10	10	9	3	9	17	10	9
Pts with CBR (N)	0	0	0	1	0	0	2	3	1

5552 **Poster Session (Board #133), Fri, 8:00 AM-11:00 AM**

First-in-human phase I study of HPN424, a tri-specific half-life extended PSMA-targeting T-cell engager in patients with metastatic castration-resistant prostate cancer (mCRPC).

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Background: HPN424 is a first-in-class, prostate-specific membrane antigen (PSMA)-targeting T-cell engager designed as a small, globular protein to enable efficient solid-tumor penetration with prolonged half-life. HPN424 is derived from the TriTAC platform (Tri-specific T-Cell-Activating Construct) and engineered with three binding domains: anti-PSMA for tumor cell engagement, anti-albumin for half-life extension and anti-CD3 for T-cell engagement. **Methods:** This Ph I study is evaluating HPN424 in progressing mCRPC patients (pts) who have received >2 prior systemic therapies. Primary endpoints are safety, tolerability and determination of MTD/RP2D. Secondary objectives are pharmacokinetics (PK), pharmacodynamics, immunogenicity, and preliminary anti-tumor activity. HPN424 is administered IV once weekly. Tumor assessments include PSA, CT, and bone scans every 9 weeks. **Results:** As of 1/17/20, 27 pts were dosed in 8 cohorts ranging from 1.3 to 72ng/kg. Pts received a median of 6 prior systemic regimens, including >1 novel AR therapy, and 59% received prior chemotherapy for mCRPC. Median PSA at baseline was 251 ng/mL (range: 0.05 – 5000). No DLTs have been observed. The most common grade >3 TRAEs were cytokine release syndrome (CRS) (3 pts) and transient elevated liver transaminases (2 pts) that occurred concurrently with CRS. All CRS events resolved and pts were successfully re-treated. Short-term steroid premedication was effective in limiting CRS and allowing long-term weekly treatment. HPN424 demonstrated dose proportional increase in Cmax and AUC with a geometric mean T1/2 of 30.5 hours. Dose-dependent, transient increases in peripheral cytokine and chemokine levels were observed. Reduction in circulating tumor cells (CTCs) was seen in 11 of 19 pts with measurable CTC at baseline. Six pts had PSA decreases from baseline ranging from -3.8% to -76%, including 2 pts with PSA decline ≥50%. Ten of 20 pts (50%) with > 18 weeks follow-up remained on study beyond week 18 and includes 8 pts on study > 24 weeks. **Conclusions:** HPN424 represents a novel half-life extended PSMA-targeting T-cell engager that can be safely administered once weekly. AEs have been transient and manageable. Cytokine increases indicate T-cell activation. CTC reductions in subset of pts suggest target engagement. Early signs of clinical activity include PSA reductions and time on study, including 8 pts on study > 24 weeks. Dose escalation is ongoing, including exploration of step dosing. Clinical trial information: NCT03577028. Research Sponsor: Harpoon Therapeutics.

5553 **Poster Session (Board #134), Fri, 8:00 AM-11:00 AM**

Primary analysis of a phase II study of metastasis-directed ablative therapy to PSMA (^{18}F-DCFPyL) PET-MR/CT defined oligorecurrent prostate cancer.

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Background: Despite maximal local therapies (MLT) (radical prostatectomy followed by radiotherapy [RT]), 20-30% of men will progress to incurable prostate cancer (PCa). Most recurrences in this scenario are characterized by rise in PSA with negative bone scan (BS) and computed tomography (CT). We conducted a phase II trial for men with rising PSA after MLT using ^{18}F-DCFPyL (PSMA) PET-MR/CT followed by metastasis-directed therapy (MDT) to PET positive foci. We report the results of our primary analysis. **Methods:** Patients with rising PSA (0.4-3.0 ng/mL) after MLT, negative BS/CT and no prior salvage ADT were eligible. All patients underwent PSMA PET-MR and PET-CT. Those with limited disease burden amenable to MDT underwent either stereotactic ablative RT (SABR) or surgery (lymph node dissection). No ADT was used. The primary endpoint was biochemical response rate (complete [undetectable PSA] or partial [PSA decline $\geq$50% from baseline]) following MDT. A Simon's two-stage study design was employed. Estimated time of delay in salvage ADT was calculated using the Kaplan-Meier method. Toxicity was prospectively recorded (CTCAE v4.0). **Results:** After a median of 63 months (range 3-180) post MLT, 72 patients underwent PSMA PET-MR/CT with median PSA 0.98 ng/mL (range 0.4-3.1). Sixteen patients had negative and 56 had positive PET-MR/CT scans, of which 37 (51%) were amenable to MDT. The median number of treated lesions was 2 (range 1-5). Of the treated patients, 30 (81%) had miT0N1M0 disease, 2 (5.5%) had miT0N1M1a, 2 (5.5%) had miT0N0M1a and 3 (8%) had miT0N0M1b. Twenty-seven patients underwent SABR (median 30 Gy in 3 fractions) and 10 had surgery. At a median of 11 months (range 1-29) post MDT, 8 patients (22%) had complete (CR) and 14 (38%) had partial (PR) responses. Among the 8 CRs, 5 had surgery and 3 had SABR; of the 14 PRs, 2 had surgery and 12 had SABR. The estimated median delay in salvage ADT for the entire cohort, PR and CR subgroups was 13 months (IQR 8-20), 16 months (IQR 13-20) and 30 months (IQR not reached), respectively. Two grade 2+ toxicities were observed, both in surgical patients: deep venous thrombosis and ureteric injury requiring stent placement. **Conclusions:** ^{18}F-DCFPyL PET-MR/CT has high detection rates (78%) in men with rising PSA after MLT. We observed a favorable therapeutic index with MDT (60% response rate) for patients with metachronous PSMA-unveiled oligometastatic PCa following MLT. Phase III studies using validated intermediate clinical endpoints are needed before integration into routine practice. Clinical trial information: NCT03160794. Research Sponsor: Terry Fox Canadian Comprehensive Cancer Centre Network (TF4CN) Pilot Project, Terry Fox Research Institute (TFRI); Abbvie CARO Uro-Oncologic Radiation Awards (ACURA); Astellas Prostate Cancer Innovation Fund, University of Toronto, Other Foundation.

5554 **Poster Session (Board #135), Fri, 8:00 AM-11:00 AM**

Cabazitaxel versus enzalutamide/abiraterone in CARD eligible mCRPC patients with or without germline HRR defects.

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Background: The CARD trial proved that in mCPRC patients (pts), previously treated with docetaxel and an androgen-receptor signaling inhibitor (ARSi), cabazitaxel (CBZ) significantly improves progression-free (PFS) and Overall Survival (OS) compared with the alternative ARSi. Concurrently, the PROFOUND study showed the superiority of olaparib vs. ARSi in pts with similar prior treatment history and genetic alterations in Homologus Recombination DNA repair related genes (HRR). **Methods:** PROREPAIR-B (NCT03075735) is a prospective study which aimed to demonstrate the prognostic role of germline deleterious mutations in (g)HRR genes and the benefit of first (1L), second (2L) and subsequent therapy lines for mCRPC. Outcomes with 1-2L have been previously reported. Here we evaluated radiographic (r)-PFS, clinical (c)-PFS, and OS in PROREPAIR-B pts who meet CARD study eligibility criteria and who received CBZ and/or ARSi. Survival analysis were performed using Kaplan Meier method and Cox regression models. **Results:** 95 out of 419 mCRPC pts included in PROREPAIR-B meet CARD eligibility criteria and received CBZ (n=60) or ARSi (n=35) including 14 gHRR carriers, 8/6 treated with CBZ/ARSi, respectively. Visceral metastases were more frequent among pts treated with CBZ (p=0.01). ECOG 2, M1 at diagnosis, Abiraterone as 1^{st} ARSi and prior radiographic PD (all $p<0.05$) were more frequent in our pts than in the CARD study. Overall, CBZ was superior to ARSi in terms of rPFS (median 6.0 vs. 3.7 months (m), p=0.03), cPFS (median 4.4 vs. 3.4 m, p=0.01) and PSA50 responses (39% vs. 17%, p=0.027). Differences in OS were not observed, although approximately 60% of patients in ARSi had crossed to CBZ at the time of the analyses. Results of subgroups analyses were similar to those reported by CARD. In this series, gHRR carriers had a significant worse prognosis (OS HR 1.9; rPFS HR 2.4; cPFS HR 2.6) than non-carriers. In gHRR carriers CBZ was not superior to ARSi in terms of rPFS (2.5 vs. 3.0 m, p=0.8), cPFS (2.5 vs. 2.4 m, p=0.8) and OS (4.5 vs. 3.7, p=0.8). Cox MVA models adjusted for unbalances and CARD grouping factors confirmed a significant interaction between treatment and gHRR status for rPFS and cPFS, suggesting that the benefit of CBZ was not observed in gHRR. **Conclusions:** Our results confirm the benefit of CBZ treatment over a second ARSi (either abiraterone or enzalutamide) in unselected mCRPC population. However, the outcomes in gHRR carriers are poor with either CBZ or ARSi supporting the need of novel therapies in this setting. Clinical trial information: NCT03075735. Research Sponsor: Spanish Society of Medical Oncology (SEOM), Spanish Oncology Genitourinary Group (SOGUG), Pharmaceutical/Biotech Company.

5555 **Poster Session (Board #136), Fri, 8:00 AM-11:00 AM**

Detection of prostate cancer and determination of its significance using explainable artificial intelligence.

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Background: The variation of the human perception has limited the potential of multi-parametric magnetic resonance imaging (mpMRI) of the prostate in determining prostate cancer and identifying significant prostate cancer. The current study aims to overcome this limitation and utilizes an explainable artificial intelligence to leverage the diagnostic potential of mpMRI in detecting prostate cancer (PCa) and determining its significance. **Methods:** A total of 6,020 MR images from 1,498 cases were considered (1,785 T2 images, 2,719 DWI images, and 1,516 ADC maps). The treatment determined the significance of PCa. Cases who received radical prostatectomy were considered significant, whereas cases with active surveillance and followed for at least two years were considered insignificant. The negative biopsy cases have either a single biopsy setting or multiple biopsy settings with the PCa exclusion. The images were randomly divided into development (80%) and test sets (20%) after stratifying according to the case in each image type. The development set was then divided into a training set (90%) and a validation set (10%). We developed deep learning models for PCa detection and the determination of significant PCa based on the PlexusNet architecture that supports explainable deep learning and volumetric input data. The input data for PCa detection was T2-weighted images, whereas the input data for determining significant PCa include all images types. The performance of PCa detection and determination of significant PCa was measured using the area under receiving characteristic operating curve (AUROC) and compared to the maximum PiRAD score (version 2) at the case level. The 10,000 times bootstrapping resampling was applied to measure the 95% confidence interval (CI) of AUROC. **Results:** The AUROC for the PCa detection was 0.833 (95% CI: 0.788-0.879) compared to the PiRAD score with 0.75 (0.718-0.764). The DL models to detect significant PCa using the ADC map or DWI images achieved the highest AUROC [ADC: 0.945 (95% CI: 0.913-0.982; DWI: 0.912 (95% CI: 0.871-0.954)] compared to a DL model using T2 weighted (0.850; 95% CI: 0.791-0.908) or PiRAD scores (0.604; 95% CI: 0.544-0.663). Finally, the attention map of PlexusNet from mpMRI with PCa correctly showed areas that contain PCa after matching with corresponding prostatectomy slice. **Conclusions:** We found that explainable deep learning is feasible on mpMRI and achieves high accuracy in determining cases with PCa and identifying cases with significant PCa. Research Sponsor: Department of Defense.

5556 **Poster Session (Board #137), Fri, 8:00 AM-11:00 AM**

Prospective evaluation of ^{18}F-DCFPyL PET/CT in biochemically recurrent prostate cancer: Analysis of lesion localization and distribution.

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Background: ^{18}F-DCFPyL, a promising PET agent targeting prostate specific membrane antigen (PSMA), is prospectively evaluated in a single academic center for detecting recurrent lesions in prostate cancer patients with biochemical recurrence (BCR). **Methods:** We prospectively enrolled 150 men (51-91 years old, mean ± SD: 70.3±7.5) with biochemical recurrence (PSA median 2.38 ng/mL, range 0.12 to 698.4) after primary definitive treatment with prostatectomy (65%), radiotherapy (35%) or both (19%). The ^{18}F-DCFPyL positive lesions compatible with prostate cancer were evaluated by two independent readers. Impact of ^{18}F-DCFPyL PET/CT on patient management was recorded from clinical chart review. **Results:** ^{18}F-DCFPyL PET/CT had an overall positivity rate of 83% (125 scans), which increased with higher prostate specific antigen (PSA) levels (ng/mL): 63% (PSA $<$ 0.5), 75% (0.5$\leq$PSA $<$ 1), 91% (1$\leq$PSA $<$ 2), 95% (2$\leq$PSA $<$ 5) and 98% (PSA$\geq$5), respectively. In the cohort who underwent prostatectomy, ^{18}F-DCFPyL PET/CT had higher positivity rate in patients with shorter PSA doubling time (PSAdt) (94% in PSAdt 0-3 months vs. 53% in PSAdt $>$ 12 months, $P<$ 0.01). No difference of ^{18}F-DCFPyL positivity rate was observed in post-radiation patients with different PSAdt, nor were there differences between patients with low grade (Gleason 6) or higher-grade prostate cancer (Gleason 7-10). 20 patients (13%) had lesions in the prostate bed only and 41 patients (27%) had oligometastatic disease (1-3 lesions), making them candidates for locally targeted therapy. We identified a total of 1455 ^{18}F-DCFPyL positive lesions, including 51 lesions in the prostate bed, 271 pelvic and 463 extra-pelvic lymph nodes, approximately 585 osseous lesions, including 5 patients with diffuse osseous metastases, and 85 lesions in other organs (most commonly in the lungs). 91 out of 150 patients (61%) had change in treatment after ^{18}F-DCFPyL PET and, most noticeably, 48 of these patients (32% total) had lesions only localized on ^{18}F-DCFPyL PET/CT despite negative conventional imaging. **Conclusions:** ^{18}F-DCFPyL PET/CT holds great potential to be a "one-stop shop" diagnostic tool in the work-up of BCR prostate cancer, with high (61%) impact on the management of these patients. Clinical trial information: NCT03501940. Research Sponsor: Progenics provided DCFPyL as part of a research access program. No other financial support.

5557 **Poster Session (Board #138), Fri, 8:00 AM-11:00 AM**

Updated results of a phase I/II prospective dose escalation trial evaluating safety and efficacy of combination ^{177}Lu PSMA 617 and idronoxil in men with mCRPC post androgen signalling inhibition and taxane chemotherapy (LuPIN trial).

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Background: There is no established standard of care post cabazitaxel in men with mCRPC. Ongoing trials in ^{177}LuPSMA-617 have demonstrated good efficacy and safety, but synergistic combinations may further improve treatment responses. Idronoxil (NOX66) inhibits external NADH oxidase type 2 with downstream pro-apoptotic actions including radio-sensitization. Herein we present updated results and an additional cohort of a prospective single arm phase I/II dose escalation/expansion trial of LuPSMA-617 and NOX66 in mCRPC. **Methods:** Men with progressive mCRPC post androgen signalling inhibition (ASI) and 2 lines of taxane chemotherapy were considered eligible. Key inclusion criteria included PSMA PET/CT intensity SUV max $>$ 15 with no discordant disease on FDG PET/CT, Hb $>$10, Platelets $>$100 and GFR $>$40mls/min. Enrolled patients received up to 6 doses of ^{177} Lu-PSMA 617 (7.5Gbq) day 1 every 6 weeks in combination with NOX66 days 1-10 each cycle. Cohort 1 (n=8) received 400mg NOX66. Cohorts 2 and 3 subsequently received 800mg and 1200mg of NOX66, respectively, following safety reviews. Data regarding safety, efficacy, pain scores, and QOL were collected. **Results:** 32 men were enrolled in cohorts 1&2 (November 2017 – June 2019) and 24 in cohort 3 (August 2019-February 2020). To date there have been no dose-limiting toxicities. Data for cohort 3 are immature. For cohorts 1 & 2: 31/32 men received $\geq$2 cycles, with 12/32 (47%) completing 6 cycles. Any PSA response was seen in 84% (27/32), with a PSA response $>$ 50% in 62.5% (20/32). Median PSA PFS is 6.1 months Of men with increased baseline pain scores $\geq$3 (24/32), 50% (12/24) had a clinically significant reduction in pain indicators. Adverse events are summarized below. Updated results for cohorts 1 and 2 and preliminary results of cohort 3 will be presented. **Conclusions:** Combination LuPSMA-617 + NOX 66 appears safe and efficacious in men with heavily pre-treated end stage mCRPC. Clinical trial information: ACTRN12618001073291. Research Sponsor: Noxopharm.

5558 **Poster Session (Board #139), Fri, 8:00 AM-11:00 AM**

Pain progression at initiation of cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) is associated with a poor prognosis: a post-hoc analysis of PROSELICA.

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Background: PROSELICA phase III trial (NCT01308580) showed that cabazitaxel 20 mg/m2 (C20) is non-inferior to C25 in mCRPC patients (pts) post-docetaxel (DOC) *(Eisenberger JCO 2017)*. Pts enrolled were symptomatic or not. This post-hoc analysis evaluates the influence of progression type at randomization on outcomes. **Methods:** Progression type at randomization was defined as follows: PSA progression only (PSA-p; no radiological progression (Radio-p), no pain), Radio-p (± PSA-p, no pain) or pain progression (pain-p, ±PSA-p, ±Radio-p). The relationship between progression type and overall survival (OS), radiological progression-free survival (rPFS) and PSA response (confirmed PSA decrease ≥ 50%) was analyzed. **Results:** All patients randomized (n = 1200) had received prior DOC and 25.7% had received prior abiraterone or enzalutamide. Progression type was evaluable in 1065 pts (PSA-p = 24.5%, radio-p = 20.9%, pain-p = 54.6%). Pain progression was associated with clinical and biological features of aggressive disease and worse outcomes (decreased PSA response, rPFS and OS) vs PSA-p or radio-p (Table). The survival (rPFS and OS) on C25 was numerically higher than on C20 in pts with radio-p and pain-p. Conversely, C20 and C25 equally benefited pts with PSA-p only. In multivariate analysis (all arms combined), pain progression was an independent predictor of poor OS. **Conclusions:** This post-hoc analysis of PROSELICA shows that pain progression at initiation of cabazitaxel in mCRPC pts previously treated with DOC is prognostic. The activity of C25 was numerically higher than C20 in patients with radiological or pain progression. Clinical trial information: NCT01308580. Research Sponsor: None.

	Progression type			
	PSA-p N = 261	Radio-p N = 223	Pain-p N = 581	Global p°
PSA response				
- Overall	35.9%	43.7%	31.3%	p = 0.02
- C20	31.2%	33.7%	26.0%	p = 0.49
- C25	41.8%	53.9%	36.0%	p = 0.02
rPFS				
- Overall	10.0 [9.3; 11.3]	8.1 [7.0; 8.8]	7.8 [6.9; 8.4]	p < 0.001
- C20	10.0 [9.0; 11.3]	7.2 [5.3; 8.3]	7.1 [6.0; 8.3]	p < 0.001
- C25	9.8 [8.9; 14.7]	8.7 [7.2; 9.8]	8.2 [7.2; 8.9]	p < 0.001
OS from mCRPC diagnosis				
- Overall	47.8 [42.6; 53.3]	41.6 [38.0; 45.9]	37.1 [34.5; 40.0]	p < 0.001
- C20	49.1 [40.1; 55.1]	41.6 [37.1; 47.6]	36.0 [31.7; 39.7]	p < 0.001
- C25	45.7 [39.0; 62.5]	41.0 [35.0; 46.6]	38.3 [34.7; 41.2]	p = 0.001
OS from randomization				
- Overall	18.4 [15.9; 21.1]	16.8 [14.3; 18.4]	12.0 [11.1; 12.8]	p < 0.001
- C20	18.5 [15.1; 22.3]	14.7 [11.1; 17.7]	11.6 [10.1; 12.5]	p < 0.001
- C25	17.9 [14.7; 21.9]	18.7 [15.1; 21.1]	12.5 [11.1; 14.4]	p < 0.001

*median [95% CI], months; °Log rank test for rPFS and OS

5559 Poster Session (Board #140), Fri, 8:00 AM-11:00 AM

Efficacy and safety in older patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) receiving cabazitaxel (CBZ) versus abiraterone (ABI) or enzalutamide (ENZ) in the CARD study.

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Background: In the CARD (NCT02485691) study, radiographic PFS (rPFS), PFS and OS were significantly improved with CBZ vs. androgen-signaling-targeted agents (ARTA; ABI or ENZ) in pts with mCRPC who had received docetaxel (DOC) and progressed within 12 months (mo) on an alternative ARTA. This analysis evaluated the impact of age ($<$ 70 vs. $\geq$ 70 years) on the efficacy and safety of CBZ and ARTAs in CARD. **Methods:** 255 pts with mCRPC were randomized 1:1 to CBZ (25 mg/m^2 IV Q3W + prednisone [P] + G-CSF) vs. ABI (1000 mg PO + P) or ENZ (160 mg PO) until disease progression, unacceptable toxicity or pt request. Pts were eligible if they had received $\geq$ 3 cycles of DOC and progressed $\leq$ 12 mo on the previous alternative ARTA. Primary endpoint was rPFS. Subgroup analysis of older ($\geq$ 70 years; n = 135) and younger ($<$ 70 years; n = 120) pts was pre-specified for rPFS; others were post hoc. **Results:** rPFS was significantly improved vs. ARTA in both older (median 8.2 vs. 4.5 mo; HR 0.58; 95% CI 0.38–0.89) and younger pts (median 7.4 vs. 3.2 mo; HR 0.47; 95% CI 0.30–0.74). Median OS for CBZ vs. ARTA was 13.9 vs. 9.4 mo (HR 0.66; 95% CI 0.41–1.06) in older pts and 13.6 vs. 11.8 mo (HR 0.66; 95% CI 0.41–1.08) in younger pts. PFS, tumor, PSA and pain responses also favored CBZ, regardless of age. Grade $\geq$ 3 adverse events (AEs) occurred in 57.8% vs. 49.3% of older pts receiving CBZ vs. ARTA and 48.4% vs. 42.1% in younger pts. AEs leading to death were more frequent with ARTA, mainly due to disease progression. **Conclusions:** CBZ had improved efficacy outcomes vs. ARTA in pts with mCRPC previously treated with DOC and the alternative ARTA, regardless of age. Grade $\geq$ 3 cardiac AEs were more frequent in older pts treated with ARTA. A higher rate of AEs was reported in older vs. younger pts, for ARTA and CBZ. CBZ and ARTA had different safety profiles in older compared with younger pts. Clinical trial information: NCT02485691. Funding: Sanofi. Research Sponsor: Sanofi.

	< 70 years		≥ 70 years	
AEs, %	CBZ n = 62	ARTA n = 57	CBZ n = 64	ARTA n = 67
Serious AE	32.3	33.3	45.3	43.3
AE leading to death	1.6	7.0	9.4	13.4
Any grade ≥ 3 AE	48.4	42.1	57.8	49.3
Infection	9.7	5.3	4.7	7.5
Cardiac disorder	1.6	0.0	0.0	9.0
Asthenia or fatigue	1.6	3.5	6.3	1.5
Spinal cord/nerve-root disorder	1.6	3.5	3.1	4.5
Febrile neutropenia	3.2	0.0	3.1	0.0

5560 **Poster Session (Board #141), Fri, 8:00 AM-11:00 AM**

Phase I dose-escalation study of PSMA-targeted alpha emitter ^{225}Ac-J591 in men with metastatic castration-resistant prostate cancer (mCRPC).

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Background: Antibodies (Abs) or small molecules can target PSMA with different biodistribution. Certain sites of PSMA expression (e.g. salivary/lacrimal glands, kidneys, small bowel) are not accessible to Abs. Given radiosensitivity of PC and potency of alpha emitters plus the ability to minimize targeting off tumor PSMA+ sites with J591, we performed a 1st in human study of ^{225}Ac-J591. **Methods:** Men with progressive mCRPC following at least 1 potent AR-pathway inhibitor (ARPI) and chemo (or unfit/refuse) without limit of # prior therapies (Ra-223 and ^{177}Lu-PSMA allowed) with ECOG PS 0-2 and adequate organ function were eligible. Baseline ^{68}Ga-PSMA11 PET was performed, but not used for eligibility. Initially 1-subject cohorts treated until transition to 3+3 at dose level 5 (predicted by dosimetry to have moderate toxicity) with a single infusion of ^{225}Ac-J591 (13.3 KBq/kg with planned escalation up to 93.3 KBq/kg). Dose-limiting toxicity (DLT) defined as attributable grade (Gr) 4 heme toxicity or Gr 3/4 non-heme tox. Imaging, genomic, patient-reported outcomes (PRO), and immune correlates embedded. **Results:** 22 men treated on 7 dose levels; median age 72.5 (range 58-89), PSA 147 (5-7168); 82% with $>$2 prior ARPI, 64% chemo, 23% Ra-223, 55% ^{177}Lu-PSMA. 1 (5%) CALGB (Halabi) good prognostic risk, 10 (45%) intermed, 11 (50%) poor risk. 1 of 6 in cohort 6 (80 KBq/kg) had DLT (Gr 4 anemia and platelets); no others had attributable Gr $>$ 2 non-heme or Gr $>$ 3 heme AE (including 0 of 6 at the highest dose level 93.3 KBq/Kg). Gr 1/2 AE's: 17 (77%) fatigue, 11 (50%) pain flare, 10 (45%) anemia (+1 Gr 3), 10 (45%) platelets, 6 (27%) nausea, 6 (27%) xerostomia (5 of 6 with prior ^{177}Lu-PSMA), 5 (23%) neutropenia, 4 (18%) AST elevation. Despite prior treatment including ^{177}Lu-PSMA and no selection for PSMA expression, 14 (64%) with any PSA decline, 9 (41%) with $>$ 50% PSA decline. 15 (68%) had initial PSA rise followed by decline from peak (delayed effect). 2 with response $>$ 1 year despite prior ^{177}Lu-PSMA. Of 15 with paired baseline and 12-wk CTC counts, 8 declined, 4 remained undetectable, 3 increased. In subset with complete PRO data (baseline to 12 wks), pain was improved or absent by BPI-SF in 63% and by FACT-P in 89%. Social and emotional well-being domains of FACT-P improved or stabilized in majority; physical well-being improved in most responders. **Conclusions:** Alpha-emitter ^{225}Ac targeting PSMA via J591 Ab is tolerable with early evidence of clinical activity in a pre-treated population with favorable PRO's. Enrollment to expansion cohort being completed. Clinical trial information: NCT03276572. Research Sponsor: Weill Cornell Medicine, Other Foundation, Other Government Agency, U.S. National Institutes of Health.

5561 **Poster Session (Board #142), Fri, 8:00 AM-11:00 AM**

Safety outcomes of darolutamide versus apalutamide and enzalutamide in nonmetastatic castration-resistant prostate cancer (nmCRPC): Matching-adjusted indirect comparisons.

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Background: Randomized nmCRPC trials comparing darolutamide (D), apalutamide (A) and enzalutamide (E) have not been reported. Safety of these therapeutics has important implications in assessing patient risk-benefit concerns. Matching-adjusted indirect comparison (MAIC) is a method to perform indirect treatment comparisons adjusting for cross-trial heterogeneity. Objective: To compare the safety outcomes of D vs. A or E using MAIC. **Methods:** Data from the ARAMIS (D vs. placebo [PBO]), SPARTAN (A vs. PBO) and PROSPER (E vs. PBO) trials were used. Key safety outcomes including adverse events (AEs) that have central nervous system relevance were compared using anchored MAIC. Individual patient level data (IPD) from ARAMIS were selected and re-weighted to match the inclusion criteria and baseline characteristics published in SPARTAN and PROSPER (no access to their IPD). The Benjamini-Hochberg approach was applied to adjust for multiplicity. The D vs A MAIC matched on 7 covariates: age, prostate-specific antigen (PSA) level and doubling time, Eastern Cooperative Oncology Group (ECOG), Gleason score, bone-sparing agent use and prior surgery. Sensitivity analyses were conducted matching on different sets of covariates. D vs. E were matched on age, region, PSA level and doubling time, ECOG, Gleason score and bone-sparing agent use. Risk difference (RD) ([DARO – PBO_{ARAMIS}] – [ENZA – $PBO_{PROSPER}$]) and odds ratio (OR) ($OR_{ARAMIS}/OR_{PROSPER}$) were calculated. RD$<$0 or OR$<$1 indicate lower AE risk for D. **Results:** For D vs. A, the effective sample sizes (ESS) of D and its placebo (PBO) arm were 604 and 391 after matching. Fall, fracture, and rash were statistically significantly lower for D vs. A (Table). For D vs. E, the ESS of D and PBO arm were 580 and 395, respectively. Fall, dizziness, mental impairment, hypertension, fatigue and severe fatigue were statistically significantly lower for D vs. E. **Conclusions:** After adjusting for trial differences, D showed favorable safety profile in fall, dizziness, mental-impairment, hypertension, rash, fatigue, and fracture. Research Sponsor: Bayer U.S. LLC.

AEs [a]	D minus A % [RD]	D/A [OR]	D minus E % [RD]	D/E [OR]
Fall	-6.3*	0.6	-6.3*	0.4**
Dizziness	-1.0	1.0	-4.9*	0.5
Mental-impairment	-2.6	0.4	-3.5*	0.3**
Hypertension	-2.4	1.2	-3.9**	0.7
Rash	-16.0*	0.5	NR	NR
Fatigue	-4.4	0.9	-12.8*	0.6**
Severe fatigue	-0.7	0.3	-2.2*	0.2
Fracture	-6.2*	0.4**	NR	NR

[a] All grades AEs with the exception of severe fatigue (grade 3+) * Raw and multiplicity adjusted p-value $<$0.05 ** Raw p-value $<$0.05 NR=not reported in PROSPER

5562 **Poster Session (Board #143), Fri, 8:00 AM-11:00 AM**

Association of detectable levels of circulating tumor DNA (ctDNA) with disease burden in prostate cancer (PC).

Gerhardt Attard, Michael Gormley, Karen Urtishak, Jason S. Simon, Deborah S. Ricci, Trilok V. Parekh, Shinta Cheng, Kim N. Chi, Matthew Raymond Smith; University College London Cancer Institute, London, United Kingdom; Janssen Research & Development, Spring House, PA; Janssen Research & Development, LLC, Raritan, NJ; Janssen Research & Development, Raritan, NJ; BC Cancer and Vancouver Prostate Centre, Vancouver, BC, Canada; Massachusetts General Hospital Cancer Center, Boston, MA

Background: PC is characterized by a relatively low prevalence of recurrent somatic point mutations. ctDNA is shed from PC and can be analyzed to profile somatic point mutations and copy number changes. We evaluated a computational approach to detect ctDNA (ie. ctDNA+) in PC based on allele frequencies of polymorphisms and mutations. We then sought to confirm the association of this biomarker with disease burden and clinical outcome. **Methods:** Customized, hybrid capture, high-depth next-generation sequencing was performed on pre-treatment (PT) plasma samples from a phase 2 line 3+ metastatic castration-resistant PC (mCRPC) study (NCT02854436, GALAHAD) and PT and end of treatment (EOT) samples from randomized Phase 3 study in non-metastatic (nm) CRPC (NCT01946204, SPARTAN) and from metastatic castration-sensitive PC (mCSPC) (NCT02489318, TITAN). Associations of ctDNA+ with bone lesions (number), visceral metastases (+/-), circulating tumor cells count (CTCc), and serum prostate specific antigen (PSA), alkaline phosphatase (AP) and lactate dehydrogenase (LD) were tested. Also, associations of ctDNA+ with overall survival (OS) and second progression free survival (PFS2) were evaluated in randomized studies using Cox regression. **Results:** ctDNA+ at PT was 7.5% in nmCRPC, 23.7% in mCSPC and 66% in heavily pre-treated mCRPC. ctDNA+ increased from PT to EOT in nmCRPC (7.5% to 27%) and mCSPC (23.7% to 63.6%). Disease burden metrics were evaluated in ctDNA+ vs ctDNA- patients. ctDNA+ was associated with higher disease burden in mCRPC (Table), nmCRPC and mCSPC. At EOT, ctDNA+ patients had shorter OS and PFS2 in nmCRPC (HR [95% CI] OS: 2.73 [1.83, 4.08], $p < 0.0001$; PFS2: 2.00 [1.38, 2.90], $p = 0.0002$) and mCSPC (HR [95% CI] OS: 7.59 [3.22, 17.91], $p < 0.0001$; PFS2: 4.84 [2.47, 9.47], $p < 0.0001$). **Conclusions:** ctDNA+ assessed using our novel, composite biomarker increases with advanced disease state and disease progression, is significantly associated with disease burden and poor clinical outcome in PC and could be a clinically relevant metric for monitoring response to therapy. Clinical trial information: NCT02854436. Research Sponsor: Janssen Research and Development, LLC.

Galahad Study	ctDNA+	ctDNA-	p-value
> 10 bone lesions (%)	70	41	0.0145
Liver metastases (%)	20	4	0.08
CTCc (median)	44	2	6.1E-9
PSA (median)	191	32	0.0003
AP (median)	201	75	8.8E-7
LD (median)	272	188	2.5E-5

5563 **Poster Session (Board #144), Fri, 8:00 AM-11:00 AM**

Results of the randomized phase II study of sipuleucel-T (Sip-T) +/- Radium-223 (Ra-223) in men with bone-metastatic castration resistant prostate cancer.

Catherine Handy Marshall, Jong Chul Park, Wei Fu, Hao Wang, Theodore L. DeWeese, Serina King, Michaella Afful, Julia Hurrelbrink, Charlotte Manogue, Patrick Cotogno, Nancy P. Moldawer, Pedro C. Barata, Charles G. Drake, Edwin Melencio Posadas, Andrew J. Armstrong, A. Oliver Sartor, Emmanuel S. Antonarakis; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Massachusetts General Hospital, Boston, MA; Department of Biostatistics and Bioinformatics, Johns Hopkins University School of Medicine, Baltimore, MD; Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Johns Hopkins University, Baltimore, MD; Duke University, Durham, NC; Tulane University Cancer Center, New Orleans, LA; Office of Clinical Research, Tulane Cancer Center, New Orleans, LA; Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA; Cleveland Clinic, Cleveland, OH; Herbert Irving Comprehensive Cancer Center, New York, NY; Duke Cancer Institute, Durham, NC; Tulane Cancer Center, New Orleans, LA

Background: It has been suggested that immune modulation can be augmented by radiation, possibly by enhancing tumor-antigen display. SipT-induced antigen-specific immune responses in mCRPC patients correlate with survival. We hypothesized that the combination of Ra223 and SipT would enhance SipT-related immune response and improve outcomes compared to SipT alone. **Methods:** Patients with asymptomatic, bone-predominant mCRPC, without visceral mets >1.0 cm, were randomized (1:1) to SipT alone or with 6 doses of Ra223 (NCT02463799). Men in the SipT+Ra223 arm started SipT between the 2nd and 3rd dose of Ra223. The primary immunologic endpoint was PA2024-specific T-cell proliferation 6 wks after the first SipT infusion. Secondary immune endpoints were PA2024-specific ELISPOT response, PAP-specific proliferation and ELISPOT, humoral responses against both antigens, and antigen spread. Clinical endpoints were radiographic PFS, PSA response (≥50% decline), AlkPhos response (≥30% decline), and safety. **Results:** 32 men were randomized, 16 per arm. Baseline characteristics in SipT+Ra223 and SipT arms were similar: age (median 71 vs. 70 yrs), Gleason (8-10: 69% vs. 69%), baseline PSA (med 25 vs. 33 ng/mL), AlkPhos (med 89 vs. 92 U/L) and ECOG score (≥1: 31% vs. 19%). There was no significant difference in prior use of abi/enza (38% vs. 44%), or chemo (0% vs. 25%). At 6 weeks, absolute PA2024-specific T-cell proliferation was 2.1-fold higher in the Sip-T arm compared to the SipT+Ra223 arm (35.6 vs. 16.6; *P*=0.03) and remained higher through week 26. Relative to baseline, the 6-week PA2024-specific T-cell proliferation change was 3.6 times greater in the Sip-T arm compared to the SipT+Ra223 arm (*P*=0.007) and remained higher through week 14. There were no significant differences in antigen spread or humoral responses. Median radiographic PFS was longer in the SipT+Ra223 arm (9.3 vs. 3.2 months; HR 0.26, 95% CI 0.11–0.61; *P*=0.007). PSA and AlkPhos responses were better in the SipT+Ra223 arm (PSA50: 5/15=33% vs. 0/14=0%; *P*=0.04; AlkPhos30: 9/15=60% vs. 1/15=7%; *P*=0.01). There was no difference in SREs (13% vs. 7%). **Conclusions:** SipT+Ra223 was associated with improved clinical outcomes and a higher rate of PSA responses compared to SipT alone, although surprisingly, the SipT arm demonstrated higher peripheral PA2024-specific T-cell proliferation. Since neither agent reliably induces PSA responses alone, these data suggest a synergistic effect of the combination. Larger randomized studies of this combination are planned. Clinical trial information: NCT02463799. Research Sponsor: Dendreon, Bayer.

5564 **Poster Session (Board #145), Fri, 8:00 AM-11:00 AM**

Cabozantinib in combination with atezolizumab in patients with metastatic castration-resistant prostate cancer: Results of cohort 6 of the COSMIC-021 study.

Neeraj Agarwal, Yohann Loriot, Bradley Alexander McGregor, Robert Dreicer, Tanya B. Dorff, Benjamin Louis Maughan, William Kevin Kelly, Lance C. Pagliaro, Sandy Srinivas, Christian Michael Squillante, Ulka N. Vaishampayan, Evelyn W. Wang, Dominic Curran, Toni K. Choueiri, Sumanta K. Pal; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Institut de Cancérologie Gustave Roussy, Villejuif, France; Dana-Farber Cancer Institute, Boston, MA; University of Virginia, Charlottesville, VA; City of Hope, Duarte, CA; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Thomas Jefferson University Hospital, Philadelphia, PA; Mayo Clinic, Rochester, MN; Stanford Cancer Institute, Stanford, CA; MD Anderson Cancer Center at Cooper, Camden, NJ; Karmanos Cancer Institute, Detroit, MI; Exelixis, Inc, Alameda, CA; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Cabozantinib (C) may enhance response to immune checkpoint inhibitors (ICIs) by promoting an immune-permissive microenvironment and has shown encouraging activity in combination with ICIs in tumor types including RCC and HCC. C and atezolizumab (A) have shown low objective response rates as monotherapy in metastatic castration-resistant prostate cancer (mCRPC) (Smith JCO 2012; Kim JCO 2018). COSMIC-021 (NCT03170960), a multinational phase 1b study, is evaluating the combination of C + A in various solid tumors. We report results for Cohort 6 in mCRPC. **Methods:** Eligible patients (pts) were required to have radiographic progression in soft tissue after enzalutamide and/or abiraterone, measurable disease, and an ECOG PS of 0 or 1. Prior chemotherapy for mCSPC was permitted. Pts received C 40 mg PO QD and A 1200 mg IV Q3W. CT/MRI scans were performed Q6W for the first year and Q12W thereafter. The primary endpoint is ORR per RECIST 1.1. Other endpoints include safety, ORR per irRECIST, duration of response (DOR), PFS, and OS. Results are presented for the first 44 pts enrolled. **Results:** Median follow-up as of Dec 20, 2019 was 12.6 mo (range 5, 20) for the 44 mCRPC pts. Median age was 70 y (range 49, 90), 50% had ECOG PS 1, 34% had visceral metastases, and 61% had extrapelvic lymph node metastases. 27% had prior docetaxel and 52% had 2 prior novel hormonal therapies. The most common any grade treatment-related adverse events (TRAEs) were fatigue (50%), nausea (43%), decreased appetite (39%), diarrhea (39%), dysgeusia (34%), and PPE (32%). One grade 5 TRAE of dehydration was reported in a 90 y/o. Median duration of treatment was 6.3 mo. ORR per RECIST 1.1 among all 44 pts was 32% (2 CRs [4.5%] and 12 PRs [27%]); 21 (48%) pts had SD resulting in a disease control rate of 80% in all pts. One pt with PD per RECIST 1.1 had an irPR per irRECIST. ORR per RECIST 1.1 was 33% in 36 pts with high-risk disease (visceral and/or extrapelvic lymph node metastases). Median DOR for all pts with response per RECIST 1.1 was 8.3 mo (range 2.8, 9.8+). 17 (50%) of 34 pts with post-baseline PSA evaluation had a decrease in PSA. In 12 responders with post-baseline PSA evaluation, 8 (67%) had a PSA decrease $\geq$50%. Tumor PD-L1 expression will also be reported. **Conclusions:** The combination of C + A had a tolerable safety profile and demonstrated clinically meaningful activity with durable responses in men with mCRPC. Given the encouraging activity in these pts, especially in those with high-risk disease, further evaluation of C + A in men with mCRPC is being pursued. Clinical trial information: NCT03170960. Research Sponsor: Exelixis Inc.

5565 **Poster Session (Board #146), Fri, 8:00 AM-11:00 AM**

Safety and clinical activity of atezolizumab (atezo) + radium-223 dichloride (r-223) in 2L metastatic castration-resistant prostate cancer (mCRPC): Results from a phase Ib clinical trial.

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Background: mCRPC patients (pts) tend to have a poor prognosis and limited treatment (tx) options, especially those with concomitant bone metastases (mets). We explored the ability of combination tx with atezo (anti–PD-L1) and r-223 (α-particle emitter) to stimulate anti-tumor immunity in mCRPC pts. **Methods:** This Phase Ib study evaluated the safety and tolerability of atezo + r-223 in pts with mCRPC and multiple bone mets, visceral mets and/or lymphadenopathy who progressed after androgen pathway inhibitor tx. The initial cohort phase evaluated the safety and tolerability of a concurrent dosing schedule (CDS), in which atezo and r-223 were administered on the same day. Following assessment of CDS, pts were randomized 1:1:1 to CDS or 1 of 2 staggered dosing schedules (atezo or r-223 introduced a full cycle before the other). This was followed by an expansion of enrollment (randomized 1:1:1). Pts got atezo 840 mg IV q2w and r-223 at 55 kBq/kg IV 6 times at 4-wk intervals until unacceptable toxicity or loss of clinical benefit. Exploratory measures of efficacy included investigator-assessed ORR (RECIST 1.1), PSA response rate, time to PSA progression, radiographic PFS (rPFS; PCWG2 criteria) and OS. Biopsy samples were collected at baseline and prior to cycle 2 to evaluate changes in the tumor microenvironment during tx. **Results:** As of Oct 4, 2019, 45 pts were enrolled and 44 had evaluable data. Baseline characteristics were generally similar across groups. All 44 evaluable pts had $\geq$ 1 all-cause AE; 23 (52.3%) had Gr 3-4 AE. Eight pts (18.2%) had Gr 5 AE as per protocol reporting of deaths; 4 (9.1%) were from disease progression. Median follow-up was 13.9 mo (range, 1.7–34.2). Confirmed ORR was 6.8% (95% CI: 1.43, 18.66). Confirmed PSA response rate was 4.5% and median time to PSA progression was 3.0 mo (95% CI: 2.8, 3.3). Median rPFS was 3.0 mo (95% CI: 2.8, 4.6) and median OS was 16.3 mo (95% CI: 10.9, 22.3). Changes in PD-L1 and CD8 IHC were consistent with the known mechanism of action of atezo, as were changes in alkaline phosphatase with radium. **Conclusions:** No dose-limiting toxicities, safety signals, or changes in serum biomarkers were observed beyond the known safety profiles of atezo and r-223. This Phase 1b study did not seem to show clinical benefit from combination tx. Ongoing subgroup and biomarker analyses may provide additional insights. Studies of PD-1/PD-L1 targeted therapies in combination with tumor-directed radiation in molecularly selected mCRPC pts are planned or underway. Clinical trial information: NCT02814669. Research Sponsor: F. Hoffmann-La Roche, Ltd.

5566 **Poster Session (Board #147), Fri, 8:00 AM-11:00 AM**

TALAPRO-1: Phase II study of talazoparib (TALA) in patients (pts) with DNA damage repair alterations (DDRm) and metastatic castration-resistant prostate cancer (mCRPC) – updated interim analysis (IA).

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Background: PARP inhibitors (PARPi) show antitumor activity in mCRPC/DDRm pts treated with novel hormonal therapy (NHT). TALAPRO-1 is an open-label study evaluating TALA (potent PARP inhibitor/trapper) in men with mCRPC/DDRm. We report a planned IA (Dec 2019). **Methods:** TALAPRO-1 (NCT03148795) is enrolling pts (N ≈ 100) with measurable soft tissue disease, progressive mCRPC, and DDRm likely to sensitize to PARPi (*ATM*, *ATR*, *BRCA1/2*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*), who received 1–2 chemotherapy regimens (≥1 taxane-based) for metastatic disease and progressed on ≥1 NHT (enzalutamide/abiraterone acetate) given for mCRPC. DDRm are defined as known/likely pathogenic variants or homozygous deletions. Pts receive oral TALA 1 mg/day (moderate renal impairment 0.75 mg/day) until radiographic progression, unacceptable toxicity, consent withdrawal or death. Primary endpoint is objective response rate (ORR). Secondary endpoints: time to OR; response duration; PSA decrease ≥50%; circulating tumor cell (CTC) count conversion (to CTC = 0 and <5 per 7.5 mL blood); time to PSA progression; radiographic PFS (rPFS); overall survival; safety. A planned efficacy/safety IA was done when 60 pts with DDRm and measurable disease completed ≥6 months of TALA/no longer followed (DDR population [DDRp]). Radiographic responses are based on investigator assessments. **Results:** 113 pts received TALA (cutoff Dec 12, 2019); 75 pts were DDRp, had measurable disease, received ≥16 wk treatment, and were evaluable for ORR (54.7% *BRCA1/2*, 4.0% *PALB2*, 22.7% *ATM*; 18.7% other DDRm).All DDRp pts had prior docetaxel; 45.3% cabazitaxel. Confirmed ORR, rPFS, and composite response (investigator-assessed) in pts who received TALA for ≥16 weeks are in the table. Most common treatment-emergent adverse events: anemia (42.5%); nausea (32.7%). **Conclusions:** TALA monotherapy has encouraging antitumor activity in docetaxel-pretreated mCRPC pts with *BRCA1/2* alterations and was generally well tolerated. Clinical trial information: NCT03148795. Research Sponsor: Pfizer Inc.

	BRCA1/2 N=46	*PALB2* N=4	*ATM* N=18	Other N=18	Total N=86
[a,b]ORR, % (response/n)	43.9 (18/41)	33.3 (1/3)	11.8 (2/17)	0	28.0 (21/75)
[b]rPFS, mths (95% CI)	9.3 (8.1-13.7)	7.4 (2-7.4)	5.5 (1.7-8.2)	3.7 (1.7-3.9)	-
[b,c]Composite response, % (response/n)	76.1 (35/46)	50.0 (2/4)	27.8 (5/18)	11.1 (2/18)	51.2 (44/86)

[a]Measurable soft tissue disease per investigator at screening; [b]DDR deficient population; [c]OR and/or PSA response ≥50% and/or CTC conversion (from CTC ≥5 to <5)

5567 **Poster Session (Board #148), Fri, 8:00 AM-11:00 AM**

Olaparib (O) in patients (pts) with prostate cancer with BRCA1/2 inactivating mutations: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study.

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Background: TAPUR is a phase II basket study evaluating anti-tumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations. Advanced prostate cancer (PC) pts with germline or somatic BRCA1/2 inactivating mutations treated with O are reported. **Methods:** Eligible pts had advanced PC, no remaining standard treatment (tx) options, measurable disease, ECOG Performance Status (PS) 0-2, and adequate organ function. Tumor genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. Pts received O tablets or capsules dosed at 300 mg (n=24) or 400 mg (n=5), respectively, orally twice daily until disease progression. Simon 2-stage design tested the null disease control (DC) (objective response (OR) or stable disease at 16+ weeks (wks) (SD16+) according to RECIST) rate of 15% vs. 35% (power = 0.85; $\alpha = 0.10$). If $\geq$2 of 10 pts in stage 1 have DC, 18 more pts are enrolled. If $\geq$7 of 28 pts have DC, the tx is worthy of further study. Pts had radiographic evaluations at 8 and 16 wks and then every 12 wks. Secondary endpoints are progression-free survival (PFS), overall survival (OS) and safety. **Results:** 29 pts with *BRCA1/2* inactivating mutations were enrolled from Aug 2016 to Jul 2019; 4 were identified as ineligible after enrollment due to bone only disease and removed from analyses. Demographics and investigator-reported outcomes are summarized in the Table. Nine pts with OR and 8 with SD16+ were observed for DC and OR rates of 68% (90% CI: 53% - 77%) and 36% (95% CI: 18% - 57%), respectively. Six pts had at least one grade 3 AE or SAE at least possibly related to O including anemia, aspiration, dehydration, diabetic ketoacidosis, fatigue, and neutropenia. **Conclusions:** Monotherapy with O showed anti-tumor activity in heavily pre-treated PC pts with germline (1/2 pts with OR or SD16+) or somatic (16/23 pts with OR or SD16+) *BRCA1/2* inactivating mutations. These findings extend results from recent trials of O in advanced prostate cancer pts with germline only BRCA1/2 mutations. Clinical trial information: NCT02693535. Research Sponsor: AstraZeneca, Pharmaceutical/Biotech Company.

Demographics and efficacy outcomes (N=25).

Median age, yrs (range)	**65 (40, 90)**
Male, %	100
ECOG PS, %	
0	44
1	56
Prior systemic regimens, %	
1-2	40
≥3	60
DC rate, % (90% CI)	68 (53, 77)
OR rate, % (95% CI)	36 (18, 57)
Median PFS, wks (95% CI)	41.0 (16.3, 53.1)
Median OS, wks (95% CI)	75.4 (49.4, NA)
1 year OS rate, % (95% CI)	79.4 (47.6, 93.1)

5568 **Poster Session (Board #149), Fri, 8:00 AM-11:00 AM**

Comparison of germline mutations in African American and Caucasian men with metastatic prostate cancer.

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Background: The relevance of germline mutations in metastatic prostate cancer is well established; however, comparison of germline genetics in African American (AA) versus Caucasian (CA) men with metastatic prostate cancer (PCa) is limited. **Methods:** Germline data from self-identified AA and CA metastatic PCa patients (pts) were collected from 5 academic cancer centers. Various commercial cancer-specific germline testing panels were used to evaluate 12-86 genes. Pathogenic (P) or likely pathogenic (LP) mutations, and variants of unknown significance (VUS), were reported according to ACMG guidelines. Self-reported family history (FH) was annotated for 99% of pts. Statistical analyses included Chi-squared and Fischer's exact tests. **Results:** A total of 821 metastatic PCa pts were assessed: 152 AAs and 669 CAs. For P/LP alterations, AAs had a frequency of 11.2% (17/152) as compared to a frequency of 14.6% (98/669) in CAs ($p = 0.302$). AA pts were more likely to have a VUS than CA pts, 61% vs 43% respectively (OR = 2.09, 95%CI [1.45, 2.99], $p < 0.001$). BRCA mutations were similar between races, but AA were more likely to have a BRCA1 P/LP alteration (OR = 6.00, 95% CI [1.33, 27.09], $p = 0.025$). AA pts were less likely to have a P/LP alteration in a non-BRCA gene (OR = 0.34, 95% CI [0.15, 0.80], $p = 0.013$). Among DNA repair genes, there were no significant difference between AA and CA pts ($p = 0.574$); however, there was a trend toward AA pts having fewer P/LP alteration in a non-BRCA DNA repair genes (OR = 0.26, 95% CI [0.06, 1.08], $p = 0.071$). In pts with >1 first degree relative (FDR) with ovarian cancer, P/LP germline alterations were more likely in CAs (OR = 2.33, 95% CI [1.05, 5.17], $p = 0.043$); but there were no significant differences in AAs ($p = 0.098$). Those with >2 FDRs with PCa were more likely to have a P/LP change in CAs (OR = 2.32, 95% CI [1.04, 5.15], $p = 0.043$), but there were no difference in AAs ($p = 0.700$). In pts with ≥ 2 FDRs with breast cancer, P/LP germline alterations were more likely in both AAs (OR = 9.36, 95% CI [1.72, 50.84], $p = 0.019$) and CAs (OR = 3.92, 95% CI [1.79, 8.59], $p = 0.001$). **Conclusions:** We did not observe a difference in the overall frequency of germline P/LP alterations between AA and CA men with metastatic PCa but VUSs were more common in AA men. These AA men have an overall frequency of BRCA mutations similar to CA men; however, BRCA1 mutations were more prevalent in these AAs. Non-BRCA P/LP mutations are significantly less frequent in AA pts. A positive family history of >2 FDRs with breast cancer was associated with P/LP alterations in both AA and CA pts. Research Sponsor: None.

5569 **Poster Session (Board #150), Fri, 8:00 AM-11:00 AM**

CARD: Overall survival (OS) analysis of patients with metastatic castration-resistant prostate cancer (mCRPC) receiving cabazitaxel versus abiraterone or enzalutamide.

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Background: The CARD trial (NCT02485691) compared cabazitaxel vs. an androgen receptor targeted agent (ART; abiraterone/enzalutamide) in mCRPC previously treated with docetaxel and the alternative ART (abiraterone/enzalutamide), in any order. These post hoc analyses assessed OS from various time points and the impact of prognostic factors. **Methods:** Patients with mCRPC previously treated with docetaxel and progressing $\leq$ 12 months on prior abiraterone/enzalutamide were randomized 1:1 to cabazitaxel (25 mg/m^2 IV Q3W + daily prednisone + prophylactic G-CSF) vs. abiraterone (1000 mg PO + daily prednisone) or enzalutamide (160 mg PO). OS was calculated from date of diagnosis of metastatic disease, date of mCRPC, and start of 1st, 2nd or 3rd life-extending therapy (LET). A stratified multivariate Cox regression analysis assessed the impact of 14 prognostic factors on OS using a stepwise model selection approach with a significance level of 0.10 for entry into the model and 0.05 for removal. **Results:** In the CARD study (N = 255), median OS was longer with cabazitaxel vs. abiraterone/enzalutamide (13.6 vs 11.0 months; HR 0.64, 95% CI 0.46–0.89; p = 0.008). OS was numerically improved for cabazitaxel vs. abiraterone/enzalutamide when assessed from the time of diagnosis of metastatic disease or mCRPC, or from start of 1st or 2nd LET (Table). In the multivariate analysis, low hemoglobin, high baseline neutrophil to lymphocyte ratio, and high PSA values at baseline were associated with worse OS. In presence of these factors, the OS benefit observed with cabazitaxel versus abiraterone/enzalutamide remained significant (HR 0.63, 95% CI 0.42–0.94, p = 0.022). **Conclusions:** Cabazitaxel numerically improved OS vs. abiraterone/enzalutamide in patients with mCRPC previously treated with docetaxel and the alternative ART (abiraterone/enzalutamide), whatever the time point considered. The robustness of this OS benefit was confirmed by stratified multivariate analysis. Sanofi funded. Clinical trial information: NCT02485691. Research Sponsor: Sanofi.

	Median OS, months	
OS from time of	Cabazitaxel n = 129	Abiraterone/enzalutamide n = 126
Metastatic disease diagnosis	54.7	42.5
mCRPC diagnosis	40.9	31.3
1st LET	36.4	30.5
2nd LET	24.2	21.9
3rd LET	13.6	11.0

Survival outcome in patients with metastatic castration-resistant prostate cancer according to first-line treatment.

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Background: Therapeutic strategy in metastatic castration-resistant prostate cancer (mCRPC) has evolved significantly with the introduction of abiraterone acetate in association with prednisone/prednisolone in first-line treatment in December 2012. This work aimed to compare the effectiveness of abiraterone acetate and docetaxel as first-line treatments for mCRPC, in real-life setting. **Methods:** Patients with mCRPC were identified in the main scheme of the National Healthcare System database (SNDS), which covers about 86% of the French population, and capturing all reimbursed healthcare expenditures and hospital discharge summaries. Those initiating docetaxel or abiraterone acetate in 1st line in 2014 were included and 1:1 matched on the previous prostate cancer stage before mCRPC status, the delay from the date of initial diagnosis and a high-dimensional propensity score. The 36-month overall survival and the 36-month discontinuation-free survival (i.e. survival time until treatment switch or death) were compared using Cox proportional hazards risk model. **Results:** In 2014, out of the 12,951 patients with prevalent mCRPC, 1,214 initiated docetaxel in 1st line and 2 444 initiated abiraterone. A total of 716 patients per group were matched with good comparability (C-statistic = 0.6). The median duration of docetaxel–defined as the time between the first and the last infusion–was 7.3 months with a median of 6 infusions. The median duration of abiraterone acetate–corresponding to the period covered by the dispensed drug–was 9.1 months. Near 70% of the docetaxel and 62% of the abiraterone acetate patients received a 2nd line of treatment. Results related to the main survival outcomes are presented in the table below. **Conclusions:** First-line treatment with abiraterone acetate in mCRPC patients results in a better 36-month overall survival and discontinuation-free survival compared to docetaxel in real-life setting. Research Sponsor: JANSSEN.

	Docetaxel n=716	Abiraterone acetate n=716	*p-value*
Overall Survival			
36-month survival probability, % [95%CI]	27.9 [25.0 – 31.2]	34.6 [31.5 – 38.1]	<0.003
Median survival, months [95%CI]	18.5 [17.1 – 20.7]	25.5 [23.0 – 27.3]	
Discontinuation-Free Survival			
36-month survival probability, % [95%CI]	2.9 [2.1 – 4.1]	13.8 [11.7 – 16.4]	<0.001
Median survival, months [95%CI]	7.4 [7.0 – 8.0]	10.8 [10.1 – 11.7]	

5571 **Poster Session (Board #152), Fri, 8:00 AM-11:00 AM**

Clinical significance of CTC enumeration on the Epic Sciences platform in metastatic castration-resistant prostate cancer (mCRPC) patients treated with AR signaling inhibitors (ARSi).

Joseph Schonhoft, Audrey Gill, Ryon P Graf, Adam Jendrisak, Ethan Barnett, Hannah Benoliel, Emily Carbone, Alisa Tubbs, Sarah Orr, Jiyun Byun, Rick Wenstrup, Howard I. Scher; Epic Sciences, Inc., San Diego, CA; Epic Sciences, San Diego, CA; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Circulating Tumor Cell (CTC) number, enumerated using the analytically valid FDA cleared Cell Search (Menarini Silicon Biosystems) platform has been shown to be prognostic for survival pre- and post-therapy, and used as an aid to monitoring breast, colorectal and prostate cancers. The assay uses antibody-based capture and defines a CTC as an EpCAM+ and CD45- intact cell. In contrast, with the Epic sciences CTC detection platform red blood cells are first lysed and all nucleated cells deposited on pathology slides, fixed, and imaged. There is no affinity selection and CTCs for this analysis were defined *in silico* as any cytokeratin (CK)+, CD45- cell with an intact DAPI+ nucleus. Here we report the prognostic significance of the CK+ CTCs detected on the EPIC Sciences platform in mCRPC patients prior to treatment with an AR signaling inhibitor. **Methods:** A pre-treatment blood sample was collected from 181 unique patients with progressing mCRPC about to start an ARSI as 1st, 2nd or 3rd line therapy at MSKCC. CTCs were enumerated on the Epic Sciences platform and verified by a trained human technician. **Results:** At least 1 CTC was detected (median = 1, 0-711 CTCs/ml) in 134 (74%) of cases, with higher counts observed in patients with visceral or multiple osseous sites relative to those with lymph node only disease. Counts increased by line of therapy. The table shows the associated risk of death for CTCs modeled as a continuous variable. **Conclusions:** The results support the clinical validity of CTC number determined on the Epic Sciences platform as a significant baseline prognostic factor. In multivariate modeling CTC number was found to be the most significant blood-based predictor of poor OS with each doubling representing a 20% greater risk of death observed with adjustment for therapy line, LDH, PSA, and ALK. Research Sponsor: Epic Sciences, Other Government Agency.

Cox proportional hazards models for assessing the prognostic value of CTCs detected on the Epic Sciences platform with association to overall survival.

Model	PSA		CTC		CTC + PSA		ALK + LDH + PSA		ALK + LDH + PSA + CTC	
Continuous Blood Based Measurement	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
CTC	1.4 (1.3, 1.6)	<0.0001	-	-	1.3 (1.2, 1.5)	<0.0001	-	-	1.2 (1.1, 1.4)	0.002
PSA	-	-	1.3 (1.2, 1.4)	< 0.0001	1.2 (1.1, 1.3)	0.0002	1.1 (1.0, 1.3)	0.0168	1.1 (1.0, 1.2)	0.064
ALK	-	-	-	-	-	-	1.3 (1, 1.6)	0.0614	1.2 (0.9, 1.6)	0.13
LDH	-	-	-	-	-	-	1.9 (1.4, 2.7)	0.0001	1.6 (1.1, 2.3)	0.012

Each continuous covariate was log2 transformed and all models adjust for line of therapy and patient age.

5572 **Poster Session (Board #153), Fri, 8:00 AM-11:00 AM**

Circulating tumor cells (CTCs) with small-cell like pathology are prevalent in metastatic castration-resistant prostate cancer (mCRPC) and show selective pharmacodynamic reductions in patients treated with platinum but not ARSI or taxane.

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Background: The increasing availability and earlier use of life prolonging drugs targeting the androgen receptor signaling axis (ARSI) has resulted in an increase in the frequency of late state tumors with "small cell/neuroendocrine (NESC) phenotypes" similar to small-cell lung cancer (SCLC). Definitive pathologic criteria to diagnose the "entity" are lacking, and the eligibility criteria across trials are inconsistent, limiting the ability to relate outcomes between studies. We hypothesized that an analytically valid assay for a rigorously defined "small-cell CTC" phenotype might serve as a unifying biomarker for the presence of NESC-like tumors in an individual for use in clinical trials. **Methods:** Using the WHO guidelines for small-cell diagnosis in tissue as reference, we defined an equivalent set of single-cell CTC criteria for defining a CTC with small-cell histology: a small and circular CD45-, CK+ cell with high N/C ratio lacking detectable nucleoli. Small-cell subtype pharmacodynamic changes were studied in 233 patients with progressing mCRPC about to start an AR signaling inhibitor ARSi (N=111), taxane (N=89), or platinum (N=33). **Results:** CTCs with small-cell morphology had lower AR protein expression compared with non-small-cell CTCs ($P<0.0001$) and increased with therapy line. The small-cell CTC subtype decreased in number from baseline to on-therapy in patients treated with platinum but not in those treated with ARSi or taxane (Table). **Conclusions:** Digital pathology analysis of CTCs defined a CTC subtype consistent with that of small-cell carcinoma that were only reduced in number with platinum-based therapy. The tracking of CTC subtypes after treatment with different drug classes may help assess drug activity in heavily treated patients that often have heterogeneous disease that of which may not be captured using standard measures of response. Research Sponsor: Epic Sciences, Other Government Agency.

Percent of patients with small-cell/neuroendocrine (NESC) CTCs by therapy class.

	CTC/mL > 0; Number of patients (N)	NESC/mL > 0; Number of patients (N)	CTC/mL > 0; Number of patients (N)	NESC/mL > 0; Number of patients (N)	P-value for decrease from Baseline to On-therapy (unadjusted/ Bonferonni adjusted), paired test
TimePoint	Baseline		On-therapy		Change
ARSi (N=111)	90 (81%)	35 (32%)	76 (68%)	29 (26%)	0.29 / 0.87
Taxane (N=89)	76 (85%)	37 (42%)	68 (76%)	23 (26%)	0.09 / 0.28
Platinum (N=33)	30 (91%)	14 (42%)	25 (76%)	7 (21%)	0.015 / 0.045

5573 **Poster Session (Board #154), Fri, 8:00 AM-11:00 AM**

Clinical outcomes and markers of treatment response in a randomized phase II study of androgen deprivation therapy with or without palbociclib in RB-intact metastatic hormone-sensitive prostate cancer (mHSPC).

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Background: Targeted therapies based on tumor molecular markers are not currently used in mHSPC. Palbociclib, a CDK4/6 inhibitor, blocked proliferation and promoted G1 arrest in a Rb-and Cyclin D-dependent manner in preclinical models of HSPC. We hypothesized that co-targeting AR (ADT) and cell cycle (palbociclib) would improve outcomes in mHSPC pts. **Methods:** mHSPC pts with Rb intact tumors based on IHC of metastatic tumor biopsy were stratified and randomized (1:2) to Arm A: ADT or Arm B: ADT+ palbociclib (125mg 3 weeks on, 1 week off). Primary endpoint was confirmed PSA RR ($\leq$ 4 ng/mL) after 28 weeks of therapy. Secondary endpoints included safety/tolerability, PFS, PSA and radiographic RR. Metastatic biopsy and primary tumors were subjected to whole exome and transcriptomic sequencing where available. CTC's were enumerated at various time points. **Results:** 72 eligible pts (median age 67 years, PSA 73ng/mL) with newly diagnosed mHSPC were registered and underwent biopsy. 97% retained RB expression (IHC). 62 pts were stratified by disease extent and early initiation of ADT, and randomized. 60 pts initiated therapy (Arm A: 20; Arm B: 40). Adverse events were reported previously. 80% of pts (Arm A: 16/20, Arm B: 32/40; p = 0.87) on both arms met primary PSA endpoint ($\leq$4ng/mL at 28 weeks). PSA undetectable rate at 28 weeks was Arm A: 50% (10/20) and Arm B: 43% (17/40; p = 0.5). Measurable disease RR: Arm A: 89% and Arm B: 89%. 12-month biochemical PFS was Arm A 69% (95%CI: 44-85%), Arm B 74% (95%CI: 57-85%). 41 patients on trial underwent sequencing of metastatic biopsy and 10 patients had matched primary prostate tumor sequencing results. CCND1 amp, 8q gain, PTEN and KMT2C mutations were each observed in metastatic, but not paired prostate primary tumors. TP53, PIK3 pathway (PIK3CA, AKT1, PTEN) mutations and 8q gains were associated with reduced PSA PFS [HR (95%CI): 3.0 (1.2-7.2), p = 0.018; 3.2(1.03-10),p = 0.044; 4.96 (1.8-12), p = 0.001, respectively]. Pretreatment CTCs were associated with lower PSA CR (p = 0.04) and shorter PFS (12-month PFS: 58% vs. 86%, p = 0.031). **Conclusions:** A tissue based biomarker preselected trial is feasible in mHSPC. ADT + palbociclib did not impact outcomes. Pretreatment CTC counts, TP53 and PIK3 pathway mutations, and 8q gain may offer prognostic value in mHSPC. Support: Movember-PCF Challenge Award, Pfizer. Clinical trial information: NCT02059213. Research Sponsor: Movember-PCF Challenge Award, Pharmaceutical/Biotech Company.

5574 **Poster Session (Board #155), Fri, 8:00 AM-11:00 AM**

A blood-based multi-mRNA liquid biopsy with >90% accuracy for diagnosis and assessment of prostate cancers.

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Background: There are a paucity of blood-based biomarkers with clinical utility for prostate cancer (PCa). We developed a circulating mRNA (27-gene) prostate cancer signature to diagnose and manage PCa. **Methods:** Gene identification: Publicly available PCa transcriptome sets (n= 1,159 samples) were evaluated and compared with normal blood-based transcriptomes using gene co-expression network enrichment, differential expression and functional enrichment analyses to identify candidate markers. Gene expression evaluation: Seven PCA cell lines and two normal prostate epithelial lines were used to assess candidate genes. Marker genes were determined in PCa tumor tissue (n= 50) and validated in the TCGA-PRAD (n= 500) dataset. Blood gene expression: Set #I: PCA: n= 132, BPH: n= 44, controls n= 55. Set #II: n= 50 (biochemical recurrence [BCR]). We constructed an artificial intelligence PCa model using classification algorithm analyses. Scoring: normalized algorithmically analyzed gene expression (0 to 100), positive score >20. PSA: BPH (n= 44) and PCa (n= 132). Clinical score assessment: Surgical cohort: (n= 47), samples: pre-surgical and post: 1 week - 14 months. Statistics: Kruskal-Wallis, Pearson-correlation, Fisher's and AUROC analyses (Mean±SEM). **Results:** Transcriptomic analysis identified 27 candidates. Cell lines/tissue: Expression levels were significantly elevated ($p< 0.001$, 2.1-35.8-fold) in cell lines and PCa surgical samples. All 27 markers were confirmed in TCGA-PRAD samples (average TPM: 58 to 10,366). *Blood*: In Set#I, levels in PCa were 47±2 ($p< 0.0001$) compared to BPH (19±1) and controls (18±0.5); AUROC: 0.92 (BPH) and 0.94 (controls), with an accuracy of 85-88%, a sensitivity of 86% and specificities 82 and 93%. For PSA, the AUROC (PCa vs. BPH) was 0.51 (p= 0.88). PSA was positive in 86% of BPH and was > 10ng/ml in 30%. PSA was positive in 83% of PCa and > 10ng/ml in 40% (Fisher's p= 0.28). PSA accuracy (> 10ng/ml) was 48%. Levels in Set#II (BCR) were 44±3. ProstaTest-was positive in 48 (96%). Surgical cohort (n= 47): Prostatest accuracy 100% pre-surgery. Resection decreased levels (KW-statistic: 57.4, $p< 0.0001$) from 52±1 to 23.5±2. **Conclusions:** A 27-gene blood signature was developed for PCa that exhibited a diagnostic accuracy of 92%; significantly better than PSA (48%, $p< 0.0001$). Surgical resection significantly ($p< 0.0001$) decreased levels. Biochemical recurrence was accurately detected (96%). A multi-gene prostate cancer liquid biopsy is likely to have clinical utility in both diagnosis and monitoring of PCa. Research Sponsor: None.

5575 **Poster Session (Board #156), Fri, 8:00 AM-11:00 AM**

Osteonecrosis of the jaw (ONJ) in radium 223 (Ra223)-treated metastatic castration-resistant prostate cancer (mCRPC) patients (pts) with exposure to zoledronic acid and/or denosumab.

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Background: Bone health agents (BHA) including denosumab, a monoclonal antibody, and Zoledronic acid (ZA), a bisphosphonate, are recommended for men with CRPC and bone metastases to prevent skeletal-related complications. ONJ occurs in about 5% of patients (pts) on BHA. The incidence of ONJ in pts treated with Ra223 and BHA remains unknown, particularly in those who receive sequential treatment of BHAs. Here we describe the rate of ONJ in a real-world setting in mCRPC pts treated with Ra223 in 3 groups: 1) denosumab alone, 2) ZA alone, and 3) sequential ZA /denosumab or vice versa. **Methods:** A retrospective analysis of a cohort of mCRPC pts with bone metastases who received Ra223. Follow-up was until date of death or last data entry. Chart inclusion criteria included patients who received Ra223 between November 2010 to August 2018 with documentations of data points. **Results:** A total of 177 pts received Ra223 between 11/2010 and 8/2018. Median age 73 at 1st Ra223 (range 40-93); Median PSA 15.8- at 1st Ra223 (range 0.1-1952); Demographics-AA-10, C-130, Asian-9, unspecified-28; Median Alk Phos 95 at 1st Ra233 (range 25-1515). 93 % (164/177) received BHA. Of the 164 who received BHA, 45% (73/164) received denosumab only, 37% (61/164) received ZA only, and 18% (30/164) received sequential treatment. ONJ developed in 9.7% (16/164) of all patients on BHA. Denosumab alone caused ONJ in 7 of 73 pts (9.6%). ZA alone caused ONJ in 6 of 61 pts (9.8%). ONJ occurred in 3 of 30 pts (10%) in the sequential group. The median number of doses of BHA before development of ONJ was 10 with denosumab, 20 with ZA, and 19.5 (denosumab) and 22 (ZA) in the sequential group. **Conclusions:** In patients treated with Ra223 and a BHA, the rate of ONJ is 9.7%. The rate of ONJ was similar in groups treated with denosumab alone, ZA alone, and sequential treatment of ZA and denosumab However, ONJ developed more quickly in patients on denosumab. We conclude that the risk of ONJ is increased in patients treated with Ra223 and BHA. ZA or sequential therapy appears to delay time to onset of ONJ compared to denosumab. Clinicians should be mindful of the toxic synergy between Ra223 and BHA. ZA may be the preferred BHA partner with Ra223. Research Sponsor: None.

5576 Poster Session (Board #157), Fri, 8:00 AM-11:00 AM

RESTORE: A single-arm, open-label phase II trial of bipolar androgen therapy (BAT) in men with metastatic castration resistant prostate cancer (mCRPC)—A comparison of post-abiraterone (Abi) versus post-enzalutamide (Enza) patients (Pts).

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Background: A paradoxical inhibition of cell growth has been observed in both androgen-sensitive and castration resistant prostate cancer cell lines following the addition of high-dose testosterone.We have conducted several clinical trials investigating a mode of supraphysiologic testosterone therapy termed, BAT, in which testosterone levels are rapidly driven to the supraphysiologic range followed by a return to near-castrate levels over 28-day treatment cycles with favorable results. We previously reported the efficacy of BAT in mCRPC pts that were progressing on enza. In this study, we compared the effect of BAT in mCRPC pts whose last therapy was abi vs. enza. In addition, we examined the benefit of abi or enza rechallenge after progression on BAT. **Methods:** 59 mCRPC pts (n = 29 post abi; n = 30 post enza) were enrolled and received at lease one dose of BAT monotherapy, 400mg intramuscularly every 28 days. After clinical or radiographic progression on BAT, pts were rechallenged with the AR targeted therapy to which they were most recently resistant. The co-primary endpoints were a 50% decline in PSA from baseline (PSA50) for BAT and for enza/abi rechallenge. **Results:** 5/29 (17.2%) of post-abi pts compared to 9/30 (30%) in the post enza group achieved a PSA50 response (P = 0.36). Post BAT rechallenge with abi (n = 19) or enza (n = 22) resulted in a PSA50 response rate of 15.8% (n = 3) and 68.2% (n = 15), respectively (P = 0.001). The total duration of benefit (i.e. PFS on BAT + PFS on rechallenge = "PFS2") was significantly longer in the post enza vs. post-abi patients (Median PFS2: 12.75 vs. 8.125 months; P = 0.04. Lastly, AR-V7 negative (n = 42) pts has a significantly longer median PFS2 compared to AR-V7 positive (n = 10) pts. (10.3 vs. 7.1 months, P = 0.005). **Conclusions:** Our data suggest that BAT may be more effective at resensitizing mCRPC to direct AR antagonists (i.e. enza) compared to abi. Detection of AR-V7 portended a worse outcome on BAT/rechallenge. Further clinical study is warranted. Clinical trial information: NCT02090114. Research Sponsor: U.S. National Institutes of Health.

	Post Abi N = 29	Post Enza N = 30	P-value
BAT PSA50 RR	17.2% (N = 5/29)	30.0% (N = 9/30)	0.360
BAT Objective RR	28.6% (N = 2/7)	50.0% (N = 6/12)	0.361
Rechallenge PSA50 RR	15.8% (N = 3/19)	68.2% (N = 15/22)	0.001

5577 **Poster Session (Board #158), Fri, 8:00 AM-11:00 AM**

Radiographic paradoxical response in patients with metastatic castrate-resistant prostate cancer (mCRPC) undergoing treatment with second-generation hormone therapy (second-HT).

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Background: Prostate specific antigen (PSA) has well-recognized limitations as a marker for treatment response and disease progression. A post hoc analysis of the PREVAIL trial reported 24.5% of chemotherapy naïve mCRPC patients on enzalutamide had radiographic progression on conventional imaging with non-rising PSA. In this study, we sought to retrospectively compare PSA levels with C-11 choline positron emission tomography/ computed tomography (PET/CT) images in patients with m-CRPC on 2^{nd}-HT with prior use of chemotherapy. **Methods:** We identified 123 patients with mCRPC on 2^{nd}-HT following prior use of docetaxel chemotherapy (Abiraterone, n = 106; Enzalutamide, n = 17). Patients underwent serial PSA testing and C-11 choline PET/ CTs every 3–6 months. Disease progression was defined by the increase in blood pool corrected maximum standardized uptake value (SUVmax) of the index lesion on C-11 choline PET/CT scan. Suspicious lesions were confirmed by biopsy and/or conventional imaging. **Results:** Approximately 43% (n = 53) of patients had radiographic disease progression while on 2^{nd}-HT. At time of radiographic progression, 60.4% of patients showed a parallel rise in PSA (Group-A), while 39.6% showed a paradoxical response; defined as radiographic progression with stable or down-trending PSA (Group-B). Median PSA at time of progression was 3.1 ng/ml for Group-A, and 1.3 ng/ml for Group-B (p-value = 0.0176). Median SUVmax was the same (4.9 Group-A, 4.6 Group-B; p-value = 0.6072). Bone-predominance progression was more significant in Group-B (90%) versus Group-A (65%) (p-value = 0.0309). The median time for radiographic progression was 9.5 months versus 3.9 months for Group-A and Group-B, respectively (Log-Rank = 0.0063). **Conclusions:** Metabolic imaging is a useful tool that should complement PSA in the evaluation of treatment response and disease progression in mCRPC patients on 2^{nd}-HT, especially considering the paradoxical response observed in our data. Research Sponsor: None.

5578 Poster Session (Board #159), Fri, 8:00 AM-11:00 AM

Quality of life (QOL) for the treatment sequence of abiraterone acetate plus prednisone (AAP) followed by enzalutamide (ENZ) versus the opposite sequence for metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized clinical trial.

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Background: A randomized cross-over phase II trial (Lancet Oncol 20(12):1730, 2019) showed the sequence of AAP followed by ENZ is associated with a better time to PSA progression compared with the opposite sequence and superior 2nd line activity of ENZ. It is unknown whether one treatment sequence is associated with better QOL than the other. **Methods:** 202 Patients were randomized (1:1) to receive either AAP followed by ENZ at PSA progression (arm A) or the opposite sequence of ENZ followed by AAP (arm B). FACT-P questionnaires were completed at baseline, cross-over and every 4 weeks on treatment. Time to QOL deterioration (TTQOLD) for the treatment sequence was determined from start of 1st line treatment to first questionnaire with a clinically meaningful decrease from baseline and compared between arms using the log-rank test. TTQOLD was also determined for 1st line and 2nd line separately. The proportion of patients with QOL deterioration for total FACT-P score and FACT-P subscores from baseline to week 12 of 1st and 2nd line treatment was compared between arms using X^2 test. **Results:** Median follow-up for 1st and 2nd line and whole sequence were 9.3, 6.6 and 22.0 months (mos) respectively and questionnaire completion rate was 81%. TTQOLD for total FACT-P score for the whole sequence for arm A vs B was 10.5 mo (95% CI 5.0-15.5) vs 10.8 mo (5.5-13.1), p = 0.74. For 1st-line AAP vs ENZ, median TTQOLD was 15.5 mo (5.5-21.2) vs 11.0 (5.5-13.3) respectively (p = 0.23). For 2nd line ENZ vs ABI, median TTQOLD was 3.7 mo (2.0-5.4) vs 5.8 (2.8-12.1), p = 0.13. There was a higher rate of deterioration in physical well-being (PWB) for 1st line ENZ (arm B) and 2nd line ENZ (arm A) (Table). **Conclusions:** There was no difference in TTQOLD between the two treatment sequences of AAP and ENZ. Although treatment with second line ENZ has been associated with greater anti-cancer effects, ENZ was associated worse PWB QOL scores. Clinical trial information: NCT02125357. Research Sponsor: Canadian Cancer Society Research Institute, Other Foundation, Pharmaceutical/Biotech Company.

Clinically significant deterioration at 12 weeks (%).

	1st-line treatment			2nd-line treatment		
FACT-P score	Arm A (1st-line AAP) n = 101	Arm B (1st-line ENZ) n = 101	P	Arm A (2nd-line ENZ) n = 77	Arm B (2nd-line AAP) n = 77	P
Total FACT-P	23	30	0.26	40	34	0.40
Functional well-being	33	43	0.15	49	36	0.10
Physical well-being	26	40	0.036	45	29	0.030
Emotional well-being	24	30	0.34	27	35	0.30
Social well-being	21	25	0.50	18	23	0.43
Prostate cancer score	35	44	0.19	49	35	0.073
Pain score	45	41	0.57	43	34	0.25

5579 **Poster Session (Board #160), Fri, 8:00 AM-11:00 AM**

Association between BRCA2 status and histologic variants (intraductal [IDC] and cribriform [CRIB] histology) in prostate cancer (PC).

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Background: IDC histology in PC has been suggested to associate with germline *BRCA2* mutations *(gBRCA2)* in small series, leading to the potential recommendation of genetic testing for all PC patients with IDC in the primary tumor. **Methods:** We conducted a case-control study in which primary PC from 58 germline *BRCA2* mutation carriers (*gBRCA2*) and 116 from non-carriers (NC) were matched 1:2 by Gleason score and specimen type (core biopsy/prostatectomy). Samples were independently reviewed by two expert pathologists blinded to genetic status who established the presence of IDC and/or CRIB morphology with supportive immunohistochemical stains in a subset of cases. Next-generation sequencing, aCGH and/or FISH were used to assess for somatic mono-/bi-allelic *BRCA2* alterations. PTEN protein loss was determined by IHC, and *TMPRSS2-ERG* was detected by FISH/qRT-PCR. Chi-square tests were used to compare the frequency of IDC and cribriform histology in *gBRCA2* vs NC, as well as to assess the associations with other variables. Logistic regression models were built to identify independent factors associated with IDC and CRIB histology. **Results:** *gBRCA2* cases were younger at diagnosis (median 61.3 vs 64, $p < 0.01$) and had T3-4 disease more often than NC cases (31% vs 10.5%, $p < 0.01$), but the two groups did not differ in any other clinical-pathologic characteristics. After independent histopathological review, 79 cases demonstrated IDC histology and 81 had CRIB histology. No differences in the prevalence of IDC (50% NC vs 36% *gBRCA2*, $p = 0.09$) or CRIB (43% NC vs 53% *gBRCA2*, $p = 0.20$) patterns were observed. The probability of IDC was higher in PC with bi-allelic *BRCA2* alterations (OR 5.1, 95%CI 2.1-12.6), PTEN loss (OR 5.1, 95%CI 1.9-13.5) or both (OR 23.0, 95%CI 4.9-107.2) compared to those without these alterations. Bi-allelic *BRCA2* alteration was also associated with higher probability of CRIB histology (OR 7.2, 95%CI 3.1-16.4). *TMPRSS2-ERG* fusions were not associated with IDC or CRIB histology. MVA confirmed the independent association of bi-allelic *BRCA2* alteration ($p < 0.01$) and PTEN loss ($p < 0.01$) with IDC histology. Bi-allelic *BRCA2* alteration ($p < 0.01$) and Gleason >8 ($p < 0.01$) were independent risk factors for CRIB histology. **Conclusions:** Primary PC with bi-allelic *BRCA2* alterations was significantly associated with IDC and CRIB histology, independent of other clinical-pathologic factors (while *gBRCA2* status alone was not). PTEN loss in primary PC was also independently associated with IDC, but not CRIB, histology. Research Sponsor: Prostate Cancer Foundation; Instituto de Salud Carlos III.

5580 **Poster Session (Board #161), Fri, 8:00 AM-11:00 AM**

Obesity and metabolic syndrome correlate with a higher risk of biochemical recurrence in high risk and intermediate risk prostate cancer patients who underwent robotic-assisted laparoscopic prostatectomy.

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Background: Obesity and metabolic syndrome (MS) is prevalent in our society, and have been linked to a higher incidence of prostate cancer (PCa). The relationship of obesity or MS and cancer control has yielded mixed results in previous studies. We examined the correlation between the incidence of biochemical recurrence (BCR) with MS and BMI in a cohort of patients with PCa who underwent robotic-assisted laparoscopic prostatectomy (RALP). **Methods:** A retrospective study of patients who underwent RALP at a single center from 2007 to 2015 was conducted. Parameters including preoperative BMI, fasting glucose, lipid profile, blood pressure, PSA, Gleason score, pathologic stage, time to BCR, and surgical margin status were analyzed. Patients were categorized in high (HR), intermediate (IR), and low-risk (LR) groups based on the National Comprehensive Cancer Network (NCCN) guidelines. WHO classification was used for MS criteria, and BCR was defined as two consecutive postoperative PSA volume of $\geq$ 0.2 ng/mL. Obesity is defined as BMI $\geq$30 kg/m^2. **Results:** A total of 726 patients with 189 in HR, 471 in IR and 66 patients in LR groups were included in this study with the median age of 59 (interquartile range [IQR] 55-64) years old. The median follow-up from surgery was 38 (IQR 22-46) months. More obese patients were found in the HR group compared to IR/LR group (46.5% vs. 33.1%, $p<0.01$). There were also more patients with MS in the HR group compared to IR/LR group (36.5% vs. 12.0%, $p<0.01$). Obese patients had a higher rate of BCR across risk groups in comparison to non-obese patients 32.1% vs. 15.4% ($P<0.001$), specifically 68% vs. 40%($p<0.01$) in HR group and 21.3% vs. 12.7% ($p=0.035$) in the IR group. Similarly, patients with MS had a higher rate of BCR in HR and IR groups in comparison to the patients without MS, 39.1% vs. 18.7% ($P<0.01$); specifically, 67.7% vs. 42.2% ($p<0.01$) in HR and 29% vs. 11.6% ($p<0.01$) in the IR group. No correlation between MS or obesity and BCR was observed in LR group. There was no statistically significant difference in the positive surgical margin rate between obese and non-obese cohorts in each risk group. **Conclusions:** Among HR and IR-PCa patietns who underwent RALP, both obesity and MS correlate with increased risk of BCR. There were significantly more obesity and MS in HR-PCa patients, suggesting a potential pathophysiologic interplay between obesity or MS and cancer progression. Research Sponsor: the Western Pennsylvania Prostate Cancer Foundation.

5582 **Poster Session (Board #163), Fri, 8:00 AM-11:00 AM**

Oncological outcomes of 356 patients undergoing salvage focal ablative HIFU or cryotherapy following radiation failure.

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Background: Patients that have previously failed radiotherapy for prostate cancer is usually limited to systemic therapy due to morbidity from salvage prostatectomy. We reviewed the outcomes following focal salvage ablative therapy with HIFU or cryotherapy within the UK's HEAT and ICE registries. **Methods:** 356 consecutive patients underwent focal ablative treatment after initial radiation treatment failure (28/1/2004-1/10/2019, 194 (54.5%) underwent HIFU (posterior recurrence) and 162 (45.5%) underwent cryotherapy (mostly anterior or T3b). Primary outcome was failure-free survival (FFS) defined as no systemic therapy, whole-gland treatment, metastases or prostate cancer-specific death. Secondary outcomes were adverse events and overall survival. **Results:** Median (IQR) age was 69years (65-73) and PSA (IQR) was 4.0ng/ml (1-7-7.2). Overall median (IQR) follow-up was 41.3 months (21.4-58.5). Quadrant ablation was performed in 128 (36.0%), hemi-ablation performed in 64 (18.0%), hockey-stick in 5 (1.4%) and 159 (43.8%) had unknown ablative patterns. Due to histological or MRI proven recurrence/residual disease, 31 (8.7%) underwent further focal salvage re-treatment. FFS (95%CI) at 3 and 6 years were 81% (76-87%) and 75% (68-83%) respectively. Median (IQR) time to failure was 15.5 months (19.7). Overall survival (95%CI) at 3 and 6 years were 97% (95-100%) and 88% (81-96%) respectively. Prostate-specific mortality was 2.8%. Overall 3 (0.8%) patients were managed for fistula formation, 16 (4.5%) were treated for UTIs. **Conclusions:** Salvage focal ablative therapy for radio-recurrent prostate cancer is safe and provides good short to medium-term oncological control. The FORECAST study is awaited to further determine oncological outcomes in this cohort. Research Sponsor: None.

5583 **Poster Session (Board #164), Fri, 8:00 AM-11:00 AM**

Cost-effectiveness of novel antiandrogens (AAs) for treatment of nonmetastatic castrate-resistant prostate cancer (nmCRPC).

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Background: FDA has approved three novel AAs [Apalutamide(A), Darolutamide(D) and Enzalutamide(E)] in combination with Androgen deprivation therapy (ADT) for treatment of (nmCRPC) patients (pts). We report the cost-effectiveness of these drugs from the US perspective to help facilitate the choice of these agents for clinical practice. **Methods:** A life time Markov state-transition model was constructed with three health states (Metastasis-Free Survival[MFS], Metastatic disease, and Death) to compare cost-effectiveness of AA therapies for treatment of nmCRPC based on US healthcare payer perspective. A network meta-analysis of MFS and OS was conducted due to the lack of head to head trials. An approximation of the original individual-level patient time-to-event data were derived from digitized Kaplan-Meier curves for OS and MFS. Weibull distributions was selected as the best fitted model fitted and extrapolated as per the NICE decision support unit recommendations. Medication costs were based on wholesale acquisition cost. Adverse event (AE) grades 3/4 management costs were incorporated in the model. Discount rate of 3% per year was applied to costs and effects. Life years (LYs) and quality adjusted life years (QALYs) for each treatment as well as the incremental cost effectiveness (ICER) and cost utility (ICUR) ratios were estimated. Base case analyses (BCA) and probabilistic sensitivity analyses (PSA) were estimated. **Results:** The table summarizes the results form BCA analyses. A+ADT offers best gain in LYs (8.37yrs) and QALYs (5.30 yrs) but at higher cost. **Conclusions:** Apalutamide was associated with gains in LYs and QALYs traded off with higher lifetime cost relative to other AA alternatives. ADT was associated with lower gains in LYs and QALYs traded off with lower lifetime cost relative to other alternatives. Based on a $150,000/QALY threshold pay off, A+ADT is likely more cost effective compared to E+ADT or ADT alone; while E+ ADT may be more cost effective compared to D+ ADT. Research Sponsor: None.

Base case analyses for MFSLY and QALY.

Treatment	Cost	LY	QALY
Apalutamide	$512,620	8.37	5.30
Enzalutamide	$458,640	6.99	3.05
Darolutamide	$379,932	7.49	4.68
ADT	$187,264	6.48	3.07
Incremental Cost Effectiveness Ratio (ICER)/Incremental Cost Utility Ratio (ICUR)			
Apalutamide	$39,116	$150,782	$172,146
$23,991	Enzalutamide	$157,416	$532,110
$214,013	$48,287	Darolutamide	$190,760
$145,900	$13,568,800	$119,670	ADT

Blue cells for ICER of LY, Gray Cells for ICUR of QALY

5584 **Poster Session (Board #165), Fri, 8:00 AM-11:00 AM**

Short-term adjuvant versus neoadjuvant hormone therapy in localized prostate cancer: A pooled individual patient analysis of two phase III trials.

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Background: The timing of systemic therapy in relation to radiotherapy (RT) is important in most malignancies. In contrast, androgen deprivation therapy (ADT) has largely been investigated in relation to its duration rather than its sequencing with RT. Herein, we conduct the first combined individual patient analysis of two phase III randomized trials to determine the optimal timing of ADT with RT in localized prostate cancer (PCa). **Methods:** Individual patient data was obtained from the Malone et al trial (JCO 2019), which randomized patients to receive neoadjuvant/concurrent or concurrent/adjuvant ADT for 6 months with prostate only RT. This was combined with the prostate only RT arms of RTOG 9413 that randomized patients to 4 months of neoadjuvant/concurrent or adjuvant ADT. The neoadjuvant/concurrent arms of both trials were combined into the "neoadjuvant" group, and the concurrent/adjuvant (Malone) and adjuvant arm (RTOG 9413) were combined in the "adjuvant" group. The Kaplan-Meier method was used to estimate overall survival (OS) and progression-free survival (PFS). Cumulative incidence of distant metastasis (DM), PCa-specific mortality (PCSM) and biochemical failure (BF) were calculated using the Fine-Gray method with non-PCa deaths as competing events. Late genitourinary (GU) and gastrointestinal (GI) toxicity are also reported. **Results:** The median follow-up was 14.9 years (yrs) and 1065 patients were included (n=531 neoadjuvant, 534 adjuvant). Groups were well balanced for all baseline characteristics. Adjuvant ADT was superior to neoadjuvant ADT in terms of BF (15yr: 33% vs 43%, HR: 1.37 (95%CI: 1.12-1.68), p=0.002), DM (15yr: 12% vs 18%, HR: 1.40 (95%CI: 1.00-1.95), p=0.04), and PFS (15yr: 36% vs 29%, HR: 1.25 (95%CI: 1.07-1.47), p=0.01). Adjuvant ADT yielded lower PCSM (15yr: 15% vs 20%, HR: 1.29 (95%CI: 0.95-1.75), p=0.10), but did not reach statistical significance. This approached statistical significance in high risk PCa (HR 1.39 (95%CI 1.00-1.93), p=0.053). OS was not significantly different between arms (15yr: 39% vs 34%, HR: 1.11 (95%CI: 0.95-1.30), p=0.20). There was no significant difference in either late grade $\geq$3 GI (p=0.21) or GU (p=0.98) toxicity. **Conclusions:** We demonstrate for the first time that sequencing of ADT with RT significantly impacts long-term oncologic outcomes in localized PCa, favoring an adjuvant rather than neoadjuvant approach, without increasing late toxicity. This data has important implications to ongoing and future clinical trial design. Clinical trial information: NCT00769548. Research Sponsor: Prostate Cancer Foundation.

5585 **Poster Session (Board #166), Fri, 8:00 AM-11:00 AM**

Treatment patterns and outcomes of patients with penile squamous-cell carcinoma (PSCC) undergoing inguinal lymph node dissection (ILND): An analysis of a multicenter contemporary database.

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Background: PSCC is a rare tumor and the administration of guidelines-based therapies is still problematic in real-world practice. Survival outcomes remain suboptimal in patients (pts) with ILN involvement. Multinational analyses of real-world patterns are needed. **Methods:** Within an international, multicenter database of 965 PSCC pts who received ILND from 1980-2019, 630 had complete information for the variables of interest, from USA (N=81), Europe (EU, N=355), South America (SA, N=90), and China (Ch, N=104). Descriptive analyses according to geographical and ethnicity/race distribution were made. Comparisons of outcomes were made with Kaplan-Meier analyses and corresponding logrank tests. **Results:** Median age at diagnosis was 59 yrs, with no differences worldwide and according to ethnicity/race. Pts from SA presented with more advanced cT-stage (cT3-4: 26.7% vs. 17.3% USA vs. 7.6% EU) while EU pts presented with more advanced cN-stage (cN3: 14.9% vs. 11% USA vs. 7.8% SA vs. 5.8% Ch) as well as pathological (p)N-stage: pN3 pts were 53% in EU, 33.3% in USA, 20% in SA, and 18.3% in Ch. Perioperative chemotherapy (pCT) was more frequently administered in EU (53.8%) vs. USA (34.6%) SA (5.6%) Ch (7.7%). cT-stage was more frequently advanced in black pts (cT3-4: 33.3% vs. 12% Caucasian, 6.2% Hispanic/latino, 0% Asian) and the same was for cN-stage (cN3: 25% in black, 13% in Caucasian, 6.2% in Hispanic/latino, 6% in Asian). Conversely, pN3 pts were more frequently Caucasian (45.6%) vs. black (25%), Hispanic/latino (19%), and Asian (18%). pCT was more frequently administered in Caucasian pts (45%) vs. black (8.3%), Hispanic/latino (0), and Asian (8%). No significant differences in overall survival (OS) were observed according to geographical region or ethnicity/race, in the total pts and in the subgroups according to cT, cN, pN-stages and pCT. Median OS after pCT and ILND was 95 months. Bilateral ILN involvement was equally observed regardless of geographical region and ethnicity/race. In the total population, pCT significantly prolonged OS in pts with bilateral ILN (p=0.04), but not in pts with pelvic LN. **Conclusions:** Treatment patterns for PSCC undergoing ILND remain heterogeneous worldwide, and adherence to guidelines is seemingly poor. However, long-term outcomes with pCT remain uniformly suboptimal with $<$50% pts alive at 10 yrs. Further collaborative efforts are needed in this orphan disease to harmonize the therapeutic paradigm. Research Sponsor: Fondazione IRCCS Istituto Nazionale dei Tumori.

TPS5586 **Poster Session (Board #167), Fri, 8:00 AM-11:00 AM**

A phase II randomized trial of RAdium-223 dichloride and SABR versus SABR for oligomEtastatic prostate caNcerS (RAVENS).

Matthew Pierre Deek, Hamza Hasan, Ryan Phillips, Robert F Hobbs, Ana Ponce Kiess, Hao Wang, Elizabeth D Thompson, Jonathan Powell, Curtiland Deville, Stephen C. Greco, Danny Song, Steven P. Rowe, Samuel R. Denmeade, Mark Christopher Markowski, Emmanuel S. Antonarakis, Michael Anthony Carducci, Mario A. Eisenberger, Kenneth J. Pienta, Channing Judith Paller, Phuoc T. Tran; Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins Hospital, Baltimore, MD; Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins Hospital, B, MD; Department of Radiation Oncology and Molecular Radiation Sciences, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD; Johns Hopkins University, Baltimore, MD; Johns Hopkins University School of Medicine, Baltimore, MD; Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; The Johns Hopkins University School of Medicine, Baltimore, MD; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, MD; Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Sidney Kimmel Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD; James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD; Johns Hopkins School of Medicine, Baltimore, MD

Background: Metastasis directed therapy (MDT) is able to prolong progression free survival (PFS) and forestall initiation of androgen deprivation therapy (ADT) in men with hormone-sensitive, oligometastatic prostate cancer (HSOPCa) compared to observation. While MDT appears to be effective in HSOPCa, a large percentage of men will have disease recurrence. Patterns of failure demonstrate patients tend to recur in the bone following MDT, raising the question of sub-clinically-apparent osseous disease. Radium-223 dichloride is a radiopharmaceutical with structural similarity to calcium, allowing it to be taken up by bone where it emits alpha particles, and therefore might have utility in the treatment of micrometastatic osseous disease. Therefore, the primary goal of the phase II RAVENS trial is to evaluate the efficacy of Stereotactic ablative radiation (SABR) + radium-223 dichloride in prolonging PFS in men with HSOPCa. **Methods:** Patients with HSOPCa and 3 or less metastases with at least 1 bone metastasis (by conventional imaging) will be randomized 1:1 to SABR alone vs. SABR + radium-223 dichloride. Eligibility criteria include PSA doubling time of $<$ 15 months and ECOG performance status of $<$ 2. Patients cannot be on ADT and must have normal testosterone levels at the time of randomization. Patients randomized to the combination arm will receive six doses of Radium-223 dichloride at four week intervals. A sample size using a 1:1 randomization scheme of 30 patients per arm will provide 80% power to detect an increase of median PFS from 10 months to 20 months with type I error = 0.1, using a one-sided log-rank test. To account for 5% early drop out, we will randomize a total of 64 patients (32 per arm). The primary end point is PFS with a primary hypothesis that SABR + radium-223 dichloride will increase median PFS from 10 months in the SABR arm to 20 months in the SABR + radium-223 dichloride arm. Progression is a composite endpoint including PSA progression per Prostate Cancer Working Group 2 (PCWG2), symptomatic progression, radiologic progression per RECIST 1.1 criteria, initiation of ADT, or death due to any cause. Secondary clinical endpoints include toxicity and quality of life assessments, local control at 12 months, locoregional progression, time to distant progression, time to new metastasis, and duration of response. Biological correlates will be evaluated including changes in circulating tumor cells following therapy, deep sequencing of circulating tumor DNA, and T-cell repertoire profiling before and after therapy. Clinical trial information: NCT04037358. Research Sponsor: Bayer.

TPS5587 **Poster Session (Board #168), Fri, 8:00 AM-11:00 AM**

DaroACT: Darolutamide and enzalutamide effects on physical and neurocognitive function and daily activity in patients with castration-resistant prostate cancer (CRPC).

Tomasz M. Beer, Neal D. Shore, Alicia K. Morgans, Kerri M. Winters-Stone, Jeffrey Scott Wefel, Jorge A. Ortiz, John A. Reeves, Daniel J. George; Knight Cancer Institute, Oregon Health & Science University, Portland, OR; Carolina Urologic Research Center, Myrtle Beach, SC; Northwestern University, Chicago, IL; Oregon Health & Science University, Portland, OR; The University of Texas MD Anderson Cancer Center, Houston, TX; Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ; Duke University School of Medicine, Durham, NC

Background: The androgen receptor inhibitors (ARIs) apalutamide and enzalutamide (Enza) are approved for the treatment of men with advanced prostate cancer. These ARIs are associated with adverse events (AEs) including fatigue, neurocognitive dysfunction, and falls. Darolutamide (Daro) is a structurally distinct ARI approved by the FDA to treat nonmetastatic CRPC, based on significantly improved metastasis-free survival vs placebo in the ARAMIS Phase III clinical trial. Daro was not associated with a significant increase in AEs beyond that of concomitant androgen deprivation therapy, compared with placebo. DaroAcT is the first prospective trial to compare the effects of Daro to those of Enza on physical and neurocognitive function, and daily physical activity, in men with CRPC. **Methods:** This randomized, open-label, multicenter, Phase IIb trial (NCT04157088), involving ~20 sites across the US, is open for enrollment. After a lead-in phase of 30 pts treated with Daro alone, approximately 120 pts will be randomized 1:1 to receive Daro (600 mg twice daily) or Enza (160 mg once daily). Eligibility criteria include CRPC (metastatic and non-metastatic); age $\geq$18 years; Karnofsky performance status $\geq$80; no prior abiraterone within 6 months of enrollment, and no prior immunotherapy or apalutamide. All patients will continue luteinizing hormone-releasing hormone agonist or antagonist treatment for the duration of the study. The primary endpoint is the proportion of pts with slowed Timed Up and Go (TUG) time during the 24-week period from baseline. Secondary endpoints include the proportion of pts with worsening in short Physical Performance Battery (sPPB), mean change from baseline in daily physical activity, the proportion of pts with a decline in neurocognitive function or worsening of fatigue, and AEs. This study uses objective measures to assess physical function, including TUG and sPPB, measurements of daily activity levels with an accelerometry device for $\geq$7 days at designated time points, and neurocognitive tests. Fatigue is measured using the Brief Fatigue Inventory. Primary completion is estimated to be December 31, 2022. Clinical trial information: NCT04157088. Research Sponsor: Bayer.

TPS5588 **Poster Session (Board #169), Fri, 8:00 AM-11:00 AM**

A phase III randomized, placebo-controlled, double-blind study of niraparib plus abiraterone acetate and prednisone versus abiraterone acetate and prednisone in patients with metastatic prostate cancer (MAGNITUDE).

Kim N. Chi, Dana E. Rathkopf, Gerhardt Attard, Matthew Raymond Smith, Eleni Efstathiou, David Olmos, Eric Jay Small, Ji Youl Lee, Deborah S. Ricci, Jason S. Simon, Xin Zhao, Nishi Kothari, Shinta Cheng, Shahneen Kaur Sandhu; BC Cancer and Vancouver Prostate Centre, Vancouver, BC, Canada; Memorial Sloan Kettering Cancer Center, New York, NY; Institute of Cancer Research and The Royal Marsden Hospital, Sutton, United Kingdom; Massachusetts General Hospital Cancer Center, Boston, MA; Department of Genitourinary Medical Oncology, Division of Cancer Medicine, Houston, TX; Prostate Cancer Clinical Research Unit, Spanish National Cancer Research Center, Madrid, Spain; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; Janssen Research & Development, Spring House, PA; Janssen Research & Development, LLC, Raritan, NJ; Janssen Research & Development, San Francisco, CA; Janssen Research & Development, Los Angeles, CA; Peter MacCallum Cancer Centre, Melbourne, Australia

Background: Preclinical data suggest synergistic antitumor activity when the PARP inhibitor (PARPi) niraparib is combined with the androgen pathway inhibitor abiraterone acetate[1]. The addition of a PARPi to abiraterone acetate plus prednisone (AAP) showed improved radiographic progression-free survival (rPFS) vs AAP alone in patients with mCRPC regardless of DNA repair gene defect (DRD) status[2]. Interim results from a phase I study support safety and tolerability of niraparib 200 mg combined with AAP in patients with mCRPC[3]. The objective of this Phase III study is to compare the efficacy and safety of niraparib plus AAP versus AAP with placebo as first-line therapy for mCRPC. **Methods:** This ongoing multicenter MAGNITUDE study (NCT03748641) will open in approximately 300 sites across 28 countries and will enroll patients with mCRPC who have not received treatment in the metastatic castrate resistant setting other than ongoing androgen deprivation therapy [ADT] and $\leq$4 months of AAP. DRD status will be determined by plasma and tissue assays. The cohort with DRD (n=400) and the cohort without DRD (n=600) will each be randomized 1:1 to niraparib + AAP or placebo + AAP. The first patient was consented in February 2019 and enrollment is ongoing. The primary objective of the study is to compare radiographic progression-free survival (rPFS) as assessed by blinded independent central radiology review in each cohort and treatment group. To test superiority of the combination vs AAP, sample sizes were estimated to provide 92% power to detect HR$\leq$0.65 rPFS in the cohort with DRD and 94% power to detect HR$\leq$0.67 in rPFS in the cohort without DRD, both at a 2-tailed level of significance of 0.05. The secondary objectives are time to symptomatic progression, time to cytotoxic chemotherapy, and overall survival. Safety and pharmacokinetic profiles will be evaluated. [1]Rajendra N, et al. Cancer Res 2019;79(13 Suppl):Abstract nr 2134. [2]Clarke N, et al. Lancet Oncol. 2018;(7):975-986. [3]Saad, et al. Ann Oncol, 2018;29 (suppl 8), mdy284.043, https://doi.org/10.1093/annonc/mdy284.043) Clinical trial information: NCT03748641. Research Sponsor: Janssen Research and Development.

TPS5589 **Poster Session (Board #170), Fri, 8:00 AM-11:00 AM**

Phase I study of AMG 509, a STEAP1 x CD3 T cell-recruiting XmAb 2+1 immune therapy, in patients with metastatic castration-resistant prostate cancer (mCRPC).

W. Kevin Kelly, Daniel Costin Danila, William Jeffery Edenfield, Rahul Raj Aggarwal, Daniel Peter Petrylak, A. Oliver Sartor, Christopher Joseph Sumey, Tanya B. Dorff, Evan Y. Yu, Nabil Adra, David Michael Waterhouse, Andrew J. Armstrong, Lisa Horvath, David William Pook, Leonard Joseph Appleman, Aubrey Lau, Mark Salvati, Hosein Kouros-Mehr; Thomas Jefferson University, Philadelphia, PA; Memorial Sloan Kettering Cancer Center, New York, NY; Prisma Health Greenville Memorial Hospital, Greenville, SC; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Yale Cancer Center, New Haven, CT; Tulane Cancer Center, New Orleans, LA; Sanford Cancer Center, Sioux Falls, SD; City of Hope, Duarte, CA; University of Washington, Seattle, WA; Indiana University School of Medicine, Indianapolis, IN; OHC (Oncology Hematology Care), Inc., Cincinnati, OH; Duke University School of Medicine, Durham, NC; Chris O'Brien Lifehouse, Camperdown, NSW, Australia; Monash University, Melbourne, VIC, Australia; UPMC Hillman Cancer Center, Pittsburgh, PA; Amgen Inc., Thousand Oaks, CA

Background: Six transmembrane epithelial antigen of the prostate 1 (STEAP1) is a cell surface antigen that is highly expressed in prostate cancer. AMG 509 is a potent bispecific XmAb 2+1 immune therapy designed to direct T-effector cells to STEAP1-expressing cells. AMG 509 contains two identical humanized anti-STEAP1 Fab domains that bind STEAP1-expressing cells, an anti-CD3 scFv domain that binds T cells, and an Fc domain, engineered to lack effector function, that extends serum half-life. In preclinical studies, AMG 509 induced potent and specific T-cell-mediated lysis of STEAP1-expressing cancer models. **Methods:** This open-label, phase I, first-in-human study will evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of AMG 509 in patients with relapsed/refractory mCRPC. The dose exploration phase (n=40) will estimate the maximum tolerated dose (MTD) or recommended phase II dose (RP2D) using a Bayesian logistic regression model. The dose expansion phase (n=30) will confirm safety, PK, and pharmacodynamics at the MTD or RP2D and collect further safety, efficacy, and biomarker data. Efficacy will be assessed by prostate-specific antigen response, circulating tumor cell response, and objective tumor response per RECIST 1.1 with Prostate Cancer Working Group 3 modifications. Key inclusion criteria: men $\geq$18 years with histologically/cytologically confirmed mCRPC who are refractory to novel hormonal therapy (e.g., abiraterone and/or enzalutamide) and have failed 1–2 taxane regimens or are medically unsuitable for or have refused taxanes; ongoing castration with total serum testosterone $\leq$50 ng/dL; evidence of progressive disease; ECOG performance status 0–1; life expectancy $\geq$3 months; and adequate hematologic, renal, hepatic, and cardiac function. In the dose exploration phase, novel antiandrogen therapy must have been given in the metastatic setting. Key exclusion criteria: pure small-cell or neuroendocrine carcinoma of the prostate; untreated CNS metastases or leptomeningeal disease; any anticancer therapy or immunotherapy, radiation therapy, or major surgery $<$4 weeks from first dose; history of or current autoimmune disease or any disease requiring immunosuppressive therapy ($\leq$10 mg/d prednisone permitted); prior STEAP1-targeted therapy; infection requiring IV antimicrobials $<$7 days from first dose. The study opened in January 2020 and is recruiting patients. Clinical trial information: NCT04221542. Research Sponsor: Amgen Inc.

TPS5590 **Poster Session (Board #171), Fri, 8:00 AM-11:00 AM**

Phase I study of AMG 160, a half-life extended bispecific T-cell engager (HLE BiTE immune therapy) targeting prostate-specific membrane antigen, in patients with metastatic castration-resistant prostate cancer (mCRPC).

Ben Tran, Lisa Horvath, Matthew Rettig, Karim Fizazi, Martijn P. Lolkema, Tanya B. Dorff, Richard Greil, Jean-Pascal H. Machiels, Karen A. Autio, Sylvie Rottey, Nabil Adra, Rohan Garje, Felicia Roncolato, Scott T. Tagawa, Shahrokh F. Shariat, Mark Salvati, Shirley Poon, Hosein Kouros-Mehr; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Chris O'Brien Lifehouse, Camperdown, NSW, Australia; University of California, Los Angeles, and VA Greater Los Angeles Healthcare System, Los Angeles, CA; Gustave Roussy Cancer Center, University of Paris Sud, Villejuif, France; Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, Netherlands; City of Hope, Duarte, CA; IIIrd Medical Department, Paracelsus Medical University Salzburg; Salzburg Cancer Research Institute-CCCIT and Cancer Cluster, Salzburg, Austria; Cliniques Universitaires Saint-Luc, Brussels, Belgium; Memorial Sloan Kettering Cancer Center, New York, NY; Drug Research Unit Ghent, Ghent University, Ghent, Belgium; Indiana University School of Medicine, Indianapolis, IN; University of Iowa Carver College of Medicine, Iowa City, IA; Scientia Clinical Research, Randwick, NSW, Australia; Weill Cornell Medicine, New York, NY; Medical University of Vienna, Vienna, Austria; Amgen Inc., Thousand Oaks, CA

Background: Prostate-specific membrane antigen (PSMA) is a clinically validated therapeutic target for the imaging and treatment of mCRPC. AMG 160 is an HLE BiTE immune therapy designed to redirect T cells to cancer cells by binding to PSMA on cancer cells and CD3 on T cells. BiTE immune therapy leads to direct tumor cell killing, T-cell activation and expansion, and the creation of a pro-inflammatory tumor microenvironment. Combining AMG 160 with a PD-1 inhibitor may enhance antitumor activity by enabling sustained T-cell-dependent killing of tumor cells in the inflamed tumor microenvironment. **Methods:** NCT03792841 is a phase I study of AMG 160 as monotherapy (part 1) and in combination with pembrolizumab (part 2) in men with histologically/cytologically confirmed mCRPC who are refractory to a novel hormonal therapy (abiraterone, enzalutamide, and/or apalutamide) and have failed 1–2 taxane regimens (or are medically unsuitable or have refused taxanes), who have ongoing castration with total serum testosterone $\leq$ 50 ng/dL, and have evidence of progressive disease. Patients who received prior PSMA radionuclide therapy may be eligible. Patients with CNS metastases, leptomeningeal disease, spinal cord compression, or active autoimmune disease will be excluded. Primary objectives are to evaluate safety and tolerability and determine the maximum tolerated dose (MTD) or recommended phase II dose (RP2D) of AMG 160 given as monotherapy or in combination with pembrolizumab. Secondary objectives are to characterize pharmacokinetics and preliminary antitumor activity. Exploratory objectives include evaluation of potential pharmacodynamic and patient selection biomarkers, immunogenicity, and patient-reported pain and functional outcomes. The part 1 dose exploration will determine the MTD/RP2D of AMG 160. The part 1 dose expansion will confirm the safety and tolerability of the MTD/RP2D. The part 2 dose exploration will estimate the MTD/RP2D of AMG 160 in combination with pembrolizumab. Evaluation of preliminary antitumor activity will be based on RECIST 1.1 with Prostate Cancer Working Group 3 modifications, PSA response, CTC response, progression-free survival (radiographic and PSA), and overall survival. PSMA PET/CT and FDG PET/CT imaging will be used for evaluation of exploratory objectives. The study opened in February 2019 and is currently recruiting patients into both part 1 and part 2. Clinical trial information: NCT03792841. Research Sponsor: Amgen Inc.

TPS5591 **Poster Session (Board #172), Fri, 8:00 AM-11:00 AM**

CYCLONE 2: A phase II, randomized, placebo-controlled study of abiraterone acetate plus prednisone with or without abemaciclib in patients with metastatic castration-resistant prostate cancer.

Matthew Raymond Smith, Neeraj Agarwal, Tilman Todenhöfer, Redas Trepiakas, Jae-Lyun Lee, Andrew Lithio, Sonya Chapman, Karim Nacerddine, Christopher Sweeney; Massachusetts General Hospital Cancer Center, Boston, MA; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Eberhard-Karls University, Tübingen, Germany; Zealand University Hospital, Naestved, Denmark; Asan Medical Center and University of Ulsan College of Medicine, Seoul, South Korea; Eli Lilly and Company, Indianapolis, IN; Eli Lilly and Company, Windlesham, United Kingdom; Eli Lilly, Neuilly-Sur-Seine, France; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Despite recent advances, nearly all patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) experience disease progression and cancer-specific mortality. Persistent or reactivated androgen receptor (AR) signaling and/or activation of pathways in cross-talk with AR signaling are key drivers of mCRPC progression. Evidence suggests that AR signaling promotes translation of D-type cyclins resulting in cyclin-dependent kinase 4 and 6 (CDK4&6) activation and cell cycle progression. Abemaciclib is an oral selective inhibitor of CDK4&6 dosed on a continuous schedule, that is FDA-approved in combination with endocrine therapy or as monotherapy to treat HR+, HER2- metastatic breast cancer pts. Preclinical studies with prostate cancer cell lines and xenograft models showed that abemaciclib induces cell cycle arrest and tumor growth inhibition. The hypothesis is that addition of abemaciclib to AR targeted therapy may be an effective treatment for mCRPC pts.
Methods: CYCLONE 2 (NCT03706365) is a phase II, randomized, double-blind, multicenter, placebo-controlled study to assess the safety and efficacy of abemaciclib in combination with abiraterone acetate plus prednisone (AA+P) as first-line treatment of pts with mCRPC. The study is designed in two parts. Part 1 is a 30-patient safety lead-in to determine the recommended phase II dose (RP2D; 150 mg or 200 mg, twice daily) of abemaciclib in combination with AA (1000 mg, once daily) + P (5 mg, twice daily). In part 2, 150 pts are randomized 1:1 to abemaciclib at the RP2D with AA+P or placebo with AA+P. Pts who received prior AA+P, enzalutamide, apalutamide, darolutamide, radiopharmaceuticals, or sipuleucel-T are excluded. Prior docetaxel for metastatic hormone-sensitive prostate cancer, but not for mCRPC, is allowed. Pts must have progressive mCRPC (by PSA and/or imaging) and an accessible metastatic lesion for tumor biopsy. The co-primary objectives are radiographic PFS (per RECIST1.1 for soft tissue and PCWG3 for bone) and time to PSA progression. Secondary objectives include safety, objective response rate, duration of response, OS, time to symptomatic progression, and pharmacokinetics. Assuming hazard ratios of 0.64 (rPFS) and 0.6 (PSA progression), the study is powered to 80% and 85%, respectively, to test the superiority of abemaciclib plus AA+P vs. placebo plus AA+P at one-sided α=0.1 using stratified log-rank tests. Part 1 is completed and part 2 is enrolling in 70 sites worldwide. Clinical trial information: NCT03706365. Research Sponsor: Eli Lilly and Company.

TPS5592 **Poster Session (Board #173), Fri, 8:00 AM-11:00 AM**

A phase I/II study of REGN5678 (Anti-PSMAxCD28, a costimulatory bispecific antibody) with cemiplimab (anti-PD-1) in patients with metastatic castration-resistant prostate cancer.

Charles G. Drake, Jingsong Zhang, Mark N. Stein, Yuanfang Xu, Frank A. Seebach, Israel Lowy, Kosalai Kal Mohan, Glenn Kroog, Elizabeth Miller; Department of Medicine and Division of Hematology/Oncology, Columbia University Medical Center, New York, NY; Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, FL; Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background: Bispecific antibodies (bsAbs) are emerging as a protein-based therapeutic strategy for directing T-cell-mediated cytotoxicity in a tumor antigen-specific manner, typically by binding to both tumor antigen and the CD3 receptor on T cells. REGN5678 is a human IgG4-based, first-in-class costimulatory bsAb designed to target prostate tumors by bridging prostate specific membrane antigen expressing tumor cells with the costimulatory receptor, CD28, on T cells, and providing amplified T-cell receptor-CD3 complex-mediated T-cell activation within the tumor through the activation of CD28 signaling. At the tumor site, REGN5678 may synergize with PD-1 inhibitors. In mouse models, REGN5678 in combination with PD-1 antibody has improved anti-tumor activity compared with either therapy alone (Skokos et al CRI/CICON 2019; oral, session 3). This study evaluates the safety and anti-tumor activity of REGN5678 alone and in combination with cemiplimab in patients with metastatic castration-resistant prostate cancer (mCRPC) who progressed after prior therapy. **Methods:** This is an open label, Phase I/II, first-in-human study evaluating safety, tolerability, pharmacokinetics (PK), and anti-tumor activity of REGN5678 alone and in combination with cemiplimab in treatment-experienced mCRPC (NCT03972657). For inclusion, patients must have received at least two approved therapies for metastatic disease, including a second-generation hormonal agent. REGN5678 is administered weekly and cemiplimab (350 mg) is administered once every 3 weeks. During dose escalation, a 3-week safety lead-in of REGN5678 monotherapy will be administered prior to the addition of cemiplimab. Study therapies are administered until disease progression, intolerable adverse events, withdrawal of consent, or study withdrawal criterion is met. The primary objectives in dose escalation are to evaluate safety, tolerability, and PK of REGN5678 alone and in combination with cemiplimab. Expansion cohort(s) will be enrolled once a REGN5678/cemiplimab recommended Phase II dose is determined. During the expansion phase, the primary trial objective is to assess clinical activity, as measured by objective response rate of REGN5678 in combination with cemiplimab per modified Prostate Cancer Working Group 3 criteria. This study is currently open to enrollment. Clinical trial information: NCT03972657. Research Sponsor: Regeneron Pharmaceuticals Inc.

TPS5593 **Poster Session (Board #174), Fri, 8:00 AM-11:00 AM**

DAROL: DARolutamide ObservationaL study patients in nonmetastatic castration-resistant prostate cancer (nmCRPC) patients.

Evan Y. Yu, Christopher Michael Pieczonka, Alberto Briganti, Declan G. Murphy, Thierry Lebret, Murilo Luz, Hiroyoshi Suzuki, Antoine Thiery-Vuillemin, Jorge A. Ortiz, Rongjin Guan, Andrew J. Armstrong; Division of Oncology, Department of Medicine, University of Washington, Seattle, WA; Associated Medical Professionals of NY, Syracuse, NY; Unit of Urology, Division of Experimental Oncology, Urological Research Institute (URI), IRCCS Ospedale San Raffaele, and Università Vita-Salute San Raffaele, Milan, Italy; Sir Peter MacCallum Department of Oncology, University of Melbourne, Peter MacCallum Cancer Centre, Melbourne, Australia; Department of Urology, Hôpital Foch, Université Versailles, St Quentin, Paris Saclay, France; Hospital Erasto Gaertner, Curitiba, PR, Brazil; Toho University Sakura Medical Center, Chiba, Japan; Medical Oncology, Centre Hospitalier Régional Universitaire, Besancon, France; Imclone Syst Inc, Miami, FL; Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ; Duke Cancer Institute, Durham, NC

Background: Patients (pts) with prostate cancer treated with prolonged androgen deprivation therapy (ADT) will eventually develop castration-resistant disease. Treatment of pts with nmCRPC with darolutamide (DARO) delays the development of metastases, which are associated with cancer-related morbidity. DARO is a structurally unique oral androgen receptor inhibitor approved by the FDA for the treatment of nmCRPC, based on prolonged metastasis-free survival (MFS) compared with placebo (median 40.4 months vs.18.4 months, respectively) in the ARAMIS phase III clinical trial. DARO showed a similar incidence of adverse events (AEs) compared to ADT alone and has a low potential for drug-drug interactions. However, phase III clinical trials cannot fully reflect all the facets of real-world pts. Therefore, non-interventional studies in the real-world setting, such as DAROL, are able to provide additional insight into the patterns of use and real-world safety profile of recently approved drugs. **Methods:** (NCT04122976) will enrol participants in the US, Brazil, Japan, and the EU. Eligible pts include men with histologically confirmed nmCRPC aged $\geq$18 yrs, life expectancy $\geq$3 months, and initiated on DARO treatment as per investigators' decision within 3 days prior to enrollment. DAROL opened for enrollment in December 2019 in the US with a projected enrollment of 1000 pts. The primary endpoint of DAROL is safety. Treatment-emergent AEs will be collected during the study. Secondary endpoints to measure clinical effectiveness are MFS, time to symptomatic skeletal event, time to prostate-specific antigen progression, survival rate, and duration of DARO therapy. Other endpoints include pt demographics and characteristics, and prior and subsequent therapy. The estimated primary completion date is December 30, 2024. Clinical trial information: NCT04122976. Research Sponsor: Bayer.

TPS5594 **Poster Session (Board #175), Fri, 8:00 AM-11:00 AM**

A phase III trial of docetaxel versus docetaxel and radium-223 (Ra-223) in patients with metastatic castration-resistant prostate cancer (mCRPC): DORA.

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Background: Ra-223, a bone-targeted alpha therapy, prolongs survival in patients (pts) with symptomatic mCRPC to bone. Docetaxel targets microtubule trafficking improving survival in the mCRPC and metastatic hormone-sensitive settings. We hypothesized that simultaneously targeting the tumor and bone compartment yields superior outcomes than targeting either alone. We previously determined the dose and schedule of co-administering Ra-223 + docetaxel in a randomized phase I/IIa trial. The combination appeared to have improved declines in prostate specific antigen (PSA) and bone markers, delayed PSA progression, and was better tolerated (with adjusted dose/schedule) relative to standard docetaxel alone. We are now conducting a phase III study to determine the clinical benefit of the regimen. **Methods:** Randomization (1:1) of 738 men with mCRPC to docetaxel or docetaxel + Ra-223 is planned with a projected hazard ratio for treatment effect (15 vs 20 months median survival) of 0.75. Pts with $\geq$2 bone lesions and progression by Prostate Cancer Working Group 3 criteria are eligible. Other key inclusion criteria are an Eastern Cooperative Oncology Group performance status of 0-1 and normal organ function. Key exclusion criteria are: use of anticancer therapy $\leq$4 weeks (wks) before randomization and use of bone-seeking radiopharmaceuticals or chemotherapy in the castration-resistant setting, and bulky visceral metastases ($\geq$3 lung and/or liver or a lesion $\geq$2 cm in the previous 8 wks). Subjects receive docetaxel 75 mg/m^2 IV q3w for 10 doses or docetaxel 60 mg/m^2 IV q3w for 10 doses + Ra-223 55 kBq/kg IV q6w for 6 doses. The primary endpoint is overall survival. Secondary and exploratory endpoints include: radiographic progression-free survival, symptomatic skeletal event-free survival, safety, markers of bone metabolism, alterations in circulating tumor cells and DNA, detection of androgen-receptor splice variant 7, changes in automated bone scan index (aBSI), and assessment of patient-reported outcome instruments (FACT-P, Brief Pain Inventory, Brief Fatigue Inventory). The study is open at 25 sites in the US and Netherlands, sponsored by Memorial Sloan Kettering Cancer Center, and managed by the Prostate Cancer Clinical Trials Consortium. Clinical trial information: NCT03574571. Research Sponsor: Memorial Sloan Kettering Cancer Center, Other Government Agency, Pharmaceutical/Biotech Company.

TPS5595 **Poster Session (Board #176), Fri, 8:00 AM-11:00 AM**

Phase III study of pembrolizumab (pembro) plus enzalutamide (enza) and androgen deprivation therapy (ADT) for patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC): KEYNOTE-991.

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Background: Pembro, an anti–PD-1 antibody, has shown antitumor activity as monotherapy and in combination with other agents in metastatic castration-resistant prostate cancer (mCRPC). As the antitumor effects of enza may be pro-immunogenic, we hypothesized that combining pembro and enza could show additive or synergistic antitumor activity. Furthermore, pembro + enza previously showed antitumor activity in pts with mCRPC for whom abiraterone failed (KEYNOTE-365, NCT02861573) and in pts with mCRPC for whom enza monotherapy failed (KEYNOTE 199, NCT02787005). These data warrant further evaluation of the combination of pembro + enza when given at the initiation of ADT.
Methods: KEYNOTE-991 (NCT04191096) is a phase III trial to evaluate the efficacy and safety of enza + ADT + either pembro or placebo in patients with mHSPC. Approximately 1232 pts will be randomly assigned 1:1 to receive enza 160 mg orally once daily + ADT + pembro 200 mg IV every 3 weeks (Q3W) or enza 160 mg orally once daily + ADT + placebo IV Q3W. ADT is receipt of an LHRH agonist or antagonist during study treatment or bilateral orchiectomy. Treatment will be stratified by prior docetaxel therapy (yes or no) and presence of high-volume disease (yes or no). Pts with mHSPC, with $\geq$2 bone lesions and/or visceral disease, who are naive to next-generation hormone agents, and who have ECOG PS 0 or 1 are eligible. Pts must provide tissue for biomarker analysis. Responses will be assessed by CT or MRI and radionuclide bone imaging per Prostate Cancer Working Group 3 (PCWG3)–modified RECIST v1.1 by blinded independent central review (BICR) Q12W from the date of randomization. Treatment will continue with pembro for up to 35 cycles, and treatment with enza will proceed continuously from day 1 of cycle 1 until disease progression, unacceptable toxicity, or withdrawal of consent. Dual primary end points are radiographic progression-free survival (PFS) per PCWG3-modified RECIST v1.1 assessed by BICR and overall survival. Secondary end points are time to first subsequent anticancer therapy, time to symptomatic skeletal-related event, PFS2 (progression after next line of therapy or death), prostate-specific antigen (PSA) response rate, time to PSA progression, PSA undetectable rate, objective response rate, duration of response, and time to radiographic soft tissue progression. Other end points are safety and patient-reported outcomes (eg, time to pain progression). Clinical trial information: NCT04191096. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS5596 **Poster Session (Board #177), Fri, 8:00 AM-11:00 AM**

A multicenter, randomized, controlled phase II study: Efficacy and safety of PSMA-targeted radioligand therapy I-131-1095 (1095) plus enzalutamide (enza) in 18F-DCFPyL PSMA scan avid, metastatic castration-resistant prostate cancer (mCRPC) patients post-abiraterone (abi) progression (ARROW).

Evan Y. Yu, David Laidley, Frederic Pouliot, Stephan Probst, Robert Sabbagh, Giuseppe Esposito, Fred Saad, A. Oliver Sartor; University of Washington, Seattle, WA; St. Joseph's Health Care, London, ON, Canada; Cancer Research Center, Centre Hospitalier Universitaire (CHU) de Québec-Université Laval, Quebec City, QC, Canada; Jewish General Hospital, Montreal, QC, Canada; CIUSSE-CHUS-Universite de Sherbrooke, Sherbrooke, QC, Canada; Georgetown University, Washington DC, DC; Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, QC, Canada; Tulane Cancer Center, New Orleans, LA

Background: PSMA is a transmembrane glycoprotein expressed in normal human prostate epithelium at low levels, but highly upregulated in metastatic prostate cancer (PC). ^{18}F-DCFPyL is a novel PSMA-targeted PET imaging agent that has shown highly promising diagnostic performance for detection of metastatic disease, with potential to identify disease amenable to theranostic targeting. 1095 is a novel PSMA-targeted small molecule that binds to the extracellular domain of PSMA selectively with high affinity. The complex is internalized, allowing the beta emitter, I-131, to kill PC cells. **Methods:** ARROW is an open-label, randomized (2:1) trial of enza plus 1095 or enza alone in pts with progressive mCRPC who previously received abi. ~120 pts (80: 1095 + enza; 40: enza alone) will be treated at ~40 sites in the US and Canada. Eligible male pts must be at least 18 yo with metastatic disease documented by bone scan or soft tissue lesions measurable per RECIST 1.1 on CT/MRI, be PSMA-avid as determined by ^{18}F-DCFPyL PET/CT, have evidence of biochemical or radiographic progression on abi, and be ineligible for or refuse to receive chemotherapy. Pts will receive enza (prescribed per approved labeling) with or without 1095 (100 mCi dose, followed by up to 3 additional dose(s) administered at least 8 weeks apart, as determined by dosimetry evaluation and occurrence of dose-limiting events). The primary objective is to determine the efficacy of 1095 plus enza compared to enza alone, based on PSA response (confirmed PSA decline $\geq$50%) rate according to Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria. Additional objectives include objective response rate based on PCWG3-modified RECIST 1.1, progression-free survival (PFS) defined as the first occurrence of radiographic progression (PCWG3-modified RECIST 1.1), unequivocal clinical progression, or death from any cause, duration of response, overall survival, and the safety and tolerability of 1095 radioligand therapy. Clinical trial information: NCT03939689. Research Sponsor: Progenics Pharmaceuticals, Inc.

TPS5597 **Poster Session (Board #178), Fri, 8:00 AM-11:00 AM**

A phase II study of M6620 in combination with carboplatin compared with docetaxel in combination with carboplatin in metastatic castration-resistant prostate cancer.

Atish Dipankar Choudhury, Wanling Xie, Mamta Parikh, Daniel Lee, Elizabeth R Kessler, David Johnson Einstein, Bose Kochupurakkal, Kent William Mouw, Eliezer Mendel Van Allen, L. Austin Doyle, Alan D. D'Andrea, Mary-Ellen Taplin, Geoffrey Shapiro; Dana-Farber Cancer Institute, Boston, MA; UC Davis Comprehensive Cancer Center, Sacramento, CA; Natl Cancer Inst, Germantown, MD; University of Colorado Anschutz Medical Campus, Aurora, CO; Beth-Israel Deaconess Medcl Ctr, Boston, MA; Dana-Farber Cancer Institute, Brookline, MA; Greenbaum Cancer Center, Baltimore, MD

Background: Alterations in DNA damage repair genes are common in metastatic castration-resistant prostate cancer (mCRPC), and are implicated in responses to carboplatin, PARP inhibitors and immunotherapeutics. The ATR kinase is involved in the DNA damage response, and ATR inhibitors have been demonstrated in preclinical models to have synergistic activity with platinum compounds due to induction of replication stress. **Methods:** This is a randomized open-label Phase 2 study of the ATR inhibitor M6620 + carboplatin vs. docetaxel + carboplatin in mCRPC. Patients (pts) previously treated with at least one secondary hormonal therapy and taxane-based chemotherapy undergo mandatory pre-treatment biopsy and are randomized 1:1 to receive Arm A (docetaxel 60 mg/m2 day 1 + carboplatin AUC 4 day 1) or Arm B (M6620 90 mg/m2 days 2,9 + carboplatin AUC 5 day 1) every 21 days. Pts randomized to Arm A who are not candidates for docetaxel receive carboplatin AUC 5 monotherapy. Stratification factors are 1) prior PARP inhibitor (yes vs. no) and 2) evaluable disease by RECIST 1.1 (yes vs. no). Pts on Arm A crossover to Arm B (M6620+carboplatin) at the earlier of PSA or radiographic progression. For the primary endpoint of overall response rate (ORR; PSA reduction by $\geq$ 50% or radiographic response by RECIST 1.1), with 65 pts on each arm (total N = 130), there will be 80% power to distinguish ORR of 40% vs. 20% using a chi-square test (one sided $\alpha = 0.05$). 136 pts will be enrolled to account for 5% dropout. Secondary endpoints include time to PSA progression, radiographic PFS, PFS by PCWG3 criteria, safety and adverse events in each arm. Biomarker studies include whole exome sequencing, RAD51 focus formation, and ATM IHC from tumor specimens. Circulating cell-free DNA from pre-treatment and progression plasma specimens will undergo ultra-low pass whole genome sequencing and deep targeted sequencing. The goal of this study is to expand therapeutic options in mCRPC through a novel approach to targeting the DNA damage response, and to identify biomarkers associating with response and resistance to both standard and trial therapy. Enrollment began June 2019 (NCI/ETCTN #10191, NCT03517969). Clinical trial information: NCT03517969. Research Sponsor: U.S. National Institutes of Health.

TPS5598 **Poster Session (Board #179), Fri, 8:00 AM-11:00 AM**

TALAPRO-2: a placebo-controlled phase III study of talazoparib (TALA) plus enzalutamide (ENZA) for patients with first-line metastatic castration-resistant prostate cancer (mCRPC).

Neeraj Agarwal, Neal D. Shore, Curtis Dunshee, Lawrence Ivan Karsh, Arun Azad, Andre P. Fay, Joan Carles, M. Luisa Paccagnella, Nicola Di Santo, Mohamed Elmeliegy, Xun Lin, Ruben G.W. Quek, Akos Czibere, Karim Fizazi; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; Carolina Urologic Research Center, Myrtle Beach, SC; Urological Associates of Southern Arizona, Tucson, AZ; The Urology Center of Colorado, Denver, CO; Peter MacCallum Cancer Centre, Victoria, Australia; Hospital São Lucas da PUCRS/Grupo Oncoclinicas, Porto Alegre, Brazil; Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; Pfizer Inc., Groton, CT; Pfizer Inc., Durham, NC; Pfizer Inc., La Jolla, CA; Pfizer Inc., San Francisco, CA; Pfizer Inc., Cambridge, MA; Institut Gustave Roussy, University of Paris Sud, Villejuif, France

Background: TALA blocks poly(ADP-ribose) polymerase (PARP) activity and traps PARP on single-strand DNA breaks, preventing DNA damage repair (DDR) and causing death of cells with DDR alterations (eg *BRCA1/2*).[a] TALA has been approved in multiple countries as monotherapy for germline *BRCA1/2*-mutated human epidermal growth factor receptor 2-negative advanced breast cancer. ENZA is an androgen receptor (AR) inhibitor and an established therapy for mCRPC. As PARP activity has been shown to support AR function, inhibition of PARP is expected to reduce AR signaling and increase sensitivity to AR-directed therapies. In addition, AR blockade downregulates homologous recombination repair gene transcription which induces '*BRCAness'.* Therefore, combining TALA with ENZA in mCRPC may be efficacious regardless of DDR alterations. TALAPRO-2 (NCT03395197) is a Phase III, 2-part study to evaluate efficacy, safety, pharmacokinetics, and patient-reported outcomes (PROs) of TALA combined with ENZA. **Methods:** Enrollment goal is 1037 patients (19 patients, part 1 dose-finding; 1,018 patients, part 2 placebo-controlled). Key eligibility criteria: age $\geq$18 years; asymptomatic/mildly symptomatic mCRPC; ECOG performance status $\leq$1; metastatic disease (no brain metastases); and no prior life-prolonging systemic therapy for nonmetastatic CRPC or mCRPC. Prior therapies (excluding novel AR inhibitors) in the castration-sensitive (CSPC) setting are allowed. ADT must continue throughout the study. The randomized double-blind portion (part 2) will evaluate safety, efficacy, and PROs of TALA (0.5 mg QD) + ENZA (160 mg QD) vs placebo + ENZA (160 mg QD). Patients are stratified by prior novel hormonal therapy or docetaxel for CSPC (yes or no) and DDR alteration status (deficient vs nondeficient/unknown). The primary endpoint is radiographic progression-free survival (rPFS), defined as time to progression in soft tissue per RECIST v.1.1 or in bone per PCWG3 criteria by independent review or death. The key secondary endpoint is overall survival. Efficacy will be assessed radiographically every 8 weeks up to Week 25 and every 8–12 weeks thereafter. rPFS will be compared between the two arms by a 1-sided stratified log-rank test. Patient recruitment is ongoing in multiple regions including US, Europe/Eastern Europe, Israel, South America, South Africa, and Asia-Pacific region. [a]DDR alterations are defined as known/likely pathogenic variants or homozygous deletions. Funding: Pfizer Inc. Clinical trial information: NCT03395197. Research Sponsor: Pfizer Inc.

TPS5599 **Poster Session (Board #180), Fri, 8:00 AM-11:00 AM**

A phase Ib trial of enzalutamide with venetoclax in metastatic castration-resistant prostate cancer (mCRPC).

Dharmesh Gopalakrishnan, Jason Kirk, John Davis, Saby George, Ellis Glenn Levine, Jan Hendrik Beumer, Leonard Joseph Appleman, Dean Tang, Gurkamal S. Chatta; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Georgetown University, Washington DC, DC; Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY; NSABP Foundation and University of Pittsburgh Cancer Institute, Pittsburgh, PA; UPMC, Pittsburgh, PA

Background: Androgen receptor (AR) signaling plays an important role in prostate cancer (PCa) cell survival and proliferation. Xenograft and PDX models demonstrate that untreated PCa harbors $AR^{-/lo}$ stem cells not critically dependent on androgens for survival.[1] Furthermore, castration and enzalutamide (enza) leads to expansion of both $AR^{-/lo}$ and $AR^{+/hi}$ resistant clones in xenograft tumors, resulting in two distinct CRPC-propagating populations.[2] However, most current CRPC treatments are directed towards $AR^{+/hi}$ cells. RNAseq revealed that BCL-2 is highly up-regulated in $AR^{-/lo}$ tumors post-castration and in $AR^{+/hi}$ CRPC tumors post-enza.[2] Strikingly, BCL-2, but not BCL-X_L and MCL-1, was selectively up-regulated in these xenograft tumors. These results were subsequently validated in patient CRPC datasets.[2,3] Venetoclax (ven), a potent and selective BCL-2 inhibitor, inhibits enza resistance in $AR^{+/hi}$ CRPC and tumor growth in $AR^{-/lo}$ xenograft models.[2] A recent phase I trial of ven combined with tamoxifen showed promising activity in ER^+ and $BCL2^+$ metastatic breast cancer.[4] We hypothesize that co-targeting $AR^{-/lo}$ and $AR^{+/hi}$ PCa clones with ven and enza will prevent the emergence of enza resistance in human mCRPC. **Methods:** This is a phase Ib, single-center, single-arm trial of enza (160mg/d) with ven in patients with mCRPC that has progressed on previous therapies which may include anti-androgens. Three dose-levels of ven (400mg, 600mg and 800mg/d q28d) will be evaluated using a 3+3 study design. Fifteen to 18 patients will be enrolled in this phase to assess dose-limiting toxicities, maximum tolerated dose, and recommended phase II dose. Aims of correlative studies include (1) assessing the pharmacokinetic interaction between enza and ven, (2) identification of potentially predictive blood and tissue biomarkers (including pre- and post-treatment CTC levels, expression of BCL2, AR, ARv7 in pre-and post-treatment biopsies and CTCs), (3) measurement of pre- and post-treatment BCL2 expression in peripheral blood mononuclear cells as a surrogate for ven activity, and (4) the development of 3D organoid models from CTCs and biopsies. The trial is open with 3 patients enrolled to dose-level 1, and 2 patients currently at dose-level 2. Correlative studies are ongoing. References: (1) Qin J, et al. *Cell Stem Cell*. 10(5): 556-69, 2012 (2) Li Q, et al. *Nat Commun*. 9(1): 3600, 2018 (3) Rajan P, et al. *Eur Urol*. 66 (1):32-9, 2014 (4) Lok SW, et al. *Cancer Discov*. 9(3): 354-69, 2019. Clinical trial information: NCT03751436. Research Sponsor: AbbVie, U.S. National Institutes of Health.

TPS5600 **Poster Session (Board #181), Fri, 8:00 AM-11:00 AM**

Initial experience of the adjuvant treatments to the local tumor for metastatic prostate cancer: Assessment of novel treatment algorithms, a multicenter, phase II randomized controlled trial (IP2-ATLANTA).

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Background: Local cytoreductive and metastasis-directed interventions are hypothesised to confer additional survival benefit beyond standard systemic therapy in patients with *de novo* synchronous metastatic prostate cancer. There is accumulating prospective evidence for local cytoreductive therapy. In particular, the phase III study STAMPEDE which demonstrated improved overall survival in a low burden subgroup of men following cytoreductive radiotherapy. Cytoreductive prostatectomy and minimally invasive ablative therapies (MIAT) are now subject to similar trial evaluation. IP2-ATLANTA will evaluate progression-free and overall survival outcomes with the addition of sequential multi-modal local and metastasis-directed treatments in patients with newly diagnosed metastatic prostate cancer compared to standard care alone. **Methods:** Phase II, multicentre, three-arm randomised controlled trial using a positive comparator arm (n=918). An internal pilot (n=80) feasibility phase is incorporated. All men with new histologically diagnosed, hormone sensitive, metastatic prostate cancer, within three months of commencing ADT and of PS 0-2 are eligible. Patients are randomised (1:1:1) to: Control (Standard of Care) OR Intervention 1 (Minimally invasive ablative therapy to the prostate +/- pelvic lymph node dissection [PLND]) OR Intervention 2 (prostate radiotherapy +/- lymph nodes OR Radical prostatectomy +/- PLND). Metastatic burden pre-specified by CHAARTED definition. Men with low-burden disease in intervention arms are eligible for metastasis-directed therapy (stereotactic ablative radiotherapy [SABR] or surgery). Standard systemic therapy given in all arms (incl. docetaxel). Follow-up: min. 2-years; max. 4 years. Primary outcome: progression-free survival (PFS). Secondary outcomes: Overall survival; urinary, sexual & rectal side-effects; patient reported outcome measures. HRA ethical approval (Ref: 19/WA0005). To date, 28/80 (35%) patients have been recruited and randomised across 9 open sites in the internal pilot. Median recruitment rate is 85.7% (IQR 55–86). Internal pilot recruitment expected to be complete by April 2020. IP2-ATLANTA addresses an important research gap in the role of local and metastasis-directed therapy in men with newly diagnosed metastatic prostate cancer. Clinical trial information: NCT03763253. Research Sponsor: Wellcome Trust Charity.

TPS5601 **Poster Session (Board #182), Fri, 8:00 AM-11:00 AM**

RTOG 3506 (STEEL): A study of salvage radiotherapy with or without enzalutamide in recurrent prostate cancer following surgery.

Edwin Melencio Posadas, Hiram Alberto Gay, Stephanie L. Pugh, Todd Matthew Morgan, James B. Yu, Stanislav Lechpammer, Felix Y Feng; Cedars-Sinai Cancer, Los Angeles, CA; Washington University School of Medicine in St. Louis, Department of Radiation Oncology, St. Louis, MO; Statistical Center, Radiation Therapy Oncology Group, Philadelphia, PA; University of Michigan, Ann Arbor, MI; Department of Therapeutic Radiology, Yale School of Medicine, New Haven, CT; Pfizer Inc., San Francisco, CA; Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: Salvage radiotherapy (SRT) is an important intervention for men with prostate cancer (PCa) who experience biochemical recurrence (BCR) after radical prostatectomy (RP). These patients are in need of cure or else they will develop metastatic disease. NRG/RTOG 9601 (WU Shipley, N Eng J Med 2017) identified a survival benefit from the addition of androgen receptor (AR) inhibition to SRT that was most prominent in men with high-risk features. Enzalutamide (Enza) is a non-steroidal anti-androgen that improves survival in castration-resistant and -sensitive PCa. We hypothesized that enhanced AR suppression with Enza would augment the benefit of SRT + androgen deprivation therapy (ADT) in BCR with high risk features. **Methods:** RTOG 3506 (STEEL, NCT03809000) is a randomized phase II study of SRT in BCR after RP with a serum PSA $\geq$ 0.2 ng/mL active in the USA and Canada. Patients are stratified by number of high-risk features including Gleason score (8-10), locoregional node involvement at RP, seminal vesicle invasion, persistently elevated PSA after RP, and PSA $>$ 0.7 ng/mL. All patients receive SRT with 2 years of ADT. The experimental arm also receives Enza 160 mg daily for 2 years. Patients are followed by PSA every 3 months. SRT can be highly individualized per treating physician beyond the mandatory treatment of the prostatic fossa. Treatment of the pelvis and/or para-aortic nodes, as well as sequential or concurrent boosts to a prostatic fossa mass and/or suspicious lymph nodes, are allowed options. This permits individualization of radiotherapy guided by CT, MRI, PET, and/or biopsy findings. The primary goal of this study is to determine whether SRT enhanced ADT with Enza, will improve progression-free survival (PFS) compared to SRT with standard ADT. PFS defined as the first occurrence of biochemical failure, clinical failure, or initiation of new anticancer treatment. STEEL is designed to demonstrate a 35% reduction in the risk of progression at 5 years. An accrual goal of 242 patients will provide 80% power with a one-sided alpha = 0.10. Secondary endpoints include disease control rates, acute and late physician- and patient-reported toxicity, and quality of life. This study was activated in February 2019. Site recruitment and activation are underway. **Conclusions:** There is an unmet and urgent need for individualized strategies to optimize systemic therapy used with SRT for men with BCR. Outcomes from this study will further clarify the approach to systemic therapy for SRT in high-risk BCR patients. Support: Provided by Pfizer. Clinical trial information: NCT03809000. Research Sponsor: RTOG Foundation.

5602 **Oral Abstract Session, Fri, 8:00 AM-11:00 AM**

HERO phase III trial: Results comparing relugolix, an oral GnRH receptor antagonist, versus leuprolide acetate for advanced prostate cancer.

Neal D. Shore, Daniel J. George, Fred Saad, Michael Cookson, Daniel R. Saltzstein, Ronald F. Tutrone, Hideyuki Akaza, Alberto Bossi, David van Veenhuyzen, Bryan Selby, Xiaolin Fan, Vicky Kang, Jacqueline M. Walling, Bertrand F. Tombal, Test Abstract Group; Carolina Urologic Research Center, Myrtle Beach, SC; Duke University School of Medicine, Durham, NC; Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, QC, Canada; University of Oklahoma Health Sciences Center, Oklahoma City, OK; Urology San Antonio, San Antonio, TX; Chesapeake Urology, Towson, MD; Strategic Investigation on Comprehensive Cancer Network, University of Tokyo, Tokyo, Japan; Institut Gustave Roussy, Villejuif, Villejuif, France; Myovant, Brisbane, CA; Myovant Sciences, Inc., Brisbane, CA; Abbvie Inc., Redwood City, CA; Myovant Sciences, Inc, Hillsborough, CA; Institut d Recherche Clinique, Université Catholique de Louvain, Brussels, Belgium

Background: LHRH agonists are the mainstay for medical castration in advanced prostate cancer; however, they cause an initial testosterone (T) surge with a delayed onset of castration and require depot injection. Relugolix is the first oral GnRH receptor antagonist, which was previously shown to rapidly suppress T levels. The HERO trial compared the safety and efficacy of relugolix with leuprolide acetate in advanced prostate cancer patients. **Methods:** HERO is a 48-week, global, pivotal phase III trial that randomized 934 patients with androgen-sensitive advanced prostate cancer in a 2:1 ratio to receive relugolix 120 mg orally QD after a single l or leuprolide acetate 3-month depot injection. The primary endpoint was to achieve and maintain serum T suppression to castrate levels (< 50 ng/dL) through 48 weeks. Key secondary endpoints included castration rates at Day 4, profound castration (< 20 ng/dL) rates at Days 4 and 15, PSA response rate at Day 15 and FSH levels at Week 25. Testosterone recovery was evaluated in a subset of 184 patients. Results: A total of 96.7% (95% CI: 94.9%, 97.9%) of men on relugolix achieved and maintained castration through 48 weeks compared to 88.8% on leuprolide. The difference of 7.9% (95% CI: 4.1%, 11.8%) demonstrated non-inferiority (margin -10%) and superiority ($P < 0.0001$) of relugolix to leuprolide. All key secondary efficacy endpoints tested demonstrated superiority over leuprolide ($P < 0.0001$) (Table). In the testosterone recovery subset, median T levels were 270.76 ng/dL in the relugolix compared to 12.26 ng/dL in the leuprolide group 90 days after discontinuation of therapy. In a prespecified analysis, the incidence of major adverse cardiovascular events (MACE) was lower in the relugolix group than in the leuprolide group (2.9% vs. 6.2%, respectively); otherwise the safety and tolerability profiles were generally similar. Conclusion: Relugolix achieved castration as early as Day 4 and demonstrated superiority over leuprolide in sustained T suppression through 48 weeks, faster T recovery after discontinuation and a 50% reduction in MACE. Relugolix has the potential to become a new standard for T suppression for patients with advanced prostate cancer. Clinical trial information: NCT03085095. Research Sponsor: None.

	Endpoint	Relugolix (N= 622)	Leuprolide (N= 308)	P-value
		%	%	
Primary Endpoint	Sustained castration rate from Day 29 to Day 337	96.7	88.8	<0.0001
Key Secondary Endpoints	Testosterone suppression to < 50 ng/dL at Day 4	56.04	0.00	<0.0001
	Testosterone suppression to < 50 ng/dL at Day 15	98.71	12.05	<0.0001
	Confirmed PSA response at Day 15 followed with confirmation at Day 29	79.4	19.8	<0.0001
	Testosterone suppression to <20 ng/dL at Day 15	78.38	0.98	<0.0001
	Mean of FSH level at Week 25 Day 1	1.72	5.95	<0.0001