LBA5000 **Oral Abstract Session**

Cabazitaxel with abiraterone versus abiraterone alone randomized trial for extensive disease following docetaxel: The CHAARTED2 trial of the ECOG-ACRIN Cancer Research Group (EA8153).

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5001 Oral Abstract Session

CYCLONE 2: A phase 3 study of abemaciclib with abiraterone in patients with metastatic castration-resistant prostate cancer.

Matthew Raymond Smith, Josep M. Piulats, Tilman Todenhöfer, Jae-Lyun Lee, Jose Angel Arranz Arija, Laura Mazilu, Arun Azad, Teresa Alonso-Gordoa, Ursula Brigid McGovern, Atish Dipankar Choudhury, Dingwei Ye, Hiroyoshi Suzuki, Rana R. McKay, Steven Ades, Aude Flechon, Christopher Michael Pieczonka, Maarten Hulstijn, Andrew Lithio, Karim Nacerddine, Neeraj Agarwal; Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA; Institut Català d'Oncologia–Bellvitge Institute for Biomedical Research, Barcelona, Spain; Studienpraxis Urologie, Nürtingen, Germany; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Hospital Universitario Gregorio Marañón, Madrid, Spain; Clinical Emergency Hospital of Constanta, Constan□a, Romania; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; Medical Oncology Department. Hospital Universitario Ramón y Cajal, Madrid, Spain; University College Hospital-London, London, United Kingdom; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; Fudan University Shanghai Cancer Center, Shanghai, China; Toho University Sakura Medical Center, Chiba, Japan; University of California, San Diego Health, La Jolla, CA; University of Vermont Larner College of Medicine, Burlington, VT; Centre Léon Bérard, Lyon, France; Associated Medical Professionals of NY, Syracuse, NY; Eli Lilly and Company, Indianapolis, IN; Huntsman Cancer Institute, Salt Lake City, UT

Background: Oncogenic addiction to androgen receptor (AR) signaling drives mCRPC progression, highlighting the unmet need for novel treatment strategies to maximize AR-directed therapy. Preclinical evidence suggests a key role for CDK4/6 in sustained AR signaling, uncontrolled proliferation, and hormonal resistance in prostate cancer. Abemaciclib (ABEMA) is a potent CDK4/6 oral inhibitor that significantly augments the efficacy of endocrine therapy in hormonally driven (ER+) high-risk early-stage and metastatic breast cancer. ABEMA also showed single-agent activity in heavily pretreated mCRPC. Here, we report the primary results of CYCLONE 2, a Phase 3 study of ABEMA plus abiraterone (ABI) in pts with 1L mCRPC. **Methods:** CYCLONE 2 was a seamless Phase 2/3 adaptive trial with a dose-finding safety lead-in. Randomization to the ABEMA or placebo (PBO) plus ABI and predniso(lo)ne was stratified by prior docetaxel receipt for mHSPC, measurable disease, and radiographic progression at study entry. Primary endpoint was investigator-assessed radiographic progression-free survival (rPFS) per RECIST v1.1 and PCWG3. The study was powered at ~90%, assuming a HR of 0.55 for rPFS, at a cumulative 2-sided alpha level of 0.05. **Results:** Between Nov 2018 and Jul 2022, 393 pts were randomized. Baseline characteristics were balanced across arms. Primary endpoint of rPFS was not met (HR 0.829; 95% CI, 0.619–1.111; p=0.2123), medians were 21.96 months for the ABEMA plus ABI group vs 20.28 months for the PBO plus ABI group. rPFS by blinded independent central review was consistent with investigator assessment (HR 0.842; 95% CI, 0.611–1.160). OS was a gated secondary endpoint and not inferentially tested (HR 0.927; 95% CI, 0.669–1.285; 38.9% maturity). Other secondary endpoints included time to PSA progression (HR 0.637; 95% CI, 0.474–0.856), time to symptomatic progression (HR 0.768; 95% CI, 0.522–1.131), and time to worst pain progression (HR 0.935; 95% CI 0.665–1.314). The most common grade ≥3 adverse events (AEs) reported in the ABEMA plus ABI group were anemia (13.6% vs 4.3% in the PBO plus ABI group), neutropenia (12.6% vs 0.5%) and ALT increased (8.7% vs 6.5%). Discontinuations of all study treatments due to AEs were 13.1% vs 4.3% in ABEMA plus ABI vs PBO plus ABI groups, while discontinuations of ABEMA or PBO alone due to AEs were 5.8% vs 1.6%, respectively. **Conclusions:** In patients with mCRPC, adding abemaciclib to abiraterone did not significantly increase rPFS. While no OS detriment was observed, secondary endpoints were not meaningfully improved. Overall, the combination was well tolerated, and safety was consistent with the known profiles of the individual medicines. Clinical trial information: NCT03706365. Research Sponsor: Eli Lilly and Company.

LBA5002 **Oral Abstract Session**

A randomized, double-blind, placebo-controlled trial of metformin in reducing progression among men on expectant management for low-risk prostate cancer: The MAST (Metformin Active Surveillance Trial) study.

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Health-related quality of life and pain in a phase 3 study of [^{177}Lu]Lu-PSMA-617 in taxane-naïve patients with metastatic castration-resistant prostate cancer (PSMAfore).

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Background: [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) prolonged radiographic progression-free survival vs change of androgen receptor pathway inhibitor (ARPI) in taxane-naïve patients with metastatic castration-resistant prostate cancer (mCRPC) in PSMAfore (NCT04689828). We now present health-related quality of life (HRQoL) and pain outcomes at second interim analysis. **Methods:** Eligible patients had mCRPC, were candidates for change of ARPI after progression on one prior ARPI, and had ≥1 PSMA-positive and no exclusionary PSMA-negative metastatic lesions by [^{68}Ga]Ga-PSMA-11 PET/CT. Ineligible patients were candidates for PARP inhibition or had received prior systemic radiotherapy, immunotherapy or chemotherapy. Patients were randomized 1:1 to open-label ^{177}Lu-PSMA-617 (7.4 GBq/6 weeks; 6 cycles) or ARPI change (abiraterone/enzalutamide). Patients with confirmed radiographic progression on ARPI change could cross over to ^{177}Lu-PSMA-617. Secondary endpoints included time to worsening (TTW) in self-reported HRQoL (FACT-P, EQ-5D-5L) and pain (BPI-SF), defined as a composite of score worsening (prespecified thresholds), clinical progression (including new anti-cancer treatment) or death. *Post hoc* analyses of TTW in FACT-P and BPI-SF excluded clinical progression and death. The study was not powered for these endpoints and type I error was not controlled. **Results:** We randomized 468 patients (234/arm) with a median age of 72 years (range, 43–94). Median duration of exposure was 8.4 months for ^{177}Lu-PSMA-617 and 6.5 months for ARPI change. ^{177}Lu-PSMA-617 delayed TTW in FACT-P, EQ-5D-5L and BPI-SF scales and subscales vs ARPI change (Table). Results were similar in non-composite analyses. Incidence of grade ≥3 adverse events (AEs), serious AEs and AEs leading to discontinuation for ^{177}Lu-PSMA-617 and ARPI change were 34% vs 44%, 20% vs 28% and 5.7% vs 5.2%, respectively. **Conclusions:** ^{177}Lu-PSMA-617 delayed TTW in self-reported pain and HRQoL vs change of ARPI in taxane-naïve patients with PSMA-positive mCRPC. Clinical trial information: NCT04689828. Research Sponsor: Novartis.

	^{177}Lu-PSMA-617 (n = 234) –median, Months (95% CI)	ARPI Change (n = 234) –median, Months (95% CI)	HR (95% CI)
FACT-P total score	7.46 (6.08, 8.51)	4.27 (3.48, 4.53)	0.59 (0.47, 0.72)
FACT-P physical wellbeing	7.20 (5.85, 8.25)	3.71 (3.25, 4.40)	0.55 (0.45, 0.68)
FACT-P emotional wellbeing	8.54 (7.39, 9.59)	4.76 (4.27, 5.78)	0.66 (0.53, 0.82)
FACT-P functional wellbeing	5.13 (4.67, 6.77)	4.40 (3.81, 4.70)	0.77 (0.63, 0.95)
FACT-P social/family wellbeing	5.13 (4.57, 6.87)	4.40 (3.94, 6.01)	0.85 (0.69, 1.06)
EQ-5D-5L utility score	6.14 (4.70, 7.92)	3.88 (3.25, 4.40)	0.61 (0.50, 0.76)
BPI-SF pain intensity	5.03 (4.40, 6.87)	3.71 (3.09, 4.37)	0.69 (0.56, 0.85)
BPI-SF pain interference	5.65 (4.57, 6.97)	3.71 (3.06, 4.40)	0.67 (0.54, 0.83)
BPI-SF worst pain intensity	5.13 (4.11, 6.14)	3.65 (3.06, 4.34)	0.70 (0.57, 0.85)

LBA5004 **Oral Abstract Session**

MANCAN2: A multicentre randomised controlled trial of self-help cognitive behavioural therapy (CBT) to manage hot flush and night sweats (HFNS) symptoms in patients with prostate cancer receiving androgen deprivation therapy (ADT).

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EMBARK post hoc analysis of impact of treatment suspension (TxS) on health-related quality of life (HRQoL).

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Background: EMBARK (NCT02319837) showed enzalutamide (ENZ) + leuprolide (L) and ENZ mono delayed metastasis-free survival vs placebo (P) + L while maintaining high global HRQoL in high-risk biochemically recurrent nonmetastatic hormone-sensitive prostate cancer. Treatment was suspended (TxS) at week 37 if PSA <0.2 ng/mL; reinstated if PSA rose to ≥2.0 ng/mL with radical prostatectomy (RP) or ≥5.0 ng/mL without RP. This analysis examined HRQoL after TxS. **Methods:** Longitudinal change in HRQoL from new baseline, week 37 (time of TxS), to subsequent assessments until week 205 were assessed via mixed model repeated measures using separate models for each instrument. Intention to treat analysis was used. **Results:** Treatment was suspended in 90.9% (321/353), 85.9% (304/354), and 67.8% (240/354) of patients treated with ENZ + L, ENZ mono, and P + L, respectively. A numerical trend inHRQoL improvement after week 37 TxS was seen in all 3 arms, which often reached clinically meaningful threshold at week 205 (Table). Post TxS, all arms reached clinically meaningful improvement in hormonal treatment side effects at the subsequent assessments of week 49 to week 97; however, patients slowly deteriorated, with clinically meaningful deterioration at week 205 relative to week 37 with ENZ + L and P + L. No statistically significant differences were observed between arms in change from week 37 to week 205. **Conclusions:** This post hoc analysis confirmed that TxS, as expected, leads to clinically meaningful improvements in HRQoL. Clinical trial information: NCT02319837. Research Sponsor: This study was funded by Astellas Pharma Inc. and Pfizer Inc., the co-developers of enzalutamide.

Instrument	PRO (range)	Clinically Meaningful Threshold (Improvement; Deterioration)	Interpretation	LSM (SE) Change From Week 37 to 205		
				ENZ + L	ENZ mono	P + L
BPI-SF	Item 3 (worst pain; past 24 hours) (0–10)	−2; +2	Higher score = worse pain	−2.9 (2.4)*	−3.3 (2.4)*	−2.9 (2.4)*
FACT-P	Total score (0–156)	+10; −10	Higher score = better HRQoL	21.3 (13.8)*	22.3 (13.9)*	19.5 (13.9)*
	Physical well-being (0–28)	+3; −3	Higher score = better HRQoL	3.3 (3.0)*	3.5 (3.0)*	3.0 (3.0)*
QLQ-PR25	Sexual activity (0–100)	+16.67; −16.67	Higher score = better functioning	17.3 (23.9)*	12.5 (24.1)	10.4 (24.1)
	Urinary symptoms (0–100)	−7.24; +7.24	Higher score = worse symptoms	−16.4 (14.0)*	−15.2 (14.1)*	−13.9 (14.0)*
	Bowel symptoms/function (0–100)	−8.33; +8.33	Higher score = worse symptoms	−10.3 (8.6)*	−11.3 (8.7)*	−10.8 (8.7)*
	Hormonal treatment-related symptoms (0–100)	−5.56; +5.56	Higher score = worse symptoms	8.3 (12.1)*	3.9 (12.2)	8.9 (12.2)*

*reached clinically meaningful change BPI-SF: Brief Pain Inventory-Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate; LSM: least square means; PRO: patient reported outcome; QLQ-PR25: European Organization for Research and Tx of Cancer QoL Questionnaire-Prostate 25; SE: standard error.

Health-related quality of life (HRQOL) results from PRESTO (AFT-19), a phase 3 randomized trial of intensification of androgen blockade in patients with high-risk biochemically relapsed castration sensitive prostate cancer.

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Background: The PRESTO trial (NCT03009981) showed that in patients with biochemically relapsed prostate cancer following radical prostatectomy with a PSA doubling time of ≤ 9 months and without evidence of metastatic disease by conventional imaging, intensified androgen receptor blockade for 52 weeks (androgen deprivation therapy [ADT] plus apalutamide [Apa], or ADT plus Apa and abiraterone acetate [Abi] plus prednisone) prolonged PSA progression-free survival compared to ADT alone (Aggarwal et al, JCO 2024). Here we report the HRQOL results. **Methods:** HRQOL measures included the Hot Flash Related Daily Interference Scale (HFRDIS), Expanded Prostate Cancer Index Composite (EPIC)-26 Sexual domain, PROMIS Fatigue Short Form and EQ-5D-5L, which assesses overall HRQOL in the 504 randomized patients. Published minimally important difference thresholds for these HRQOL measures are: HFRDIS 1.66 points, EPIC Sexual 10-12, PROMIS Fatigue 3-5, and EQ-5D-5L 0.06. General linear mixed modeling was used to estimate between-arm mean differences in HRQOL according to an intent-to-treat approach. **Results:** Mean changes from baseline to end of treatment (EOT) for each arm and for each HRQOL measure are summarized in Table. No statistically significant mean difference was reported between intensified androgen receptor blockade (Arm B, Arm C) vs ADT alone (Arm A) in any HRQOL measure. Further, numerical differences across arms for all HRQOL measures are below published minimally clinically important difference thresholds. **Conclusions:** Intensified androgen receptor blockade with Apa or Apa/Abi added to 52 weeks of ADT improves PSA progression-free survival without negatively affecting HRQOL. These HRQOL results add further support to intensification of androgen blockade in patients with high-risk biochemically recurrent prostate cancer. Clinical trial information: NCT03009981. Research Sponsor: Alliance Foundation Trials, LLC; Johnson & Johnson; https://acknowledgments.alliancefound.org.

HRQOL mean change from baseline to EOT and between-arm mean comparisons.

	A) ADT alone	B) ADT + Apa	C) ADT + Apa + Abi	P-value (B vs A)	P-value (C vs A)
HFRDIS	14.3	14.3	15.0	>0.99	0.78
EPIC Sexual	-15.3	-15.8	-16.0	0.87	0.82
PROMIS Fatigue	5.3	6.9	7.0	0.09	0.08
EQ-5D-5L Index	-0.01	-0.02	-0.01	0.77	0.55

A clinical-genetic (CG) circulating tumor DNA (ctDNA)-based prognostic model for predicting overall survival (OS) in men with metastatic castrate-resistant prostate cancer (mCRPC) treated with potent androgen receptor inhibition (Alliance).

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Background: We have previously developed and validated a clinical prognostic model of OS in mCRPC men that included these variables: performance status, disease site, opioid analgesic use, lactate dehydrogenase, albumin, hemoglobin, prostate specific antigen, and alkaline phosphatase. The goal of this analysis is to improve upon the clinical model of OS by incorporating ctDNA pathogenic genetic alterations (PGAs). **Methods:** Data from the A031201 phase 3 trial of enzalutamide+/- abiraterone were used to develop and validate the CG model of OS. Cell-free DNA was isolated from plasma and analyzed using a 69-gene targeted DNA-sequencing assay for detection of ctDNA PGAs. Genetic features were identified based on feature importance using a random survival forest and the final CG model was trained including clinical and selected genetic factors. Model discrimination was assessed using time-dependent area under the receiver operating characteristic curve (tAUC). **Results:** Data were available on 776 patients. In addition to clinical variables, the model included in this order: gains in *AR* and the *AR* enhancer, *MYC*, *RSPO2*, and losses and/or PGAs of *ZBTB16*, *PTEN*, *MSH6*, *PPP2R2A*, *NKX3-1*, *TP53*, *FANCA*, *RB1*, *APC*, *CHD1*, and *BRCA2*, and ichorCNA tumor fraction. tAUCs in clinical and CG models were 0.72 (95% CI=0.72-0.73) and 0.77 (95% CI= 0.76-0.77). Median OS and the hazard ratios by the three- and four- prognostic risk groups are presented in the table. **Conclusions:** CG model identified novel ctDNA PGAs prognostic of OS and can be utilized to classify patients into risk groups useful in selecting patients in future trials of mCRPC. Clinical trial information: NCT01949337. Research Sponsor: National Cancer Institute; 5R01-CA256157; U10CA180821, U10CA180882, U24CA196171; https://acknowledgments.alliancefound.org; Astellas.

Median OS and hazard ratios by the three- and four-prognostic risk groups.

Prognostic Risk Groups*	Median Overall Survival (95% Confidence Interval (CI)), months	Hazard Ratio (95% CI)
3-Prognostic Risk Groups		
Low	58.9 (50.1- NR)	0.22 (0.17- 0.27)
Intermediate	35.5 (32.3- 40.2)	0.42 (0.35- 0.51)
Poor	19.3 (17.3- 21.5)	Reference
4-Prognostic Risk Groups		
Low	64.2 (52.8- NR)	0.15 (0.11- 0.19)
Low Intermediate	43.6 (38.2- 48.9)	0.26 (0.20- 0.33)
Intermediate Poor	31.1 (28.3- 33.6)	0.43 (0.34- 0.53)
Poor	17.0 (16.0- 18.9)	Reference

*Patients classified into prognostic risk groups based on the tertile or the quartile of the predicted risk.

Baseline ctDNA analyses and associations with outcomes in taxane-naive patients with mCRPC treated with ^{177}Lu-PSMA-617 versus change of ARPI in PSMAfore.

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Background: [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) prolonged radiographic progression-free survival (rPFS) versus androgen receptor pathway inhibitor (ARPI) change in taxane-naive patients with metastatic castration-resistant prostate cancer (mCRPC) in PSMAfore (NCT04689828). In this exploratory analysis, associations between baseline circulating tumor DNA (ctDNA) and outcomes were assessed. **Methods:** Patients were randomized 1:1 to ^{177}Lu-PSMA-617 (7.4 GBq Q6W; 6 cycles) or ARPI change (abiraterone/enzalutamide). Patients known to have actionable mutations (e.g. *BRCA*) were excluded. The primary endpoint was rPFS. Baseline plasma ctDNA was analyzed using a customized 585-gene sequencing assay. ctDNA fraction was assessed in all samples passing quality control. Alterations in key prostate cancer drivers (prevalent in >10% participants) were assessed in samples with ctDNA fraction >1%. Univariate Cox regression (reference: ARPI change) was used to assess association of ctDNA fraction or alterations with rPFS, prostate-specific antigen response (≥50% decline; PSA50) and RECIST response (RR) at the June 21, 2023 data cutoff. **Results:** Of 360 samples from 468 patients, 255 passed quality control and 156 had ctDNA fraction >1% (median 5.85%; range 0–85). Detection of ctDNA alterations was comparable between arms and with published data. Median rPFS was shorter for patients with ctDNA fraction > versus ≤1% (HR 2.753; 95% CI 1.957–3.872; $p<0.0001$) (Table); ctDNA fraction >1% was also associated with worse RR and PSA50 response. Median rPFS was shorter for patients with detected versus undetected *AR*(HR 1.954; 95% CI 1.333–2.865; $p<0.001$), *TP53*(1.655; 1.13–2.426; $p<0.01$) and *PTEN*(1.62; 1.018–2.578; $p<0.05$)alterations. Median rPFS was longer with ^{177}Lu-PSMA-617 versus ARPI change in patients with detected *AR*, *TP53*, *PTEN*(Table), PI3K pathway and DNA repair pathway alterations. There was no significant association between ctDNA alterations and PSA50 or RR. **Conclusions:** ctDNA fraction >1% and *AR*, *TP53*and *PTEN*alterations were associated with worse outcomes in PSMAfore regardless of treatment. Nonetheless, patients with these negative prognostic biomarkers did better with ^{177}Lu-PSMA-617 than with ARPI change. Clinical trial information: NCT04689828. Research Sponsor: Novartis.

	^{177}Lu-PSMA-617	ARPI Change	^{177}Lu-PSMA-617	ARPI Change	^{177}Lu-PSMA-617	ARPI Change
	Median rPFS, Mos (95% CI)		PSA50 Non-Responders (<50% decline), n		RR Non-Responders, n	
ctDNA fraction > v ≤1%	**N=120**	**N=153**	**N=49**	**N=88**	**N=28**	**N=52**
	7.9 (5.8–11.3) v 17.1 (11.5–NE)	2.4 (2.3–4.2) v 6.0 (5.6–13.7)	32 v 17	53 v 35	20 v 8	35 v 17
Alteration detected v undetected	**N=74**	**N=82**	**N=32**	**N=53**	**N=20**	**N=35**
AR	5.0 (2.7–8.6) v 11.6 (6.2–NE)	2.3 (2.1–5.6) v 2.7 (2.2–6.0)	13 v 19	20 v 33	9 v 11	15 v 20
TP53	6.1 (3.1–9.3) v 9.2 (6.2–NE)	2.4 (2.2–4.3) v 2.7 (2.3–5.8)	12 v 20	22 v 31	8 v 12	15 v 20
PTEN	3.6 (2.5–NE) v 7.9 (6.1–11.6)	2.1 (2.0–NE) v 3.1 (2.3–5.8)	7 v 25	10 v 43	4 v 16	8 v 27

DCO Jun 2023.

A phase II trial of pembrolizumab plus platinum-based chemotherapy as first-line systemic therapy in advanced penile cancer: HERCULES (LACOG 0218) trial.

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Background: Over the last six decades, platinum-based chemotherapy has been the standard of care first-line treatment for advanced penile squamous cell carcinoma (PSCC). Advanced PSCC has poor prognosis with limited treatment options. Immune checkpoint inhibitors (ICI) have been associated with improved efficacy in different types of malignancies, however the benefit in PSCC is uncertain. **Methods:** LACOG 0218 (NCT04224740) is a phase II single arm trial evaluating pembrolizumab plus platinum-based chemotherapy as first-line treatment in advanced PSCC. Patients (pts) with metastatic or locally advanced disease (recurrent or TanyN3M0 or T4NanyM0) not amenable to curative-intent therapy received: 5-FU 1000mg/m²/day IV D1-D4; cisplatin 70mg/m² (or carboplatin AUC 5) IV D1; and pembrolizumab 200mg IV D1 every 3 weeks (Q3W) for 6 cycles, followed by pembrolizumab 200mg IV Q3W up to 34 cycles. The primary endpoint is confirmed overall response rate (cORR) assessed by investigator (INV) according to RECIST 1.1. Considering a drop-out rate of 10%, 33 patients were required to reject the null hypothesis that ORR is 20% or less, if the true ORR is 40% (two-sided alpha level of 0.10, power 78.5%). **Results:** From Aug2020 to Dec2022, 37 pts were enrolled in 11 Brazilian centers and 33 pts were eligible for efficacy analysis. Median age was 56y (range, 30-76), 64.9% of pts had metastatic disease, 21.6% had recurrent disease, and 13.5% had locally advanced disease. Efficacy results are presented in the table. cORR by INV was 39.4% (95% CI 22.9-57.9); with 1 complete response and 12 partial responses. cORR INV according to PD-L1 status (66.7% in CPS 0% vs. 33.3% in CPS≥1%); TMB status (75% in high vs. 36.4% in low); and HPV16 status (HPV16 positive 55.6% vs. 35.0%). The most frequent genomic alterations detected by NGS were: TP53(57.1%), CDKN2A (51.4%), and TERT (31.4%). Treatment-related adverse events (AE) rate of any grade was 91.9% and grade 3-4 was 51.4%. Ten pts experienced Grade 5 AE, none of them related to study treatment. Immune-related AEs of any grade was 21.6% and grade 3-4 was 5.4%. 10.8% discontinued treatment due to AE. **Conclusions:** HERCULES is the first trial to demonstrate the efficacy of ICI in advanced PSCC with manageable safety profile. HPV16 and TMB are potential predictive biomarkers for efficacy. ICI combined with platinum-based chemotherapy is a promising treatment for advanced PSCC warranting further investigation. Clinical trial information: NCT04224740. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, U.S.A. (MSD), Brazil.

Efficacy Outcomes	Total (n=33)
Confirmed ORR INV, % (95%CI)	39.4 (22.9-57.9)
Confirmed ORR Central Review, % (95% CI)	42.4 (25.5-60.8)
Unconfirmed ORR INV, % (95% CI)	45.5 (28.1-63.7)
CBR (CR+PR+SD ≥ 24 weeks) INV, % (95% CI)	45.5 (28.1-63.7)
Median DOR (95%CI), months	5.9 (4.4-9.0)
Median PFS INV (95% CI), months	5.4 (2.7-7.2)
Median OS (95% CI), months	9.6 (6.4-13.1)
Median follow-up 24.0 months (95%CI 13.5-26.4); cut-off date 24Jan2024	

A phase 1 study of JNJ-69086420 (JNJ-6420), an actinium-225 (^{225}Ac) -labeled antibody targeting human kallikrein 2 (hK2), for metastatic castration-resistant prostate cancer (mCRPC).

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Background: hK2 (encoded by the *KLK2*gene) is a novel target expressed on the cell surface of prostate cancer cells with restricted expression elsewhere. JNJ-6420 is a first-in-class anti-hK2 antibody–based targeted radiotherapy delivering ^{225}Ac, a high-energy short-range alpha-particle emitter, to prostate cancer cells. Here we report the first-in-human study evaluating JNJ-6420 in heavily pretreated biomarker-unselected participants (pts) with mCRPC who received ≥1 prior androgen receptor pathway inhibitor. **Methods:** Intravenous JNJ-6420 was escalated from 50 μCi to 400 μCi every 8-12 weeks in the outpatient setting with no residential radioprotective restrictions. Prior radioisotopic therapy was an exclusion criterion. Primary objectives were safety and defining a recommended phase 2 dose (RP2D). Secondary objectives included preliminary assessment of clinical activity. **Results:** As of January 5, 2024, 67 pts received ≥1 JNJ-6420 dose. Exposure and clinical activity for the 57 pts in the ≥150 μCi JNJ-6420 cohorts are summarized (see Table); 35/57 (61.4%) experienced grade ≥3 TEAEs, and 21 (36.8%) had a serious TEAE. TEAEs of note included thrombocytopenia (63.2%) and interstitial lung disease (ILD, 9%). All instances of ILD occurred at cumulative doses ≥500 μCi and prior to implementation of pulmonary function surveillance. Grade ≥3 TEAEs (≥10%) included anemia (26.3%), thrombocytopenia (17.5%), lymphopenia (10.5%), and leukopenia (10.5%). 9/57 (15.8%) pts discontinued treatment due to TRAEs; 4 TRAEs resulted in death. At doses ≥150 μCi, the PSA50 rate was 45.6%. To date, across all dose cohorts, 31 pts (46%) remained on treatment for ≥24 weeks. Prolonged clinical, biochemical, and radiographic responses were noted in pts receiving doses of 150 μCi and higher. Durable responses included pts on treatment for 112 weeks (96 weeks since last dose), 88 weeks (13 weeks since last dose), and 46 weeks (after a single dose). **Conclusions:** In this first-in-human study, key TEAEs of JNJ-6420 were thrombocytopenia and ILD, both associated with repeated dosing. At ≥150 μCi, 1-2 doses of JNJ-6420 elicited profound and durable biochemical and radiographic responses. Evaluation of the RP2D is ongoing. These data highlight hK2 as a novel target for targeted alpha-particle therapy. Clinical trial information: NCT04644770. Research Sponsor: Janssen Research & Development LLC.

JNJ-6420 exposure and clinical activity.

Parameter, median (range) or n (%)	≥150 μCi JNJ-6420 (n = 57)
No. of prior therapies	4 (1-12)
No. of doses	2 (1-6)
Cumulative dose, μCi	493.5 (145-912)
Confirmed objective response rate[a]	3 (12.5)[a]
Complete response	1 (4.2)
Partial response	2 (8.3)
Disease control rate at 6 months[b]	16 (28.1)
PSA50	26 (45.6)
PSA90	8 (14.0)

[a]In pts with measurable disease at baseline (n = 24).
[b]Proportion alive and radiographic progression free for ≥6 months from the start of treatment.

5011 Rapid Oral Abstract Session

ARV-766, a proteolysis targeting chimera (PROTAC) androgen receptor (AR) degrader, in metastatic castration-resistant prostate cancer (mCRPC): Initial results of a phase 1/2 study.

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Background: Patients with mCRPC inevitably develop resistance to available therapies, eg, novel hormonal agents (NHAs), and experience disease progression. Certain mutations that can develop in the ligand-binding domain (LBD; amino acids 671–920) of the *AR* gene during mCRPC treatment have been associated with poor outcomes. ARV-766 is a novel, potent, orally administered PROTAC AR degrader that targets wild-type *AR* and clinically relevant *AR* LBD mutants, including the most prevalent *AR* L702H, H875Y, and T878A mutations. We report initial results from a phase 1/2 study (NCT05067140) of ARV-766 in men with mCRPC and disease progression on prior NHA therapy. **Methods:** Eligible patients had progressive mCRPC and ongoing androgen deprivation therapy. The phase 1 dose escalation portion evaluated the safety and tolerability of escalating doses of ARV-766 (20–500 mg once daily [QD]) in patients who had progressed on ≥2 prior systemic therapies (including ≥1 NHA). The phase 2 cohort expansion portion is evaluating the clinical activity and safety of 2 doses of ARV-766 (100 or 300 mg QD) in patients who had received 1–3 prior NHAs and ≤2 prior chemotherapy regimens. Here we report safety in all patients treated with ARV-766 across the phase 1/2 study and clinical activity (proportion of patients with best prostate-specific antigen [PSA] declines of ≥50% [PSA_{50}] after ≥1 month of PSA follow-up) in the subgroup of patients with *AR* LBD mutations. **Results:** As of December 15, 2023, 103 patients received ARV-766 (34 in phase 1 and 69 in phase 2). Patients had received a median of 4 prior therapies (range: 1–9), including 56% with ≥1 prior taxane and 46% with ≥2 prior NHAs. Patients with *AR* LBD mutations (n=30) had received a median of 4 prior therapies (range: 1–9), including 60% with ≥1 prior taxane and 57% with ≥2 prior NHAs. In phase 1, there were no dose-limiting toxicities, and a maximum tolerated dose was not reached. Across 103 phase 1/2 patients, treatment-emergent adverse events led to dose reduction and treatment discontinuation, respectively, in 7 (7%) and 10 (10%). Any grade treatment-related adverse events (TRAEs) reported in ≥10% of patients were fatigue (36%; 3% grade 3), nausea (19%; 1% grade 3), diarrhea (15%; 1% grade 3), alopecia (14%), increased blood creatinine (13%; 0 grade 3), and decreased appetite (11%; 0 grade 3); there were no grade 4 TRAEs. In 28 PSA-evaluable patients with *AR* LBD mutations, PSA_{50} was 50.0%. Preliminary pharmacokinetics indicated dose-dependent increases in ARV-766 exposure up to 320 mg QD, with exposure accumulation ranging from ≈5- to 8-fold at steady state. **Conclusions:** In this phase 1/2 study of pretreated patients with mCRPC, ARV-766 was well tolerated and showed promising clinical activity in those with tumors harboring *AR* LBD mutations. ARV-766 warrants further development in advanced prostate cancer. Clinical trial information: NCT05067140. Research Sponsor: Arvinas Androgen Receptor, Inc.

Phase 1b study of tarlatamab in de novo or treatment-emergent neuroendocrine prostate cancer (NEPC).

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Background: NEPC is an aggressive form of prostate cancer with poor prognosis and no standard treatment approach. NEPC can be characterized by late, treatment-emergent transformation from adenocarcinoma to high-grade neuroendocrine carcinoma (NEC), in 10–15% of mCRPC patients (pts). DLL3 is overexpressed in high-grade NECs, including NEPC, and minimally expressed on normal tissue. Tarlatamab, a bispecific T-cell engager immunotherapy with clinical activity in small cell lung cancer (SCLC), binds DLL3 and CD3 resulting in T-cell mediated tumor lysis. Here, we report primary analysis data of tarlatamab in NEPC (NCT04702737). **Methods:** This is an open-label phase 1b study evaluating tarlatamab monotherapy in adult (≥18 years [y]) pts with metastatic de novo or treatment-emergent NEPC by histologic, genomic, or immunohistochemistry (IHC) criteria. The starting dose was the highest safe and tolerable dose in the phase 1 SCLC trial (NCT03319940). Safety was the primary objective; anti-tumor activity and pharmacokinetics were secondary objectives. Exploratory analysis of DLL3 expression was assessed by IHC using the Ventana SP347 assay. **Results:** As of 28 March 2023, 40 pts received ≥1 tarlatamab dose (1 mg step dose, 100 mg target dose). Median (range) age was 64.5 (43–83) y, prior lines of therapy was 3 (1–9), prostate specific antigen at baseline was 0.2 (0.0–5000.0) μg/L. Treatment-related adverse events (TRAE) occurred in all patients, with no fatal TRAE. Most common TRAEs were cytokine-release syndrome (CRS; 65.0%), pyrexia (52.5%) and dysgeusia (42.5%). CRS occurred primarily in treatment cycle 1; events were mostly grade 1–2 (one grade 3 event). Treatment discontinuation due to TRAE was low (7.5%). Tarlatamab serum exposures were consistent with tarlatamab SCLC studies. Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) was 10.5% (95% CI, 2.9, 24.8); median progression free survival (mPFS) was 1.9 months (m) (95% CI, 1.7, 3.5). Retrospective DLL3 IHC analysis showed that 18 of 32 (56.3%) biopsy evaluable pts had ≥1% DLL3 tumor positivity (DLL3+). As of 24 January 2024, ORR in DLL3+ pts was 22.2% (95% CI, 6.4, 47.6); durations of response in the 4 pts with response were 25.8 m, 9.2 m, 5.5 m, 3.7 m; mPFS in DLL3+ pts was 3.75 m (95% CI, 1.87, 11.01). Efficacy is shown in Table. **Conclusions:** Findings from this phase 1 study of tarlatamab in pts with NEPC demonstrated manageable safety with encouraging anti-tumor activity in DLL3 expressing NEPC. Further investigation is ongoing. Clinical trial information: NCT04702737. Research Sponsor: Amgen Inc.

Tarlatamab response per RECIST v1.1 (local assessment).

Variable, n (%)	Evaluable Patients (N=38)	DLL3+ (N=18)
Best overall response		
Complete response	0	0
Partial response	4 (10.5)	4 (22.2)
Disease control rate	12 (31.6)	10 (55.6)
Progressive disease	17 (44.7)	5 (27.8)
No post baseline scan	9 (23.7)	3 (16.7)

DLL3+ defined as ≥1% DLL3 tumor positivity.

5013 Rapid Oral Abstract Session

Nivolumab and ipilimumab for metastatic prostate cancer with an immunogenic signature: The NEPTUNES multi-centre two-cohort, biomarker-selected phase 2 trial.

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Background: Responses to checkpoint inhibitor (CPI) monotherapy in patients with metastatic castration resistant prostate cancer (mCRPC) have been limited. This is likely due to a "cold" tumour immune microenvironment. We hypothesised that patients with mCRPC would be more likely to respond if they had a positive immunogenic signature (ImS+). We report a phase 2 trial of two different dose schedules for nivolumab (NIVO) + ipilimumab (IPI) in patients with ImS+ mCRPC. **Methods:** Patients with mCRPC who progressed following ≥1 line of therapy and ImS+ were eligible. ImS+ was defined by ≥1 of the following: 1) mismatch repair deficient (MMRD) by immunohistochemistry (IHC); 2) DNA damage repair deficient (DDRD) detected by the UW-OncoPlex targeted exome sequencing assay and; 3) High Tumour infiltrating lymphocytes (TILs) on multiplexed IHC (≥20% of nucleated cells). There were two patient cohorts conducted sequentially: NIVO 1 mg/kg + IPI 3 mg/kg (C1) then NIVO 3 mg/kg + IPI 1 mg/kg (C2) Q3W for 4 doses; both followed by NIVO 480 mg every 4 weeks up to 1 year. Primary endpoint was composite response rate (CRR) defined by ≥1 of the following: 1) confirmed radiological response by RECIST 1.1; 2) confirmed PSA response ≥50%; 3) conversion of circulating tumour cells (CTC) at week 9. CRR ≥40% would be clinically favourable (minimum of 20%). Secondary endpoints included toxicity, duration of response (DOR), and overall survival (OS). Tissue collection for biomarker analyses was mandated. **Results:** Between May 2018 and June 2022 119/380 (31%) screened patients were ImS+, of whom 35 (C1) and 36 (C2) enrolled in the trial. The CRR in C1 was 14/35 (40%, 90%CI: 26-55%) and in C2 was 9/36 (25%, 90%CI: 14-40%). The combined CRR was 23/71 (32%, 90%CI: 23-43%). Grade 3-4 treatment-related adverse events occurred in 22/35 (63%) in C1 and 11/36 (31%) in C2. The most common G3-4 event was diarrhoea present in 15 (42%) and 3 (8%) patients for C1 and C2. The median DOR was 10.4 (C1) and 6.4 (C2) months. After a median follow-up of 47 (C1) and 21 (C2) months, median OS was 16.2 months (95%CI 9.2-22.8m) and 15.2 months (95%CI 8.9-NA) respectively. The ImS+ determinants in responding patients were MMRD (8/10), BRCA1/2 (4/8), high TILs (8/21), CDK12 (2/8), ATM (1/13) and CHD1 (1/9). In C1 4/9 (44%) of patients with exclusively high TILs responded. Exploratory biomarker analyses are ongoing. **Conclusions:** Inflammatory infiltrate is a promising prospectively tested predictive biomarker in pre-treated mCRPC. Although NIVO 1 mg/kg + IPI 3 mg/kg had more toxicities than NIVO 3 mg/kg + IPI 1 mg/kg, the efficacy results were consistently better. This dose schedule and biomarker should now be tested in a phase 3 clinical trial. Clinical trial information: NCT03061539. Research Sponsor: BMS, Rosetrees.

LBA5014 **Rapid Oral Abstract Session**

Blood-based markers of differential efficacy of bipolar androgen therapy and enzalutamide in the randomized TRANSFORMER trial.

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5015 Rapid Oral Abstract Session

Clinical utility of transcriptomic signatures to identify androgen receptor and neuroendocrine signaling in prostate cancer.

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Background: Neuroendocrine prostate cancer (NEPC) is a relatively androgen receptor (AR)-independent and aggressive variant of PC that can arise from adenocarcinoma with varied degrees of adenocarcinoma and high-grade neuroendocrine histologic features seen during its progression. This study evaluated the clinical and molecular features of histologic subtypes of prostate tumors (adenocarcinoma, NEPC, mixed adeno-NE) based on previously validated AR signaling and NEPC transcriptomic signatures of PC. **Methods:** Whole exome (WES) and whole transcriptome sequencing (WTS) were performed on PC tumors. Molecular subsets were defined by AR signaling signature [AR score positive (+) vs negative (-)] and NEPC gene signature [NE score positive (+) vs negative (-)]. The prevalence of key molecular alterations (RB1, TP53, PTEN, AR, FANC, SLFN11 expression) were investigated. Genes encoding cell surface antigens with potential therapeutic implications were described across signature groups. Overall survival (OS) was obtained from claims data and analyzed with Kaplan-Meier estimator. **Results:** A total of 4,476 prostate tumors were analyzed in this study including: 3,623 prostate adenocarcinoma, 56 NEPC, and 25 tumors with mixed adeno-NE. Tissue from 2,641 (67%) tumors were collected from prostate and 1,326 (33%) were metastatic tumors [lymph node (14%), bone (9%), liver (7%), lung (2%), CNS (2%)]. The four AR/NEPC signature-defined subtypes were AR+/NE+ (N=649, 14%), AR+/NE- (N=1614, 36%), AR-/NE+ (N=875, 20%), and AR-/NE- (N=1358, 30%). AR+/NE- was most common in prostate (39%), LN (42%) and lung metastasis (35%); AR-/NE+ was most common in bone (34%) and liver metastasis (43%); AR-/NE- was most common in CNS metastasis. The most common gene alterations in each molecular subtype are defined in Table. AR-/NE+ tumors had the lowest mRNA expression of FOLH1(P-SMA), STEAP1, TACSTD2 (Trop-2), CD276 (B7-H3), and PSCA among the four groups. DLL3 expression was higher among NE+ subtypes. FOLH1 and PSCA expression were higher among NE- subtypes. The median OS (months) was longer in NE- than NE+ subtypes [AR+/NE- (78.3), AR-/NE- (78.7) vs AR+/NE+ (70.7), AR-/NE+ (69.1)]. In the platinum-treated subgroup (N=146), the median OS was numerically longer among tumors with SLFN11 overexpression (17.6 vs 12.0) although this was not statistically significant (p-value: 0.99). **Conclusions:** Molecularly distinct subtypes of PC can be further characterized by AR signaling signature, NEPC gene expression signature, and co-occurring molecular alterations. The phase II biomarker-driven PREDICT trial will integrate the above signatures/molecular alterations to allocate treatment regimens in metastatic castration-resistant PC. Research Sponsor: None.

	AR+/NE+	AR+/NE-	AR-/NE+	AR-/NE-
TP53	38.4%	29.3%	46.2%	34.3%
RB1	5%	3.3%	16%	4%
PTEN	8.3%	7.7%	10%	8.6%
SPOP	7.7%	9.2%	6.2%	11.1%
LOH	28.7%	26.8%	41.3%	32.2%

Prognostic PSMA-PET PROMISE nomograms for patients with prostate cancer.

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Background: Prostate Specific Membrane Antigen Positron-Emission-Tomography (PSMA-PET) was introduced for prostate cancer staging in 2012. PSMA-PET reported by standardized PROMISE criteria delivers accurate staging with potential prognostic value. Here we assess the prognostic value of PSMA-PET including tumor volume in a large prostate cancer dataset with overall survival follow-up and compare it head-to-head to clinical risk scores. **Methods:** Prostate cancer patients, who underwent PSMA-PET between October 2014 and December 2019 at the Essen University Hospital, were analyzed retrospectively. We collected PSMA-PET stage using the molecular imaging TNM system (miTNM), tumor volume, SUVmean and overall survival follow-up. The dataset was split into development and validation cohorts (2:1). We created a visual and quantitative nomogram based on Cox regression models with LASSO penalty using the development cohort. Performance of nomograms in the validation cohort were measured using C-index and calibration plots. Head-to-head comparison to clinical risk scores for each staging group was examined using ROC-curves and C-index. **Results:** The cohort includes 1612 prostate cancer patients across all disease stages with 567 (35.2%) recorded deaths. PSMA-PET based predictors included into the quantitative PSMA-PET nomogram were locoregional lymph node metastases (miN2), distant metastases (miM1a, miM1b pattern, miM1c), tumor volume and tumor SUVmean (Table). The visual nomogram includes distant metastases and total tumor lesion count. Overall C-indices were 0.81 or 0.78 for the quantitative or visual nomogram, respectively. The quantitative PSMA-PET nomogram was superior to STARCAP at initial staging (AUC: 0.72 vs. 0.53; p=0.02), to EAU risk score at BCR (AUC: 0.69 vs. 0.52; p<0.001), and to NCCN groups at any timepoint (AUC: 0.81 vs. 0.73; p<0.001). The visual PSMA-PET nomogram was superior to EAU risk score (AUC: 0.64 vs. 0.52; p<0.001) and NCCN groups (AUC: 0.79 vs. 0.73 p<0.001). **Conclusions:** Our prognostic PSMA-PET nomograms based on PROMISE criteria were accurate in early and late stages of prostate cancer. Prediction of overall survival was superior when compared to clinical risk tools. Multi-center validation in the PROMISE registry is ongoing. Development cohort (n=1110 patients) univariate regression findings for PROMISE variables included in the quantitative PSMA-PET nomogram for prediction of overall survival. Research Sponsor: None.

Variable		Hazard Ratio (95% CI)		Number of Positive Cases (%)		p
Locoregional lymph node metastases (miN)	N2	2.71	(2.18 - 3.37)	257	(23.2%)	< 0.001
Distant metastases (miM)	M1a	3.85	(3.15 - 4.72)	270	(24.3 %)	< 0.001
	M1b (diss or dmi)	11.73	(9.31 - 14.78)	222	(20.0 %)	< 0.001
	M1c	5.36	(4.06 - 7.08)	74	(6.7 %)	< 0.001
Tumor volume	per 1 liter	3.64	(3.25 - 4.07)			< 0.001
Tumor SUVmean	per 1 unit	1.04	(1.03 - 1.05)			< 0.001

diss: disseminated metastases; dmi: diffuse marrow infiltration.

5017 Rapid Oral Abstract Session

Oncogenic alteration rates, race, and prostate cancer specific mortality in Veterans with metastatic prostate cancer undergoing somatic tumor next generation sequencing.

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Background: National guidelines recommend next generation sequencing (NGS) of tumors from patients diagnosed with metastatic prostate cancer (PCa) to identify potential actionable alterations. We sought to determine associations between alteration frequencies of PCa-related genes and pathways, self-identified race, and PCa specific mortality (PCSM) in Veterans. **Methods:** This comprehensive retrospective cohort study evaluated the association of somatic alterations with race in Veterans with metastatic PCa who obtained NGS through the Veterans Affairs National Precision Oncology Program. NGS data was linked to clinicopathologic and social determinants of health (SDOH) data elements. Multivariate logistic regression permitted associations between race and genomic alteration frequencies, adjusted for specimen tested and clinical and SDOH co-variates. Cox proportional hazards models permitted associations of race, alteration frequencies, and PCSM, stratified by genomic alteration frequencies and adjusting for race, clinicopathologic features, and SDOH. **Results:** 5015 Veterans with metastatic PCa and self-identified race/ethnicity as non-Hispanic Black (NHB, n=1784) and non-Hispanic White (NHW, n= 3231) were included. NGS was conducted on primary tumors (n= 2359), metastases (n = 1011), and cfDNA (n = 1644). NHB Veterans were younger, had higher PSA at PCa diagnoses, were less likely to report Agent Orange exposure, and resided in more deprived neighborhoods. Upon adjusting for tissue sequenced and clinicopathologic variables, NHB race/ethnicity was significantly associated with a higher rate of genomic alterations in immunotherapy targets, *SPOP* and *BRAF*($p<0.05$ for all).Furthermore, NHB race/ethnicity was significantly associated with lower rates of genomic alterations in the AKT/PI3K pathway, AR axis,and tumor suppressor genes including *TP53*and *PTEN*($p<0.05$ for all). While alterations in *TP53* (HR 1.5 [1.1-2.0], p=0.007), and tumor suppressor pathways (HR 1.3 [1.0-1.8], p=0.04) conferred a significantly higher risk of PCSM in all men on adjusted analysis, race was not independently associated with PCSM. **Conclusions:** In this diverse cohort of Veterans undergoing NGS for metastatic PCa in the equal access VA healthcare system, we observed significant differences in alteration rates of several oncogenic genes/pathways by race. While alterations in tumor suppressor genes were significantly associated with PCSM, race was not. Thus, there remains a critical need for integrating personalized approaches to patient selection for metastatic PCa treatments in order to improve disease-specific outcomes across diverse populations. Research Sponsor: None.

^{68}Ga-PSMA PET/CT response and clinical outcomes in patients treated with enzalutamide as first-line therapy for metastatic castration-resistant prostate cancer (mCRPC): Results of a prospective study.

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Background: ^{68}Ga prostate specific membrane antigen positron emission tomography/computed tomography (^{68}Ga-PSMA PET/CT) is a highly sensitive diagnostic tool whose adoption is constantly increasing in prostate cancer patients, also for monitoring response to therapies. We evaluated the impact of ^{68}Ga-PSMA PET/CT response, as compared to prostate-specific antigen (PSA) response, in patients treated with enzalutamide as first-line therapy (1L) for mCRPC. **Methods:** From Oct 2017 to May 2022, in an observational prospective study, 70 consecutive mCRPC patients were treated with 1L enzalutamide 160 mg QD and underwent 68Ga-PSMA PET/CT within 3 weeks before (baseline) and 12 weeks (SD: ±4 weeks) after treatment initiation. We measured at both the timepoints the sum of metabolic total volume (sMTV), mean and maximum standardized uptake volume (sSUVmean and sSUVmax, respectively) and total lesion activity (sTLA), which is the product of MTV and SUVmean, for a maximum of 20 lesions. On the basis of EAU/EANM criteria, patients were categorized as PSMA responders (PET-R, in case of complete/partial response or stable disease) or PSMA non-responders (PET-NR, in case of progressive disease). Based on prostate-specific antigen (PSA), patients were classified as biochemical responders (PSA-R, in case of PSA decrease ≥ 50%) or non-responders (PSA-NR in all other cases). Survival analysis was performed using the Cox regression hazard model and the Kaplan-Meier method. **Results:** At the data cut-off (31st Dec 2023), 69 mCRPC patients were considered fully evaluable. The median age was 75 years (range: 47-91), GS was <8 in 24 (35%) and ≥8 in 37 (53%), the median baseline PSA was 2.57 μg/L (range: 0.09-197). We observed a median sSUVmax of 41.6, median SSUVmean of 28.2 and median sTLA of 44.8. The median follow-up was 57 months. In the Table, we reported survival results according to PSA and PET response. Differences between the discordant groups were not statistically significant for both median progression-free survival (mPFS) and median overall survival (mOS) (p=0.09 and 0.41, respectively), even if a positive trend for PET was shown. At multivariate analysis, only sTLA at 12 weeks was significantly associated with both mPFS (p=0.0004) and mOS (p=0.0006). **Conclusions:** 68Ga-PSMA PET/CT response appeared more accurate than PSA monitoring to predict survival to enzalutamide initiation in mCRPC. Some PET parameters may better predict survival benefit and need future validation. Research Sponsor: None.

Group n	Progression-free Survival Median (mo)	Overall Survival Median (mo)
PET-NR / PSA-NR 5	3.5	13.2
PET-NR / PSA-R 5	5.4	36.8
PET-R / PSA-NR 11	28.9	66.6
PET-R / PSA-R 48	47.8	Not reached
p	<0.001	<0.001

Mo: months; PET-NR: PSMA non-responder; PET-R: PSMA responder; PSA-NR, biochemical non-responder; PSA-R, biochemical responder.

Prevalence of HER3 expression in prostate adenocarcinoma and its clinicopathological characteristics.

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Background: Human epidermal growth factor receptor 3 (HER3) has been found upregulated in a wide variety of cancers and has been associated with disease progression and resistance to EGFR-targeted therapies in HER2-positive malignancies. Several studies have reported expression of HER3 in prostate cancer (PCa). Furthermore, concurrent expression of HER2 and HER3 in PCa has been associated with androgen resistance, development of metastatic disease, and less favorable outcomes. However, due to conflicting results, the exact nature of the relationship between HER2 and HER3 in PCa requires further investigation. **Methods:** 194 patients diagnosed with PCa between 2000-2021 at the Washington DC Veterans Affairs Medical Center who had adequate formalin-fixed paraffin embedded prostate tissue available were selected from our previously published cohort of patients. HER3 immunostaining was performed and independently scored by two pathologists as 0 (absent), 1+ (weak), 2+ (moderate), or 3+ (marked). HER2 immunostaining data and clinical information was retrieved. Statistical analysis included Fisher's exact test and linear regression models. **Results:** In our self-identified predominantly African American (85%) patient cohort, a 94% overall prevalence of HER3 positivity (1+, 2+, or 3+) was observed. Notably, the majority of positive patients was found to have HER3 expression of either 2+ (~60%; 116/194) or 3+ (~17%; 33/194). HER3 positivity was associated with a higher PSA ($p=0.023$), a higher Grade Group (GG) ($p=0.017$), and a higher AJCC disease stage ($p=0.006$) at time of diagnosis (Table 1). A significant association was observed between positivity for both HER2 and HER3 ($p=0.031$). HER3 positivity independently predicted GG ($p=0.02$) and AJCC disease stage ($p=0.01$) when adjusted for HER2 positivity. **Conclusions:** In this predominantly African American cohort, a high prevalence of HER3 positivity was observed across PCa disease stages. Higher expression levels of HER3 were observed in more advanced stages of the disease. Because of the observed efficacy of HER3-antibody drug conjugates in other HER3-expressing malignancies, the high prevalence of HER3 in PCa makes it an attractive therapeutic target that warrants further evaluation. Research Sponsor: Prostate Cancer Foundation.

Association of HER3 expression and clinicopathological characteristics in PCa.

	HER3 Negative	HER3 Positive	p-value
Grade Group 1 (n (%))	10 (14.3)	60 (85.7)	*0.017*
Grade Group 2 (n (%))	0 (0)	42 (100)	
Grade Group 3 (n (%))	1 (4.2)	23 (95.8)	
Grade Group 4 (n (%))	1 (2.4)	40 (97.6)	
Grade Group 5 (n (%))	0 (0)	17 (100)	
AJCC I (n (%))	10 (14.7)	58 (85.3)	*0.006*
AJCC II (n (%))	1 (1.9)	52 (98.1)	
AJCC III (n (%))	1 (2.6)	37 (97.4)	
AJCC IV (n (%))	0 (0)	35 (100)	
Highest PSA (Median (IQR)) (ng/mL)	5.5 (4.475, 6.975)	7.3 (5.225, 16.3)	*0.023*

Utility of ctDNA burden as a prognostic biomarker for efficacy in TALAPRO-2: A phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) vs placebo (PBO) + ENZA as first-line (1L) treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).

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Background: TALAPRO-2 (NCT03395197) demonstrated that 1L TALA + ENZA significantly improved radiographic progression-free survival (rPFS) vs PBO + ENZA for pts with mCRPC. ctDNA burden is a candidate prognostic biomarker with potentially broad utility across treatments and tumor types. We assessed the potential prognostic utility of baseline (BL) ctDNA burden and changes in ctDNA burden at Week 9 (WK 9) in TALAPRO-2 pts. **Methods:** Retrospectively analyzed serial ctDNA samples from BL and WK 9 were assessed using FoundationOneLiquid CDx. Plasma tumor fraction was calculated based on aneuploidy (Husain et al. *JCO Precis Oncol*. 2022. PMID: 36265119). We categorized ctDNA burden as high (ctDNA burden quantifiable) vs low (unknown ctDNA burden). Data cutoff date was August 16, 2022. **Results:** In the all-comers intent-to-treat population, 678 pts were evaluable for ctDNA burden at BL: 26% (89/337) of TALA + ENZA pts were ctDNA-high and 74% (248/337) were ctDNA-low; 29% (98/341) of PBO + ENZA pts were ctDNA-high and 71% (243/341) were ctDNA-low. High ctDNA burden at BL was prognostic of inferior rPFS in the TALA + ENZA and PBO + ENZA arms (Table). A relatively favorable median rPFS was observed for pts with low ctDNA at BL and WK 9 for TALA + ENZA (n=206) and PBO + ENZA (n=207), as reported in the Table. At WK 9, 72 pts in the TALA + ENZA and 77 pts in the PBO + ENZA arms were evaluable for ctDNA conversion from high to low. In both treatment arms, conversion from high to low ctDNA was prognostic of improved rPFS vs pts who remained ctDNA-high (Table). Pts who remained ctDNA-low had a more favorable rPFS vs conversion from high to low ctDNA: TALA + ENZA, hazard ratio (HR) 95% confidence interval (CI), 0.45 (0.29–0.71), P=0.0003; PBO + ENZA, 0.34 (0.23–0.52), $P<0.0001$). **Conclusions:** High ctDNA burden at BL was negatively prognostic, and ctDNA conversion from high to low at WK 9 was prognostic of improved rPFS in TALAPRO-2. Limitations included not all clinical trial sites were able to perform ctDNA collection and most samples were below the limit of quantification. These results support the broad prognostic utility of ctDNA burden in mCRPC. Clinical trial information: NCT03395197. Research Sponsor: Pfizer Inc.

ctDNA	TALA + ENZA Median rPFS (95% CI), mo/n	HR (95% CI)	PBO + ENZA Median rPFS (95% CI), mo/n	HR (95% CI)
High at BL	12.5 (8.4–18.2)/89	2.63 (1.83–3.77); $P<0.0001$[a]	8.3 (5.9–11.0)/98	3.35 (2.39–4.69); $P<0.0001$[a]
Low at BL	NR (33.1–NR)/248		30.3 (22.5–NR)/243	
High at BL and high at WK 9	5.5 (1.7–10.8)/12	4.10 (1.87–9.00); P=0.0002[a]	2.6 (1.9–5.6)/21	5.80 (2.51–13.40); $P<0.0001$[a]
High at BL and low at WK 9	16.6 (11.1–NR)/60		10.9 (8.2–16.5)/56	
Low at BL and low at WK 9	NR (33.1–NR)/206		30.5 (25–NR)/207	

Low at BL and high at WK 9 not displayed (n=1 for TALA + ENZA, n=8 for PBO + ENZA)
[a]2-sided test. n, number of patients; NR, not reached.

Discovery of a novel non-negative matrix factorization (NMF)-based homologous recombination deficiency (HRD) score and subsequent exploration in TALAPRO-2 (TP-2), a phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) vs placebo (PBO) + ENZA as first-line treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).

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Background: TP-2 (NCT03395197) demonstrated significantly improved radiographic progression-free survival (rPFS) in pts with mCRPC who received TALA + ENZA (n=402) vs PBO + ENZA (n=403). We discovered a novel NMF-based HRD score and used it to explore potential associations of HRD with efficacy in TP-2. **Methods:** The Cancer Genome Atlas Prostate Adenocarcinoma (TCGA-PRAD) dataset was used to train a novel NMF-based HRD predictive score incorporating gene expression (RNA seq) and homologous recombination repair (HRR)12 genomic features (mutations possibly or probably damaging by PolyPhen, deleterious by SIFT, or shallow/deep deletion; HRR12 genes: *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *ATR*, *CHEK2*, *FANCA*, *RAD51C*, *NBN*, *MLH1*, *MRE11A*, *CDK12*). A previously published composite HRD score incorporating genomic loss of heterozygosity, large scale transitions, and telomeric allelic imbalances (Knijnenburg et al. *Cell Rep*. 2018;23:239-254.e6) was used as the "original" HRD reference score. HRR12 genomic features in TCGA-PRAD were associated with higher original and predicted HRD scores. Two datasets were used to generate the HRD score for TP-2: a FoundationOneLiquid CDx (F1LCDx) dataset (Azad et al. ASCO 2023, #5056) of prospectively collected/retrospectively analyzed plasma samples (n=681) and a tumor transcriptomic dataset generated via HTG's Oncology Biomarker Panel (with 10 additional genes implicated in PARPi sensitivity; n=304). This NMF-based HRD score was then applied to the evaluable TP-2 safety population (n=285). Predicted HRD scores for TP-2 were categorized as high (≥0.46 [median]) or low (<median). **Results:** Although predicted HRD score is primarily based on gene expression, it proved significantly associated with HRR12 gene alteration (HRR12m) status based on F1LCDx variant calling of retrospectively sequenced ctDNA (Wilcoxon test P=3.3e-10). Of 89 pts with HRR12m by F1LCDx, 74% were HRD-high and 26% were HRD-low. Conversely, of 196 pts who were non-HRR12m by F1LCDx, 39% were HRD-high and 61% were HRD-low, suggesting the presence of a subgroup of pts who had HRD in the absence of detected HRR12m. In all-comers, TALA + ENZA demonstrated more favorable rPFS than PBO + ENZA in both HRD-high (hazard ratio [HR]=0.49, P=0.0036) and HRD-low (HR=0.48, P=0.0062) pts. A similar trend was evident in the subgroup of pts lacking HRR12m. **Conclusions:** Our exploratory analysis of TCGA-PRAD resulted in discovery of a novel HRD score, incorporating both gene expression and HRR12 genomic attributes. In TP-2, this score was associated with ctDNA HRR12m status. HRD-high and HRD-low pts exhibited comparable rPFS benefit in terms of HR favoring TALA + ENZA over PBO + ENZA. Clinical trial information: NCT03395197. Research Sponsor: Pfizer Inc.

Association between prostate-specific antigen (PSA) level <0.2 ng/mL and risk of radiological progression in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC): Follow-up analysis of ARAMIS.

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Background: In pts with nmCRPC, metastatic progression was not consistently associated with PSA progression in a prior analysis of ARAMIS (Morgans AK, et al. J Clin Oncol 2022;40:5044). We evaluated prostate cancer (PC)-specific survival in ARAMIS, and the patterns of disease progression were determined overall and for pts who achieved PSA <0.2 ng/mL. **Methods:** Pts with nmCRPC received darolutamide (DARO n=955) or placebo (PBO n=554) + ADT in ARAMIS. Using the primary data cutoff (Sept 2018) excluding pts with baseline metastases, PC-specific survival accounting for other deaths as competing risk was analyzed. Treatment group–generated state sequence plots characterized pts by different events: radiological progression, PSA progression, or death. Based on PSA levels and conventional imaging q16 weeks during ARAMIS, the cumulative incidence of time to radiological progression was compared between pts with PSA <0.2 ng/mL and those without. In pts with PSA <0.2 ng/mL and who experienced radiological progression, we evaluated PSA levels at the time of radiological progression. **Results:** DARO increased overall survival in ARAMIS vs PBO (HR 0.69; 95% CI 0.53–0.88) and notably reduced PC-related deaths. PC was the leading cause of death in pts with nmCRPC in both treatment arms. Fewer pts receiving DARO vs PBO had PSA progression alone (7.8% vs 35.9%) or both PSA and radiological progression (5.4% vs 21.4%) at 12 months. Pts on DARO vs PBO had lower PSA levels at the time of radiological progression (median, 2.4 vs 3.7 ng/mL). DARO led to deep and durable PSA response vs PBO, with 25.1% vs 0.5% of pts achieving PSA <0.2 ng/mL, and DARO delayed time to PSA progression overall (median, 33.2 vs 7.3 months; HR 0.13; 95% CI 0.11–0.16). DARO pts with PSA <0.2 ng/mL had a lower risk of radiological progression vs those with PSA ≥0.2 ng/mL, with rates of 8.7% vs 33% at 24 months. At 36 months, the cumulative incidence of radiological progression remained at 8.7% for DARO pts with PSA <0.2 ng/mL and increased to 50% in pts with PSA ≥0.2 ng/mL. For the 11 pts with PSA <0.2 ng/mL and radiological progression, PSA levels at the time of radiological progression (range, 0.02–438.46 ng/mL) and time to radiological progression (4–22 months) did not follow any patterns. **Conclusions:** In pts with nmCRPC by conventional imaging, DARO increased overall survival vs PBO. Adding DARO to ADT resulted in deep and durable PSA response vs ADT alone. DARO was associated with low rates of PSA progression ± radiological progression. In DARO pts with PSA <0.2 ng/mL, the risk of radiological progression ± PSA progression was low over 24 months and did not increase through the end of the study. These post hoc results may raise questions about the frequency of conventional imaging for disease progression in pts with nmCRPC. Clinical trial information: NCT02200614. Research Sponsor: Bayer.

Exploration of circulating tumor cell (CTC) conversion and CTC0 as prognostic biomarkers for efficacy in TALAPRO-2: Phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) vs placebo (PBO) + ENZA as first-line (1L) treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).

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Background: In TALAPRO-2 (NCT03395197), pts unselected for homologous recombination repair (HRR) gene alterations received TALA + ENZA or PBO + ENZA in 1L mCRPC. TALA + ENZA significantly improved radiographic progression-free survival (rPFS) vs PBO + ENZA. In a previous analysis of five randomized phase 3 mCRPC trials, CTC reduction from ≥5 to <5 per 7.5 mL of blood (CTC conversion) or from >0 to 0 (CTC0) at a Week 13 timepoint was shown to be prognostic for overall survival, with higher discriminatory power than PSA reduction (Heller et al. *J Clin Oncol.* 2018;36:572-580). We examined CTC conversion and CTC0 as candidate prognostic biomarkers for rPFS in TALAPRO-2. **Methods:** Blood was serially collected and shipped real-time for CTC enumeration using CELLSEARCH (Menarini Silicon Biosystems) at a central laboratory (Covance). Collection timepoints were screening, Weeks 1, 9, 17, and 25, and safety follow-up visit. Baseline CTC counts were based on Week 1 (screening results were used if Week 1 results were unavailable). CTC reductions were assessed in the safety population as CTC conversion or as CTC0. Data cutoff date was August 16, 2022. **Results:** At baseline, 653 pts in the intent-to-treat population were evaluable for CTC counts: 213/653 (33%) had CTC counts ≥5 per 7.5 mL of blood, and 353/653 (54%) had CTC counts >0. At Week 9, 144 pts were evaluable for CTC conversion (71 TALA + ENZA, 73 PBO + ENZA), with 254 evaluable for CTC0 (119 TALA + ENZA, 135 PBO + ENZA). CTC conversion at Week 9 proved prognostic for rPFS benefit for TALA + ENZA (hazard ratio [HR]=0.13, 95% CI [0.06–0.32], 2-sided $P<0.0001$) and PBO + ENZA (HR=0.16 [0.07–0.40], $P<0.0001$). Similarly, CTC0 at Week 9 was prognostic for TALA + ENZA (HR=0.33 [0.19–0.57], $P<0.0001$) and PBO + ENZA (HR=0.41 [0.24–0.69], $P=0.0006$). At Week 17, 132 pts were evaluable for CTC conversion (64 TALA + ENZA, 68 PBO + ENZA), with 227 evaluable for CTC0 (114 TALA + ENZA, 113 PBO + ENZA). CTC conversion at Week 17 proved prognostic for rPFS benefit for TALA + ENZA (HR=0.28 [0.10–0.73], $P=0.0065$) and for PBO + ENZA (HR=0.26 [0.11–0.59], $P=0.0006$). CTC0 at Week 17 was also prognostic for TALA + ENZA (HR=0.16 [0.09–0.30], $P<0.0001$) and for PBO + ENZA (HR=0.36 [0.20–0.64], $P=0.0004$). **Conclusions:** CTC reduction at Week 9 and 17 proved prognostic of improved rPFS in both treatment arms in TALAPRO-2. To our knowledge, this is the first time such an association has been demonstrated in a phase 3 trial featuring a PARP inhibitor. Not all regions supported CTC collection, and missing results mainly reflected technical and logistical limitations. These results support the broad prognostic utility of CTC enumeration in mCRPC, particularly in the context of PARP inhibitor therapy. Clinical trial information: NCT03395197. Research Sponsor: Pfizer Inc.

Evaluation of homologous recombination repair (HRR) status in metastatic prostate cancer by next-generation sequencing and functional tissue-based immunofluorescence assays.

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Background: Metastatic prostate cancer (mPC) is enriched for HRR gene alterations; these biomarkers have prognostic and predictive value. Next-generation sequencing (NGS) allows for patient stratification, but widespread clinical implementation is still limited. Moreover, not all mutations in HRR genes result in functional HRR loss in the tumor. We investigated the correlation between genomic and functional loss of HRR, using NGS and an optimized RAD51 immunofluorescence (RAD51-IF) assay in mPC biopsies. **Methods:** Observational study including patients with mPC. Either primary tumor or metastatic biopsies underwent NGS (custom VHIO-300 targeted panel (Panel) and/or whole-exome sequencing (WES)), and RAD51-IF from FFPE tissue specimens. A previously defined threshold of 10% RAD51-IF positive cells was used to defined HRD based on RAD51-IF. Genomic scars (LOH, LST, NtAI, and HRD-sum) were obtained from Panel and WES data. Clinical data was extracted from electronic patient records. **Results:** 219 tumor tissues from 187 patients were acquired, including primary (151/219) and metastatic (68/219) cases collected either in the hormone-sensitive (HSPC) (169/219) or castration-resistant (CRPC) (50/219) setting. Genomic profiling was obtained for 181/219 samples (Panel n=139, WES n=80, both n=38). Gene alterations were common in *TP53* (40%), *PTEN* (14%), *AR* (15%), *MYC* (10%), *BRCA2* (9%), *ATM* (8%) and *BRCA1* (2%). Tissue for RAD51-IF was available for 206 samples; of those, 140/206 (68%) were evaluable for RAD51-IF. The median RAD51-IF score was 28.5. 21% samples had RAD51-low results compatible with HRR deficiency (HRD). No RAD51-IF score differences were seen between primary/metastatic tumors (p=0.7) nor HSPC/CRPC (p=0.49). Sample matched RAD51-IF and genomics data were obtained for 128 biopsies (117 patients). BRCA1/2 alterations associated with lower RAD51-IF scores (median 3.5, IQR 9.8 – 8.5 for *BRCA1/2* altered vs median 29.7, IQR 19.0 - 44.5 for *BRCA1/2*-WT), resulting in high sensitivity (71%) and specificity (85%) to identify cases with BRCA1/2 alterations (sensitivity 68% and specificity 87% when considering a larger set of HRR genes. RAD51-IF was able to classify as HRR proficient BRCA1/2 altered cases after secondary resistance to platinum or with retained BRCA1 expression by IF. Based on HRD-sum (HRD>=42) 27.5% and 20.1% cases were classified as HRD on WES and Panel, respectively. CRPC samples were more likely to be classified as HRD-sum "high" (OR 4.07 WES, OR 5.21 targeted panel) HRD-sum was significantly associated with BCRA1/2 (Panel, p= 0.004; WES, p=0.002), and with RAD-IF low for Panel (p=0.021) and for WES once adjusted by castration-sensitivity status (p=0.03). **Conclusions:** RAD51-IF is feasible in clinical samples from mPC patients and associates strongly with clinically relevant HRR gene alterations. Research Sponsor: Department of Defense CDMRP; PC170510P1; ESMO.

5025 Poster Session

Dissecting the significance of *ACP1* gene alterations in prostate cancer (PCa).

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Background: The acid phosphatase 1 (*ACP1*) gene encodes low molecular weight protein tyrosine phosphatase (LMPTP), which is overexpressed in PCa. Previous studies demonstrate that LMPTP plays a critical role in PCa growth and metastasis and is evolving as a potential therapeutic target. Thus, we analyzed *ACP1* expression in primary and metastatic PCa samples and the association of *ACP1* with molecular profiles and clinical outcomes. **Methods:** NextGen sequencing of DNA (592-gene/whole exome) and RNA (whole transcriptome) was performed for PCa specimens (n=5028) submitted to Caris Life Sciences. *ACP1*-High/Low expression was defined as quartile 4 (Q4) and 1 (Q1) of RNA transcripts per million (TPM). DNA mutational profiles were analyzed for samples stratified by *ACP1* expression quartiles. Gene set enrichment analysis was used to assess the Hallmark collection of cancer pathways. Tumor cell *PD-L1*+ status (≥2+, ≥5%; SP142) was tested by immunohistochemistry. Immune cell fractions in the tumor microenvironment (TME) were estimated by RNA deconvolution using QuanTIseq. Overall survival (OS) was assessed from the time of specimen collection to death or last follow-up, with hazard ratio (HR) calculated using the Cox proportional hazards model, and P values calculated using the log-rank test. **Results:** Samples included 3058 (60.8%) derived from the prostate, 634 (12.6%) from lymph node metastases (LNM), and 1307 (26.0%) from distant metastases (DM). *ACP1* expression was higher in LNM and DM than in the prostate (49.8 and 47.9, respectively, vs 44.1 TPM, $p<0.0001$ each). *TP53* mutations were enriched in the highest ACP1 quartile (37.9% Q4 vs 27.0% Q1, $p<0.001$) among prostate samples but not LNM or DM. Pathways associated with cell cycle regulation, oxidative phosphorylation, and androgen response were enriched in Q4, while epithelial-mesenchymal transition and *TNF-*α signaling via *NFKB* pathways were enriched in Q1. Both neuroendocrine and androgen receptor signaling increased in Q4. M2 macrophages and NK cell fractions were increased, while T cells and M1 macrophages were decreased in Q4. PD-L1 expression did not differ by *ACP1* expression. High *ACP1* was associated with worse OS among prostate tumors (63.4 vs 86.3 months (mos) in *ACP1*-high vs low tumors, HR 1.5, 95% CI 1.3-1.7, $p<0.0001$) and DM (22.0 vs 27.7 mos in *ACP1*-high vs low tumors, HR 1.2, 95% CI 1.0-1.4, $p<0.05$) but not LNM (31.9 vs 30.9 mos in *ACP1*-high vs low tumors, HR 1.0, 95% CI 0.8-1.3, p=0.88). OS from the start of ARSI and taxane chemotherapy was similar in *ACP1* high/low groups across prostate, LNM, and DM. **Conclusions:** In the largest study investigating the significance of *ACP1* expression in PCa, we demonstrate that *ACP1*-high tumors exhibit a distinct molecular profile enriched for *TP53* alterations and associated with a 'cold' TME. Our findings may provide a rationale for novel therapeutic targeting of *ACP1*-high tumors. Research Sponsor: None.

5026 Poster Session

Clinical and genomic landscape of neuroendocrine prostate cancer (NEC) vs. prostate adenocarcinoma (AdenoK).

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Background: NEC represents an aggressive form of prostate cancer, characterized by a high incidence of visceral metastases and a poor prognosis [PMID: 23169519]. A previous study has shown that, in a cohort of 30 patients (pts) with NEC, there was a significant enrichment for the loss of *RB1* and the mutation or deletion of *TP53* in these pts compared to those with AdenoK [PMID: 26855148]. Herein, we sought to compare the genomic landscape of pts with NEC to those with AdenoK using a large real-world genomic dataset. **Methods:** In this IRB-approved retrospective study, the de-identified Tempus Lens dataset was used to identify patients diagnosed with NEC and AdenoK across all stages and having comprehensive genomic profiling (CGP). Baseline demographic information was collected. Pathological variables were summarized using descriptive statistics to compare the NEC and AdenoK groups, using the Chi-square test with a significance threshold of $P < 0.05$. Genomic alterations with an incidence of $\geq 5\%$ were included in the analysis. Homologous recombination repair (HRR) alterations in 14 pre-specified genes per the olaparib FDA label were also compared between both groups. **Results:** A total of 13,683 pts (AdenoK: 13472; NEC: 211) were included in the analysis. The median age of the NEC cohort was 65 [24 – 90+], with 55.9% of pts identified as White. Of pts with NEC, 37.9% were never smokers, while 32.7% were ex-smokers. In the AdenoK cohort, the median age was 66 [21- 90+], with 45.4% of patients identified as White. 36.62% of pts never smoked and 29.33% were ex-smokers. In the NEC cohort, the three most common alterations were *TP53*(63.98%), *RB1*(53.08%), and *PTEN*(28.91%). Compared to AdenoK, the NEC cohort had a significantly higher prevalence of *TP53* (63.98 vs 34.97%; P<0.001), *RB1* (53.08 vs 6.09%; P<0.001), *PTEN* (28.91 vs 18.1%; P<0.001), *BRCA2*(15.17 vs. 10.05%; P=0.01), *TMPRSS2-ERG*(25.12 vs. 19.29%; P=0.03), *MYC*(7.11 vs. 2.78%; $P < 0.001$), *CDKN1B*(6.16 vs. 2.11%; $P < 0.001$), and a lower frequency of *SPOP* (2.84 vs 9.22%; P=0.01), and *ATM* (6.64 vs 12.33%; P=0.01). HRR alterations frequency was similar between the NEC and AdenoK, respectively (38.83 vs. 38.66%, P=0.73). **Conclusions:** This is the largest real-world study characterizing the genomic features of prostate NEC compared to AdenoK. Our findings are consistent with prior studies suggesting a distinct genomic profile of NEC. These data can help in an improved understanding of the genetic drivers of this aggressive form of prostate cancer.
Research Sponsor: None.

PHAROS, a real-world multi-country European study on patients with high-risk localised and locally advanced prostate cancer receiving radical treatment.

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Background: Primary radical therapy with curative intent is standard of care for patients diagnosed with high risk (HR) localised (LPC) and locally advanced prostate cancer (LAPC). However, many patients relapse and detailed epidemiological data on natural history, routine management, and clinical outcomes in this setting are sparse. We aimed to explore real world data (RWD) to gain insights into the understanding of the disease pathway. **Methods:** PHAROS is a retrospective, observational study conducted in five academic centres across four European countries from 1989 to 2022 (France, Germany, Switzerland, Spain). All patients with HR LPC and LAPC, according to EAU guidelines, and treated by primary radical prostatectomy (RP) or radiotherapy (RT) (alone or with ADT) were eligible. Data were structured and analysed to describe the patient characteristics at the time of radical therapy, subsequent treatment patterns and clinical events including biochemical recurrence (BCR), event-free survival (EFS) [defined by loco-regional relapse, BCR, metastasis or death] and overall survival (OS) that were estimated by Kaplan-Meier method. **Results:** The table summarizes baseline characteristics and intermediate endpoints for a total of 2303 patients, mostly diagnosed between 2005 and 2020, with a mean follow-up of 6.8 years. RP patients were younger and more likely to be node-positive (N+) as compared to RT patients. EFS at 5 years was 48 % [0.43-0.54] in the RP cohort (N=1539), and 74% [0.66-0.81] in the RT cohort (N=764). At 5 years after radical treatment, 21% of the RP cohort developed distant metastases and rates were higher (30%) in centres with routine access to PSMA PET. The rate was lower (12%) in the RT cohort potentially because of extended hormonal treatment. The principal reported treatment after the first BCR in the RP cohort was salvage RT ±ADT and ADT for the RT cohort. Only 249 and 311 deaths were observed in the RP and RT cohort with an estimated 10-year OS of 73 % [0.66-0.80] and 69% [0.57-0.80], respectively. **Conclusions:** In this large RWD cohort of HR LPC & LAPC, initial results suggest that a significant proportion of patients fail after primary curative treatment within 5 years, indicating an unmet medical need to improve outcomes. Further analysis of the PHAROS dataset will bring better understanding of the real-world patient pathway in this setting and the role of intermediate endpoints. Research Sponsor: Janssen-Cilag.

	RP Cohort (N=1539)	RT Cohort (N=764)
Mean follow-up, year (std)	6.0 (4.4)	8.5 (5.1)
Age year (mean, std)	65.7 (7.1)	70.7 (7.7)
PSA ng/mL (mean, std)	14.6 (14.4)	24.0 (19.1)
Gleason $\geq$ 8	45 %	52 %
cT $\geq$ T3	33%	33%
N+	19 %	8%
5-year EFS [CI]	48% [0.43-0.54]	74% [0.66-0.81]
5-year BCR free survival [CI]	54 % [0.48-0.59]	82% [0.75-0.89]
5-year survival without metastasis [CI]	79% [0.75-0.83]	88% [0.82-0.94]

CI: Confidence Interval.

Predictors of long-term prostate cancer mortality in men continuing prostate-specific antigen screening after age 70.

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Background: Continuing prostate-specific antigen (PSA) screening after age 70 might benefit men at elevated risk of prostate cancer-specific mortality (PCSM), such as Black men with long life expectancies. However, the relative value of race, PSA value, and life expectancy in predicting long-term PCSM and identifying elderly men who may benefit from continued screening is unknown. **Methods:** Using national Veterans Health Administration (VHA) clinical data, we identified all men turning 70 years old between 2008 and 2020 with the most recent PSA ≤4 ng/mL from age 65-69, 5+ years of clinical data, and no prior history of prostate cancer or prostate biopsy. We quantified the presence, intensity, and predictors of continued PSA screening after age 70. We developed competing risk regressions to predict 10-year individualized risk of PCSM using race, baseline PSA value, and 10-year overall survival predictions from an internally developed XGBoost machine learning model using high dimensional clinical data to represent competing mortality risk. Decision curve analyses compared the net benefit of continuing screening past age 70 based on race, PSA, or competing mortality risk predictions alone versus an integrated model combining all three predictors. In sensitivity analyses, we modeled metastatic prostate cancer risk instead of PCSM. **Results:** The cohort included 921,609 recently screened men turning 70 years old: 82% were White and 11% were Black. Most patients (77%) had a baseline PSA <2.0 ng/mL. Screening continuation from age 70-80 was nearly universal: 87% had undergone at least one additional PSA screen and mean cumulative number of additional screens was 5. Screening frequency after age 70 did not vary substantially by competing mortality risk or race. The 10-year cumulative incidence of PCSM was 0.26% overall, and 95% of men had a 10-year risk <0.73%. Baseline PSA was the strongest predictor of 10-year PCSM (0.79% for 3.0-3.99 ng/mL vs. 0.097% for 0.2-0.99 ng/mL; 8.1x difference). Associations with 10-year PCSM risk were more limited for race (0.36% for Black vs 0.25% for White; 1.4x difference) and competing mortality risk predictions (0.24% for highest quintile vs 0.21% for lowest quintile; 1.1x difference). Decision curve analyses suggested minimal net benefit of adding race or competing mortality risk predictions to models containing baseline PSA. Similar results were found in models predicting metastatic prostate cancer incidence. **Conclusions:** Almost 9 of 10 patients in VHA continue PSA screening after age 70 despite most having very low risk of PCSM over the next decade. Recent PSA values are substantially more informative for PCSM risk prediction than race or competing mortality risk predictions under contemporary standards of care. Efforts to personalize screening decisions in men aged 70+ with no history of prostate cancer should focus on recent PSA values. Research Sponsor: None.

5029 Poster Session

Association between body mass index and physical activity among prostate cancer survivors.

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Background: Prostate cancer (PCa) has become a chronic disease due to advances in treatment and earlier detection. Therefore, factors that modify survival post-diagnosis are important. Obesity is associated with increased PCa recurrence and mortality. Thus, interventions that reduce obesity, e.g., physical activity (PA) may prolong survival. We assessed the association between body mass index (BMI) and PA among prostate cancer survivors as well as other modifiable predictors of PA. **Methods:** We conducted a cross-sectional analysis of data from the 2018-22 Behavioral Risk Factor Surveillance System, an ongoing national population-based telephone survey conducted in the U.S. The outcome variable is PA after PCa diagnosis. We classified BMI (exposure) using standard cut points defined by the WHO. Multivariable weighted logistic regression was used to examine the association between BMI and PA adjusting for confounders. All significance tests were two-sided and p-value < 0.05 was significant. The data were analyzed accounting for the complex sample survey design. **Results:** Of the 4,944 prostate cancer respondents, 78% were 65 years or older and 69% were White. 23% were obese class I and 11% were obese class II & III. Obese class I and obese class II & III respondents were significantly less likely to report PA (OR=0.48; 95% CI: 0.28-0.84 and OR=0.37; 95% CI: 0.20-0.67; respectively). Men who received a summary of their cancer treatment were significantly more likely to report PA (OR=1.53; 95% CI: 1.03-2.28). Current smokers were less likely to report PA (OR=0.50; 95% CI: 0.26-0.96). **Conclusions:** Obese men and current smokers were less likely to report PA. Men who received a summary of their cancer treatment were more likely to report PA. Healthcare providers should talk to their patients about the benefit of exercising and refer patients to available exercise programs. Key words: Prostate Cancer Survivorship; Body Mass Index; BRFSS; Quality of Care, Healthy Behaviors. Research Sponsor: None.

Impact of mental health illness (MHI) prior to prostate cancer (PC) diagnosis (Dx) on treatment (Tx) received and PC outcomes.

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Background: We previously showed that men with MHI are 20% less likely to be diagnosed with PC, but when diagnosed, are nearly 2 times more likely to have aggressive PC compared to non-MHI men (Klaassen et al. ASCO 2023). It is unknown whether men with MHI and PC receive definitive Tx (DTx) and have comparable post-Tx outcomes to non-MHI men with PC. This study assessed (i) receipt of DTx, (ii) adherence to surveillance (surv) after Tx, and (iii) biochemical recurrence (BCR) rates among MHI vs non-MHI men. **Methods:** This national, retrospective study used a matched cohort of male veterans who were diagnosed with PC following recent MHI Dx (within 3 yrs prior to PC Dx) or diagnosed with PC in the absence of MHI from 2000-2020. Men were included if they were active users of the VA system (≥2 encounters with a VA provider within a 5-yr period from 2000-2020), their age at Dx was 40> and <80 yrs, and they had no prior malignancy. Competing risks (CR) models and cumulative incidence estimates were used to assess the association (assoc) between MHI and time from PC Dx to receipt of DTx (radical prostatectomy (RP) or radiotherapy (RT)), with death treated as a CR. Logistic regression models were used to test the assoc between MHI and adherence to surv (≥3 PSAs within the first yr following DTx, and at least 1 PSA in each yr to follow for the next 4 consecutive yrs) among treated men. CR models were used to assess the assoc between MHI and time from DTx to BCR (1 PSA >0.2 ng/mL, 2 PSA ≥0.2 ng/mL, or secondary Tx for elevated PSA for RP patients (pts), and a rise of ≥2 ng/mL or more above nadir after RT) among treated men. **Results:** 52,407 men diagnosed with PC (n=19,976 with MHI) were included. The cumulative incidence of DTx was higher for MHI vs non-MHI men (36% vs. 27% after 10 yrs). Men with pre-existing MHI were significantly more likely to receive DTx for PC than men without MHI in both univariable (UVA) (HR: 1.37, 95% CI: 1.32-1.41) and multivariable (MVA) (HR: 1.34, 95% CI: 1.30-1.39) analysis. Among men treated for PC (n=10,086), a similar proportion of MHI men met criteria for adhering to surv as non-MHI men (45% vs. 46%). The odds of adhering to surv did not differ significantly between MHI vs non-MHI men in UVA (OR: 0.96, 95% CI: 0.89-1.04); however, in MVA, the odds of adhering were lower in MHI vs non-MHI men (OR: 0.92, 95% CI: 0.85-1.00, p=0.049). The cumulative incidence of BCR following DTx was higher in MHI vs non-MHI men (31% vs. 28% after 15 yrs). The risk of BCR was significantly higher in MHI vs. non-MHI men in both UVA (HR: 1.08, 95% CI: 1.01, 1.15) and MVA (HR:1.07, 95% CI: 1.00-1.14). **Conclusions:** Men with MHI prior to PC Dx are more likely to receive DTx compared to non-MHI men with PC. Given that men with MHI and PC have more aggressive disease than non-MHI men with PC, more DTx is encouraging, however poorer post-Tx surv adherence and increased risk of BCR presents an opportunity for intervention to improve outcomes in these pts. Research Sponsor: U.S. Department of Defense; W81XWH-20-1-0073.

5031 Poster Session

Metastatic pure seminomas with early relapse: Prognostic roles of high dose chemotherapy and surgery of residual disease.

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Background: Metastatic seminomatous germ cell tumors (mSGCT) are a rare form of cancer. Few studies focused on early relapse (< 12 months) after first-line chemotherapy (ChT). We aimed to evaluate the impact of salvage retroperitoneal lymph node dissection (RPLND), and high-dose ChT with hematopoietic stem cell transplantation (HDCT-HSCT) in mSGCT patients in a situation of early relapse. **Methods:** Ninety-one mSGCT patients treated between 2005 and 2022 in 7 French expert centers for an early recurrence after an initial favorable response to 1st-line ChT were retrospectively included. Patient clinical characteristics, progression-free survival after first relapse (PFS) and overall survival (OS) were evaluated. We also assessed the role of HDCT-HSCT as first salvage treatment, and the impact of complementary RPLND after salvage ChT. **Results:** After a median follow-up of 56 months, 3-year PFS and OS rates were 77.6% (95%CI, 68.3-88.1) and 88.4% (95%CI, 81.0-96.4), respectively. HDCT-HSCT was not associated with longer PFS or OS compared to standard-dose 2^{nd}-line ChT. In contrast, patients who underwent RPLND after salvage ChT demonstrated significantly longer PFS (at 3-years: 97.1% vs 63%; HR 0.15; 95%CI 0.03-0.65; p=0.012) and a notable trend towards improved OS (at 3-years: 97.0% vs 81.8%; HR 0.15; 95%CI 0.02-1.23; p=0.078). **Conclusions:** In mSGCT patients with first-year relapse, RPLND after salvage treatment is correlated with longer PFS and tends to be associated with longer OS. Identification of a subpopulation that might benefit from HDCT-HSCT ought to be performed since it did not confer survival benefits in the overall population. Research Sponsor: None.

Utilization patterns and outcomes of radiotherapy for patients with germ cell tumor relapsing with brain metastases, with a focus on stereotactic radiosurgery.

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Background: Brain metastases (BM) from germ cell tumors (GCT) are a poor-prognostic feature. Nonetheless, many patients (pts) relapsing with BM achieve long-term disease control. Radiotherapy (RT) is a key component of GCT BM management, alongside salvage chemotherapy (CT), but minimal data are available to guide its use. Outcomes of stereotactic radiosurgery (SRS) alone, without whole brain RT (WBRT), are seldom reported. We describe treatment patterns and outcomes of pts with GCT who received RT for BM relapse. **Methods:** Male pts with extracranial GCT who received RT for BM relapse between 2005 and 2023 were included. Four subgroups were defined based on incorporation of RT into the broader BM treatment strategy: RT without concurrent salvage CT (Group 1), RT with salvage conventional-dose CT (CDCT) (Group 2), RT with high-dose CT (HDCT) (Group 3), and salvage RT for progressing BM initially treated with CT alone (Group 4). RT approach included WBRT and SRS. Primary outcomes were overall survival (OS) and intracranial progression (IP) from RT completion. Local progression (LP) after SRS was also assessed. Associations with outcomes were modeled with Cox regression and competing risk regression, accounting for death. **Results:** Sixty pts were included. Median age at BM diagnosis was 28 years. Median follow-up among those alive was 87 months. At 3 years after RT, OS was 39%, and IP was 44%. Groups 1, 2, 3, and 4 included 20, 17, 13, and 10 pts, respectively. Groups were not significantly associated with other baseline features, including RT approach. Outcomes by Group are reported (Table). OS was not significantly different in any Group. There was a trend for worse IP in Group 4, compared with all other groups (HR 2.2, 95% CI 0.99-5.1, p = 0.05). WBRT and SRS alone were used in 32 and 27 pts, respectively. RT approach was not significantly associated with other baseline features. Outcomes by RT approach are reported (Table). OS and IP were not significantly different. Among 53 BM treated with SRS, LP was 8% at 3 years. Among 27 pts treated with SRS, $\geq$ 2 BM (13 pts) predicted increased risk of death (HR 4.9, 95% CI 1.5-16, p = 0.01) and IP (HR 3.6, 95% CI 1.2-11, p = 0.02). This was not observed after WBRT. **Conclusions:** We found heterogeneous patterns of RT use for BM relapse: RT alone, RT with CDCT, RT with HDCT, and salvage RT after initial CT alone. Long-term survival and intracranial control are achievable with each strategy and with both WBRT and SRS. This analysis includes the largest reported series of GCT BM treated with SRS; local control after SRS is excellent, but caution is advised for pts with multiple BM, given elevated risk of IP and death. Research Sponsor: None.

	N	3 year OS, 95% CI	3 year IP, 95% CI
Overall	60	39%, 29–54	44%, 31–56
Group 1	20	49%, 31–77	35%, 15–56
Group 2	17	29%, 13–65	50%, 23–72
Group 3	13	37%, 18–77	31%, 9–67
Group 4	10	40%, 19–86	70%, 27–91
WBRT	32	31%, 19–52	41%, 23–56
SRS alone	27	47%, 31–72	50%, 29–67

Prognostic reclassification and survival outcomes in intermediate- and poor-risk nonseminomatous germ cell tumors (NSGCT).

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Background: Intermediate and poor-risk nonseminomatous germ cell tumors (NSGCT) form a large group of patients with varying prognosis. There is a need to revisit the existing International Germ Cell Cancer Collaborative Group (IGCCCG) classification to identify the 'poorest subset' of patients. **Methods:** We retrospectively analysed the outcomes of consecutive patients with intermediate and poor-risk NSGCT who were diagnosed between 2015 to 2021 at our centre and had received first-line chemotherapy. Overall survival (OS) and relapse-free survival (RFS) were calculated by Kaplan-Meier analysis. A multivariate risk factor model was constructed out of the prognostic factors for OS and RFS. Concordance statistic (c-statistic) was computed and compared between the proposed model and IGCCCG classification and bootstrap sampling was used to evaluate this comparison. **Results:** A total of 360 patients were included, having a median age of 29 (IQR: 24-34) years, with 149 in the intermediate-risk and 211 in the poor-risk according to the IGCCCG classification. Most of the patients had testis as the primary site of the tumor (336 patients, 93.3%). Median follow-up was 58.0 months (95%CI 50.7-65.3). The 5-year OS was 84.4% (95%CI 78.5-90.8) in the intermediate-risk versus 55.3% (95%CI 48.4-63.1) in the poor-risk ($p < 0.001$). RFS at 5 years was 76.8% (95%CI 70.0-84.3) in the intermediate-risk and 46.2% (95%CI 39.7-53.9) in the poor-risk ($p < 0.001$). Age above 35 years, baseline alpha-fetoprotein (AFP) >10,000 ng/mL, presence of liver and brain metastasis were identified to be poor prognostic risk factors for OS, while lung metastasis in addition to the above factors was prognostic for RFS by multivariate analysis. The multivariate model using the above four risk factors for OS had a higher c-statistic (0.668) than the existing IGCCCG classification (0.632) with an improvement of 0.036 (Table). This model also showed a similar improvement in c-statistic over IGCCCG classification for RFS (0.659 vs 0.625). **Conclusions:** The proposed model showed better discriminatory ability than the existing IGCCCG classification. This emphasizes the need to revise the risk stratification to identify the 'very-high risk' subset of patients for potential treatment intensification. Research Sponsor: None.

Comparison of proposed risk factor model with the IGCCCG classification for OS.

	Classification	n	5-year OS (95% CI)	Hazard Ratio (95% CI)	p- value	c-statistic (95% Bootstrap CI)
IGCCCG risk	Intermediate	149	84.4 (78.5 - 90.8)	1	<0.001	0.632 (0.590-0.671)
	Poor	211	55.3 (48.4 - 63.1)	3.229 (2.034-5.126)		
Number of risk factors*#	0	153	82.1 (75.9 - 88.8)	1	<0.001	0.668 (0.612-0.718)
	1	112	58.2 (49.1 - 68.9)	2.659 (1.633-4.328)		
	2	30	40.7 (24.5 - 67.6)	4.474 (2.363-8.471)		
	3	7	0	14.860 (5.627-39.243)		

*There were no patients having all the four risk factors #Proposed model included 302 patients as baseline AFP value was not available in 58 patients.

Longitudinal evaluation of circulating tumor DNA (ctDNA) as a prognostic biomarker to detect minimal residual disease (MRD) in testicular cancer.

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Background: Serum tumor markers (STM) (AFP, hCG) are currently utilized in the management of patients (pts) with testicular cancer. However, in a substantial proportion of pts STM can be normal or falsely elevated. We evaluated the clinical utility of longitudinal ctDNA monitoring as a prognostic marker in pts with testicular cancer. **Methods:** Longitudinal analysis was performed on a multi-institutional cohort of pts with stages I-III testicular cancer using a clinically validated, personalized, tumor-informed 16-plex PCR ctDNA assay (Signatera, Natera Inc.). ctDNA was evaluated pre-orchiectomy, during the MRD (1-12 weeks post-orchiectomy) and surveillance windows (>12 weeks post-orchiectomy, after retroperitoneal lymph node dissection [RPLND], and/or chemotherapy). The correlation between ctDNA status and event-free survival (EFS) was assessed. EFS is described as the interval from orchiectomy to the date of radiological recurrence or any evidence of residual/persistent disease post-completion of chemotherapy or RPLND. This analysis includes 28 pts from Icahn School of Medicine, 20 pts from Indiana University, and 7 pts from City of Hope. **Results:** Plasma samples (n=197) were collected from 55 pts - %stage I/II/III: 42/22/36; %seminoma/non-seminoma: 31/69. The median age was 34 years (range: 16-67), and the median follow-up was 11 months (range: 2-76). Disease management post-orchiectomy included surveillance in 27% (15/55), RPLND in 11% (6/55), chemotherapy in 40% (22/55), and chemotherapy+RPLND in 22% (12/55) of the pts. Pre-orchiectomy ctDNA was detectable in 14/15 pts - 91.6% (11/12) of pts with stage I, and 100% (3/3) of pts with stage II/III disease. ctDNA evaluation pre-RPLND (N=7; 1 seminoma, 6 non-seminoma) revealed ctDNA-positivity in 6 pts. Six pts had ctDNA testing performed pre- and post-completion of chemotherapy for stage II/III disease; ctDNA exhibited a median MTM/mL reduction of 96.5% (range: 75.6–100) post-treatment completion. Seventeen pts had ctDNA testing post-RPLND or chemotherapy; 0/9 pts with undetectable ctDNA relapsed while 4/8 pts with detectable ctDNA experienced clinical recurrence at the most recent evaluation with follow-up ongoing. During the MRD (N=27) and surveillance (N=36) windows, pts with detectable vs. undetectable ctDNA showed a significantly inferior EFS (MRD: HR= 5.27, 95% CI: 1.22-22.71; p=0.026. Surveillance: HR= 10.8, 95% CI: 2.53-46.01; p=0.001). During the surveillance window, elevated STM vs. normal STM was not associated significantly with worse EFS (HR= 2.01, 95%Cl: 0.71-5.72; p=0.191). **Conclusions:** Tumor-informed ctDNA analysis shows promise for MRD detection in pts with testicular cancer. With further study, ctDNA monitoring may have utility in clinical decision-making. Larger prospective trials are planned for validation of clinical utility. Research Sponsor: None.

Management of relapsed stage I nonseminomatous germ-cell tumor with retroperitoneal only relapse.

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Background: For patients (pts) with stage 1 NSGCT on active surveillance (AS), the most common site of relapse is the retroperitoneum (RP). For those with RP only relapse and normal tumor markers, treatment (tx) options include chemotherapy (chemo) or retroperitoneal lymph node dissection (RPLND). We describe the characteristics of pts on AS with stage I NSGCT who relapsed in RP only and were treated w/ either chemo or RPLND. **Methods:** The prospectively maintained Indiana University testicular cancer database was queried for pts with stage 1 NSGCT on AS w/ RP relapse only between 1990-2023. Pts were categorized into a chemotherapy or surgery group based on tx at relapse. Comparisons between groups were done using Chi-square tests for categorical variables or Wilcoxon test for continuous variables. Kaplan-Meier method was used to analyze progression-free survival (PFS) and overall survival (OS) using the log rank test to compare groups. **Results:** We identified 143 pts with stage 1 NSGCT on AS w/ disease relapse in the RP only. The median age at diagnosis was 28.8 yrs (range, 15.6-61.5). Predominant histology was embryonal in 49.0%, mixed in 16.1%, seminoma in 15.4%, teratoma in 10.5%, yolk sac tumor in 7.7%, and choriocarcinoma in 0.7%. IGCCCG risk was good in 140 pts (98.0%) and intermediate in 3 (2.1%). At time of RP relapse, 116 pts (81.1%) were treated with chemo and 27 (18.9%) w/ RPLND. For those treated w/ chemo, the median time to relapse on stage I AS was 5.2 months (0.5-259.2) vs. 9.0 months (1.68-75.24) for those treated w/ RPLND (p=0.01). Chemo regimens used were BEPx3 (82.8%), EPX4 (9.5%), BEPX3 +EPX1 (2.6%), and other (5.2%). 55 of the 116 pts (47.4%) treated w/ chemo required a post-chemo RPLND (pcRPLND). In those treated w/ surgery, RPLND path was pure GCT in 16 pts (59.0%), pure teratoma in 4 (14.8%), malignant transformation (MT) of teratoma in 3 (11.1%), both GCT and teratoma in 2 (7.4%), both teratoma and MT in 1 (3.7%), and normal in 1 (3.7%). Tumor markers were normal for all 27 pts treated w/ surgery. All but two pts treated w/ surgery had RP lymph nodes <3cm in size. With a median follow-up of 34.4 mos, 20 pts relapsed after initial tx: 17 (14.7%) in the chemo group and 3 (11.1%) in the surgery group (p=0.001). The 3 in the surgery group were treated w/ chemo at time of relapse; 2 of those pts remain NED. The other pt remains AWD w/ MT of teratoma. The 5-yr OS for pts treated w/ chemo was 93% vs 100% for surgery, and 5-yr PFS was 80% for chemo vs 74% for surgery. **Conclusions:** In pts on AS with stage I NSGCT w/ RP only relapse, there was no difference in 5-yr PFS or OS for those treated w/ RPLND vs. chemotherapy. Almost half of the pts treated w/ chemo needed a pcRPLND. When pts were carefully selected for RPLND at time of relapse, most were cured with single-modality therapy. In those treated w/ surgery, most had RP lymph nodes <3cm, all had normal tumor markers, and the median time to relapse while on AS for stage I disease was longer. Research Sponsor: Internal Funding.

Management of progressive brain metastases in patients (pts) with relapsed germ-cell tumor (GCT) treated with salvage high-dose chemotherapy (HDCT).

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Background: Previous data confirm that pts with relapsed GCT and progressive brain metastases (mets) can be cured with HDCT and peripheral blood stem cell transplantation (PBSCT)[1]. Still, there is uncertainty with the optimal management sequence of these pts prior to transplant. Here, we describe the management and outcomes of a larger cohort of these pts. **Methods:** The prospectively maintained Indiana University testicular cancer database was queried for pts with relapsed metastatic GCT who were to undergo HDCT with PBSCT and were noted to have progressive brain mets at time of relapse. Baseline characteristics were summarized. The Kaplan-Meier method was used to analyze progression free survival (PFS) and overall survival (OS). **Results:** 49 pts met eligibility. Median age was 28.7yrs (16.6-51.5). Primary site was testis in 44 (90.0%), mediastinal in 4 (8.2%), and retroperitoneum in 1 (2.0%). All patients had nonseminomatous disease. Primary tumor predominant histology was choriocarcinoma (34.7%), embryonal (32.7%), mixed (18.4%), teratoma (6.1%), yolk sac tumor (4.1%), and seminoma (2.0%). IGCCCG risk at diagnosis was poor in 91.8%, intermediate in 2.1%, and good in 6.1%. 24 pts (49%) were platinum refractory at HDCT. 17 pts (34.7%) had brain mets at diagnosis; the rest developed at relapse. The table lists pt characteristics. 26 pts (53.1%) went straight to HDCT without localized treatment to progressive brain mets. 8 (16.3%) underwent craniotomy and 8 (16.3%) had radiation prior to HDCT. 3 of the pts who had radiation had stereotactic radiosurgery (SRS); 5 had whole brain radiotherapy (WBRT). 7 pts (14.3%) underwent craniotomy then radiation prior to HDCT. 5 pts (15.2%) were symptomatic from progressing brain mets at HDCT. 1 of these had mild visual symptoms and went straight to HDCT. 1 pt began having headaches the day before HDCT and given proximity to initiation, HDCT was continued. The other 3 symptomatic pts had previously failed localized treatment for brain mets. 22 pts (44.9%) progressed after HDCT. At a median follow-up of 3.8 yrs (0.6-14.8), 16 pts (32.7%) were alive with no evidence of disease, 10 (20.4%) were alive with disease, 20 (40.8%) died of disease, and 3 (6.1%) died of other causes. 2-yr PFS was 43.9%; 2-yr OS was 73.2%. **Conclusions:** Pts with relapsed GCT with progressive brain mets can be cured with HDCT with PBSCT. Management of progressive brain mets should be individualized for each pt, taking into account extent of brain mets and presence of symptoms. Reference: 1. Kalra M, et al. *Cancer.*2020; 126(6): 1202-1207. Research Sponsor: None.

Baseline pt characteristics at HDCT.

Baseline Characteristic	Total (N=49)
HDCT line of therapy:	
2nd	43 (87.8)
3rd	5 (10.2)
5th	1 (2.0)
Median AFP at HDCT1	6.8 (1.0-1571.3)
Median hCG at HDCT1	164.7 (0.5-49769.4)
Completed 2 cycles of HDCT	39 (79.6)
≥G3 toxicity with HDCT	37 (75.5)
≥G3 neurologic toxicity with HDCT	5 (10.2)
Death from HDCT	4 (8.2)

Post chemotherapy retroperitoneal lymph node dissection (PC-RPLND) for metastatic pure seminoma.

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Background: Surgical resection of post-chemotherapy residual masses for metastatic seminoma is discussed controversially with regard to oncological and functional outcome. Furthermore, the role of FDG-PET/CT to detect vital seminoma is still unclear. It is the aim of this study is to report the outcomes of patients with pure seminoma who underwent PC-RPLND. **Methods:** In this retrospective multi-institutional study, pure seminoma patients whounderwent PC-RPLND for marker negative, FDG-PET/CT positive residual masses > 3cm or marker negative retroperitoneal relapse following first line chemotherapy between 2000 and 2023 were included. Patients with residual masses and negative FDG-PET/CT, inadequate systemic chemotherapy, insufficient clinical data, positive markers, or with residual or relapsing masses following salvage chemotherapy were excluded. Perioperative and long-term outcomes were reviewed. **Results:** 109 patients were included. All patients received first-line cisplatin-based chemotherapy. Clinical features of the patients are presented in the table. 92.6% of PC-RPLNDs were performed via an open transperitoneal approach. 61 (55.9%) and 48 (44.1%) pts underwent unilateral and a full bilateral resection, resp. Adjunctive surgery was performed in 46 (42%) pts, the most common of which were ureteral resection/repair in 16 (15%) pts, and vascular resection/repair in 14 (13%) pts. Median (IQR) blood loss and length of hospital stay were 550 (300 – 5800) mL and 4 (2 – 18) days, resp. Clavien - Dindo complications ≥ 3a developed in 11 (10.1%) pts. Final pathology revealed necrosis/fibrosis in 75 (69%) and seminoma in 34 (31%). FDG-PET/CT for residual masses > 3cm showed a positive predictive value of only 20%. Except for marker negative progression ($p<0.001$), no reliable clinicopathologic parameters were identified to predict presence of viable seminoma. With a median (IQR) follow-up of 56 (2 – 164) months, 15 (14%) patients relapsed (12 with lymph node, 3 with visceral/skeletal metastases). 3 (3%) patients died of disease. **Conclusions:** One third of patients with progressive or > 3cm FDG-PET-CT positive residual retroperitoneal masses following first-line chemotherapy for metastatic seminoma may have viable tumor. FDG-PET/CT has a poor positive predictive value and might be omitted as staging procedure. In selected cases, PC-RPLND may be a valuable option if performed in high-volume centers with expertise in testicular cancer management. Research Sponsor: None.

Clinical features of the patients.

Variable	Value
Age at surgery, median (IQR), year	40 (31 – 68)
Orchiectomy laterality, n (%)	
Right	37 (34)
Left	56 (51)
bilateral	3 (2.7)
Extragonadal/NA	13 (12)
Clinical stage at initial diagnosis, n (%)	
I	8 (7.3)
IIA/ IIB	31 (26)
IIC	50 (46)
III	20 (18)
IGCCCG risk group, n (%)	
Good	88 (81)
Intermediate	21 (19)
Preoperative mass size, median (IQR), cm	3,82 (2.1-14.9)

Real-world evidence of overall survival (OS) and treatment patterns of patients (pts) with testicular germ cell tumors (GCT) receiving palliative chemotherapy in the United States.

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Background: Pts with relapsed/refractory (R/R) GCT have a poor prognosis, with only palliative options remaining. Real-world data in this population, particularly around prior salvage strategies with high-dose (HDCT) or conventional-dose chemotherapy (CDCT), are needed to inform future treatment standards. **Methods:** Adult males with R/R testicular GCT who received palliative chemotherapy between 01/2016 to 03/2023 were identified in the Komodo Research Database Demographics were described on the index date, defined as the date of palliative chemotherapy initiation. OS, defined as the time from index date to death and stratified by prior HDCT exposure, was assessed among pts with 12 months (mos) follow-up time using the Kaplan-Meier method. Additionally, treatment patterns were analyzed in a subgroup of pts with an eligible health plan continuously from diagnosis to index date. **Results:** Of 57,508 pts with testicular GCT, 248 received palliative chemotherapy, among whom 97 (39.1%) had sufficient claims data to confirm prior exposure to salvage HDCT (+/- CDCT) or only CDCT (57 HDCT; 40 CDCT only). Median (interquartile range [IQR]) age on the index date for these 97 pts was 32 (25-42) years and most had commercial (47.4%) or Medicaid (36.1%) insurance. Observed index palliative regimens included gemcitabine + oxaliplatin (46.4%), oral etoposide (12.4%), and gemcitabine + paclitaxel (12.4%); 24.7% of pts received multiple palliative regimens (median 2, range 2-5). Median (95% confidence interval) OS was 8.0 (6.3-9.7) mos; 7.0 (5.7-9.7) mos for those HDCT exposed, and 9.3 (7.5-22.6) mos for those exposed to CDCT only. The treatment patterns subgroup comprised 51 pts observed for a median of 19.9 (IQR: 15.6-28.8) mos after diagnosis. Median (IQR) time from diagnosis to first-line (1L) chemotherapy was 0.9 (0.5-2.1) mos and to palliative chemotherapy was 12.5 (9.0-16.8) mos. Prior to palliative chemotherapy, 33 pts (64.7%) received salvage chemotherapy, including HDCT (+/- CDCT) in 23 pts (69.7%) and only CDCT in 10 pts (30.3%). Of 18 pts (35.3%) who did not receive salvage chemotherapy prior to palliative chemotherapy, median time from end of 1L chemotherapy to index date was 4.1 (IQR: 2.4-8.0) mos and 13 pts (72.2%) had renal insufficiency. **Conclusions:** Real-world data was able to capture treatment patterns, palliative chemotherapy use, and outcomes for pts with R/R testicular GCT. Surprisingly, more than 1/3 of pts did not receive a salvage chemotherapy regimen prior to palliative chemotherapy and of those who did, >30% did not receive HDCT. Renal insufficiency may be a major reason for lack of salvage chemotherapy use. These data provide prognostic information and variables influencing poor outcome in this understudied population for whom novel treatments are urgently needed. Research Sponsor: BioNTech.

5039 Poster Session

Multicenter analysis of high-dose chemotherapy (HDCT) regimens for the treatment of patients (pts) with recurrent germ cell tumors (GCTs).

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Background: Although HDCT is an established salvage treatment for pts with GCTs, there is no multi-center comparative analysis of the two most common dosing regimens: 1.) carboplatin 700 mg/m2 and etoposide 750 mg/m2 (CE) given for two cycles, and 2.) carboplatin AUC 7-8 and etoposide 400 mg/m2 given for three cycles, typically after two cycles of paclitaxel 200 mg/m2 and 2000 mg/m2x (TICE). To address this gap, we pooled data from four high-volume referral centers to evaluate the clinical efficacy of HDCT approaches. **Methods:** Demographic and clinical characteristics were retrospectively abstracted from electronic medical charts. Adult pts who received HDCT for recurrent GCT from 1/1/2010 to 1/1/2023 and received either CE or TICE were included. Differences among groups were tested using the Fisher's exact and the Wilcoxon rank-sum tests for qualitative and quantitative variables, respectively. Relapse-free survival (RFS) and overall survival (OS) were estimated and compared using the Kaplan-Meier method and log-rank test. All statistical analyses were conducted in R Statistical Software, version 4.3.1. **Results:** Seventy-two pts were identified across four institutions, of whom 46 received CE (64%) and 26 received TICE (36%). Most CE pts were treated at UCSF (39%) or UCLA (22%); TICE was predominantly given at COH (46%) or UCSF (46%). Median age at diagnosis was 30 (range, 18-58), a majority were Hispanic (51%), and most pts had a non-seminomatous GCT (79%). Ethnicity and tumor histology were similar between all two cohorts (P=NS for both). Most pts had Stage IIIC disease at diagnosis (44%) and most received HDCT in the 3rd line setting (71%). Tumor marker normalization prior to HDCT was more prevalent among CE (35%) than TICE (15%). Most pts who received CE (89%) and TICE (77%) completed their planned two and three cycles of HDCT, respectively. With a median follow-up of 54.0 months from the date of the last transplant, no difference was observed in the median RFS between TICE vs CE (10.2 vs 4.5 months, HR of 0.87, 95% CI [0.51, 1.49], P=0.610. We observed a trend toward improved median OS between TICE vs CE (56.5 vs 17.9 months, HR 0.54, 95% CI [0.29, 1.01], P=0.057). There was no difference between the rates of post-transplant relapse among pts who received HDCT in the 2nd line vs 3rd line (76.9% vs 61.7%, P=0.51). **Conclusions:** In the first multicenter comparative analysis of contemporary HDCT regimens, there was no difference in RFS between CE and TICE. However, we observed a trend toward improved survival among pts who received TICE. Additionally, we detected no difference in the rates of post-transplant relapse among pts treated in the 2nd line versus the 3rd line, supporting the application of HDCT in either setting. These findings represent the first of an ongoing regional collaboration that aims to leverage real-world data to improve clinical outcomes for pts with recurrent GCTs. Research Sponsor: None.

High dose chemotherapy in male patients with germ cell cancer: A population-based study by the SWENOTECA group.

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Background: Selected patients with advanced germ cell tumors have a poor prognosis. These include patients with brain, bone or liver metastases, very elevated tumor markers or primary mediastinal tumor. High-dose chemotherapy (HDCT) with autologous stem cell support is recommended in the Swedish and Norwegian Testicular Cancer Group (SWENOTECA) guidelines in selected poor risk patients with poor response to/relapse after intense primary treatment. From the year 2011, the HDCT-regimen consisted of two cycles of carboplatin and etoposide. Our aim of this study was to evaluate survival and toxicity in patients treated with HDCT within the population-based SWENOTECA cancer care program in 2011-2021. **Methods:** All patients treated with HDCT according to guidelines in Sweden and Norway between 2011-2021 were included, in total 80 patients (76 non-seminoma and 4 seminoma). This reflected approximately 3% of all non-seminoma patients. HDCT was administered in three different clinical situations: delayed tumor marker decline during primary or intensified primary treatment (n=26), progressive disease during primary treatment (n=29) (defined as progressive disease within <3 months from last cycle of chemotherapy), or relapse with poor prognosis (n=25). The overall survival (OS) and failure-free survival (FFS) were calculated, and the toxicity was described. **Results:** The 5-year overall survival (OS) and failure free survival (FFS) after HDCT was 55% and 43% respectively. HDCT due to delayed tumor marker decline had a more favorable outcome, 5-year OS of 75% and 5-year FFS of 53%. HDCT due to relapse resulted in a 5-year OS of 61% and 5-year FFS of 58%. Patients treated with HDCT due to progressive disease during primary treatment had a markedly less favorable 5-year OS of 29% and 5-year FFS of 18%. Four patients (5%) died due to treatment. The most common treatment-related grade 3-4 toxicities were infections (n=69, 86%). **Conclusions:** In this population-based study, we have shown that HDCT for patients with advanced germ cell cancer according to the SWENOTECA cancer care program is achievable and leads to favorable OS and FFS rates. Furthermore, even though patients that receive HDCT due to progressive disease have a relatively poor outcome, 20-30% of patients do achieve long-term survival. Research Sponsor: None.

High-dose chemotherapy in Sweden and Norway 2011-2021. Overall survival at 1, 2 and 5 years, all patients. Survival probability %; (95% CI).

Indication for HDCT	Patients, n	Deaths Overall, n	1-Year Survival Probability	2-Year Survival Probability	5-Year Survival Probability
Overall	80	36*	70; (60-81)	62; (52-73)	55; (44-68)
Delayed marker decline	26	8	88; (76-100)	80; (66-97)	75; (60-95)
Progression	29	20	48; (33-70)	33; (19-56)	29; (16-52)
Part of relapse treatment	25	8	76; (61-95)	76; (61-95)	61; (41-91)

*Mortality due to HDCT-treatment 4/80 (5%).

Long term cardiovascular adverse outcomes in testicular cancer survivors: Real-world U.S. population-based study.

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Background: The focus of Testicular Cancer (TC) has shifted towards survivorship due to the high cure rates. With the increase in TC survivors population, long-term cardiovascular disease (CVD) have been suggested to be strongly linked with earlier treatment for TC by various hospital based small studies. As it is crucial to investigate this relationship at a population level to develop early prevention strategies to improve TC survivors' overall quality of life (QoL), we analyzed the U.S. The Behavioral Risk Factor Surveillance System (BRFSS) to describe the long-term outcomes of TC survivors in a real-world random population sample. **Methods:** Using BRFSS cycles between 2014 and 2022, we pulled all patients who reported having a history of TC and compared them to the rest of the men's population sample who had no history of cancer diagnosis. Using national complex weights, we estimated each group outcomes proportions. Further, we evaluated several complex-weighted logistic regression models adjusted for different covariates to describe the association of high blood pressure, high cholesterol, diabetes, BMI of >25, angina, myocardial infarction (MI), and coronary heart disease (CHD). **Results:** Out of 3,077,806 participants, we identified 308 with a history of TC and 1,169,061 men with no history of cancer. After calculating descriptive demographics, our modeling analysis showed a consistent significant association in reporting history of Angina (OR range from 3.84 to 4.27), CHD or MI (OR range from 2.92 to 3.14). see table. **Conclusions:** Real-world data indicate alarming results of high prevalence CVD in TC survivors; our results confirm previously reported results from hospital-based cohorts. Our findings support immediate actions to develop and implement preventative strategies in TC survivors. Research Sponsor: None.

Model	OR [95% CI]	P value
History of angina		
A	**3.844 [2.168 - 6.815]**	**<0.001**
B	**4.273 [2.255 - 8.099]**	**<0.001**
C	**3.918 [2.003 - 7.665]**	**<0.001**
D	**3.977 [2.018 - 7.838]**	**<0.001**
Ever had an MI		
A	**2.495 [1.297 - 4.801]**	**0.006**
B	**2.614 [1.281 - 5.334]**	**0.008**
C	**2.425 [1.047 - 5.617]**	**0.039**
D	2.376 [0.994 - 5.675]	0.051
Coronary heart disease (CHD) or myocardial infarction (MI)		
A	**2.917 [1.782 - 4.776]**	**<0.001**
B	**3.143 [1.806 - 5.469]**	**<0.001**
C	**3.024 [1.668 - 5.481]**	**<0.001**
D	**3.01 [1.635 - 5.542]**	**<0.001**

A; non-adjusted. B; Adjusted for Age. C; Adjusted for Age, Race, Income, Education, marital status, reported health status, exercise, and smoking status. D; Adjusted for Age, Race, Income, Education, marital status, reported health status, exercise, smoking status, physical status, and mental health status.

Survival associated with chemotherapy and prognostic biomarkers in penile cancer at a reference hospital in the Northeast Brazil from 2000 to 2021.

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Background: Penile cancer is a rare neoplasm worldwide. Despite a higher incidence in the Brazilian Northeast region, data regarding chemotherapy (CHT) treatment of penile cancer in Brazil is scarce. The relationship between markers of immunosuppression in the tumor microenvironment of penile cancer and MDSCs (Myeloid Derived Suppressor Cells) is still poorly understood. **Methods:** 294 patients affected by Squamous Penile Cancer treated at the Haroldo Juaçaba Hospital (Ceará-Brazil) between 2000 and 2021 (82 underwent chemotherapy: 27 adjuvant, 31 neoadjuvant and 24 palliative) were retrospectively evaluated due to their clinical and histopathological characteristics and the following immunohistochemical markers: PD-L1, CD8t (intratumoral), CD163t (intratumoral), CD84, HLA-DR II. We sought to correlate these biomarkers to clinical staging, type (neoadjuvant, adjuvant or palliative) and response to CHT, PFS post-Chemotherapy (PFS-CHT), Overall Survival by stage (OS) and OS post-Chemotherapy (OS-CHT). **Results:** The median age for all patients was 62,9 years (18-103). Partial penile amputation was the most common surgery (74%), followed by inguinal lymphadenectomy (56%). Platinum Doublet was administered in 95% of cases. OS at 5 years for stages I, II, III e IV was 95,3%, 93,6%, 87,4% and 14,8%, respectively. The response rate (RECIST) (PR, SD and PD) in those who underwent Neoadjuvant CT was 29% 22% and 48%, while in the Palliative group was 5%, 11% and 82% respectively. Median OS-CHT was 49 months in the adjuvant, 21 months in neoadjuvant and 12 months in palliative group ($p<0.001$ adjuvant vs neoadjuvant/palliative); PFS-CHT was 11 months, 4 months and 1 month in the adjuvant, neoadjuvant and palliative group, respectively ($p<0.001$). In the neoadjuvant group, those who underwent surgery (70%) had a PFS-CHT of 6 months versus 2 months in those who were not operated ($p<0.001$). In univariate analysis, PFS-CHT was significantly higher in those who had lower expression of CD8t (9 vs 5 months; $p=0.02$), or CD163t (7 vs 5 months; $p=0.043$) or CD84 (7 vs 5 months; $p =0.043$). **Conclusions:** This is the largest retrospective study on chemotherapy and survival outcomes in Brazil. Patients who underwent surgery and adjuvant CHT had the best prognosis in terms of survival followed by those operated after neoadjuvant CHT. Lower expression CD163t, or CD84 (marker of MDSCs) or CD8t correlated with greater PFS-CHT. These data may help to understand the suppressive microenvironment in penile cancer and response to chemotherapy. Research Sponsor: None.

Albumin-bound paclitaxel, cisplatin, and bleomycin combination with tislelizumab for stage IV squamous cell carcinoma of the penis without surgical indications: A single-arm, single-center prospective phase II clinical study.

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Background: In recent years, preclinical studies of the penile cancer microenvironment have shown the presence of a relatively dense immune cell infiltrate and high PD-L1 expression. Here, we present findings to explore the efficacy and safety of albumin-bound paclitaxel, cisplatin and bleomycin combined Tislelizumab regimen for stage IV penile squamous cell carcinoma without surgical indication. **Methods:** Prospective inclusion of patients with stage IV squamous cell carcinoma of the penis without indications of surgery who are not received chemotherapy or immune checkpoint inhibitors. Patients were treated with chemotherapy combined with Tislelizumab for 4-6 cycles, sequential immunotherapy is permitted for patients who have responded well to local therapy (surgery +/- radiotherapy) . Positive expression of PD-L1 was defined as TPS≥5%. The primary endpoint was ORR, the secondary endpoint was PFS、OS and Safety. **Results:** 28 patients with stage IV penile squamous cell carcinoma (22 cases with regional lymph node metastasis、6 cases with distant metastasis and 11 cases of local ulceration) were treated with albumin-bound paclitaxel, cisplatin and bleomycin combination with Tislelizumab. The median age of the patients was 56 years (range 38-74 years), the median chemotherapy cycle was 4 cycles (2-6 cycles), the median immunotherapy cycle was 4 cycles (1-9 cycles), and the median follow-up was 10.4 months. 1 patient (3.5%) were evaluated as CR, 22 patients (78.5%) were evaluated as PR, and 3 patients (10.5%) were evaluated as SD. The ORR was 82.0%. It was significantly higher than the 50% ORR of chemotherapy alone reported in the previous literature. The median PFS was 13.7 months, and The median OS is not arrived. Among the 22 patients with regional lymph node metastasis, 12 patients (54.5%) received surgery or radiotherapy due to good treatment effects. PD-L1 expression was positive in 16 cases (57.1%). 1 case (3.6%) was HPV positive. In adverse event: The incidence of grade 3-4 adverse reactions was 32.1%. 4 cases (32.1%) had grade 3-4 rash with pruritus, 3 cases (10.7%) had grade 3-4 myelosuppression, 1 case (3.6%) had grade 3 pneumonia, 1 case (3.6%) had grade 3 fatigue, and 1 case(3.6%) had grade 3 alopecia. All adverse reactions resolved after treatment. 2 case (3.6%) stopped immunotherapy due to grade 4 rash with immune pneumonia, and no treatment-related death occurred. **Conclusions:** Stage IV penile squamous cell carcinoma treated with chemotherapy combined with Tislelizumab has a high objective response rate and controllable adverse reactions, A high proportion of patients with regional lymph node metastases had the opportunity to regain surgery or radiotherapy. It is expected to change the poor effect of chemotherapy alone for stage IV squamous cell carcinoma of penis. Clinical trial information: ChiCTR2000040095. Research Sponsor: None.

Implications of HPV infection on survival outcomes in patients with penile squamous cell carcinoma: Insights from a nationwide study.

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Background: Human Papilloma Virus (HPV) infection is a favorable prognostic marker in certain cancers, particularly oropharyngeal and vulvar (SCC). Patients with pSCC have risk profile and clinical course like pSCC. However, the impact of HPV status on survival in pSCC remains uncertain. **Methods:** We conducted a retrospective study using the National Cancer Database and included patients with pSCC tested for HPV between 2004-2021. Survival outcomes were analyzed and reported as median overall survival (mOS, 95% CI). Multivariate analysis adjusting for age, disease stage, treatment modalities, and comorbidities, was performed using Cox proportional hazards models and reported as hazard ratios (HR, 95% CI). **Results:** Out of 1371 men with pSCC, 539 (39.3%) were HPV positive (HPV +ve). At diagnosis, most HPV +ve men with pSCC presented with early-stage cancer(I-III), and 6% were stage IV. The mOS for HPV +ve patients was 123.96 months (98.96 - 148.40) vs. 104.38 months (89.13 - 115.98) in HPV negative patients with pSCC (P=0.01). In the adjusted analysis, the presence of HPV infection was associated with HR for death of 0.79 (0.65-0.98; P = 0.03) compared to patients without HPV (table). **Conclusions:** HPV infection in patients with pSCC is associated with improved survival. These findings highlight HPV status as a prognostic Indicator in pSCC irrespective of clinical profile. Therefore, testing for HPV at the time of diagnosis should be performed routinely in patients with pSCC. Research Sponsor: None.

Variable	Hazard Ratio	P-value	95% CI
AGE < 65	ref		
>= 65	2.02	0.00	[1.65, 2.49]
White	ref		
Black	1.10	0.49	[0.82, 1.49]
Stage 0-III	ref		
Stage IV	2.93	**<0.01**	[2.15, 3.98]
No Radiotherapy	ref		
Radiotherapy	1.21	0.35	[0.80, 1.82]
No systemic therapy	ref		
systemic therapy	1.06	0.67	[0.79, 1.41]
HPV absent	ref		
HPV present	0.79	**0.02**	[0.64, 0.97]
Organ preserving procedures.	ref		
definitive surgery	1.49	<**0.01**	[1.20, 1.85]
Charlson Dayson score =0-1	ref		
Charlson Dayson score =2-3	1.67	<0.01	[1.28, 2.19]

Effect of concomitant medications on treatment response and survival in non-metastatic castrate resistant prostate cancer: Secondary analysis of the SPARTAN trial.

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Background: While exposure to concomitant medications (conmeds) have been found to influence survival and treatment response in patients with metastatic prostate cancer, it is unclear if exposure to these medications affect treatment response and survival in men with non-metastatic castrate resistant prostate cancer (nmCRPC) treated with androgen receptor signaling inhibitors (ARSI). We performed an exploratory analysis of the SPARTAN trial to determine whether receipt of conmeds influenced the effect of apalutamide on overall survival (OS) and metastasis-free survival (MFS) in patients with nmCRPC. **Methods:** SPARTAN is a phase III randomized controlled trial in which nmCRPC patients were randomly assigned 2:1 to receive apalutamide or placebo in addition to androgen deprivation therapy (ADT). We focused on 5 groups of commonly prescribed classes of conmeds: biguanides (metformin), HMG-CoA reductase inhibitors (statins), angiotensin converting enzyme inhibitors (ACEI), acetylsalicylic acid derivatives (ASA), and proton pump inhibitors (PPI) given their plausible biologic and clinical rationale. To determine the potential effect-modification, we applied Cox regression models with interaction term between the conmed class, the randomized treatment in addition to a minimally sufficient set of confounders. To determine the independent association of each class of conmeds with outcome, we applied IPTW-based survival analysis and log-rank test. **Results:** Overall, 1152 patients (772 and 380 in the apalutamide and placebo arm, respectively) were eligible for this secondary analysis. For OS, we did not find any statistically significant heterogeneity of treatment effect from ADT plus apalutamide across subgroups stratified by concomitant exposure to the conmeds listed above. We noted a significant difference (p=0.01) in treatment effect from apalutamide on MFS between patients with concomitant receipt of statins (adjusted hazard ratio [aHR]: 0.20; 95% CI: 0.15-0.28) vs without statins (aHR: 0.31 [0.24-0.39]). On IPTW-based analysis, patients with concomitant metformin (median: NR vs 31 months (mos); p=0.002) and concomitant ACEI (median: 37 vs 29 mos; p=0.006) had significantly superior MFS. Patients with exposure to all of metformin, ACEI, and statin had significantly improved MFS (median: NR vs 31 mos; $p<0.001$). **Conclusions:** In this post-hoc exploratory analysis, treatment effects from apalutamide on MFS and OS were consistent across subgroups stratified by exposure to conmeds. Exposure to concomitant metformin or ACEI was associated with a significant improvement in MFS. Research Sponsor: None.

A phase 1, multi-center, open-label, dose-escalation, and dose-expansion study of CBP-1018, a bi-ligand-drug conjugate in patients with heavily treated advanced solid tumors.

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Background: CBP-1018 is a first-in-class bi-ligand-drug conjugate targeting both PSMA and FRα with monomethyl auristatin E (MMAE) as payload. It delivers the conjugated payload into target cells highly efficiently and specifically which had been proven by preclinical studies. CBP-1018 shows good antitumor activity in various Patient-Derived Tumor Xenograft/Cell Derived Xenograft (PDX/CDX) models of lung cancer, ovarian cancer, prostate cancer, breast cancer and pancreatic cancer, up to 96% Tumor growth inhibition (TGI). **Methods:** This phase 1 study includes both dose-escalation and expansion stage. In the dose-escalation stage, an accelerated titration was conducted in single patient at 0.03mg/kg followed by an i3+3 design for dose levels (DLs) ≥ 0.06 mg/kg, Q2W. In dose-expansion stage, 0.12 mg/kg and 0.14 mg/kg were selected for dose expansion. The primary objectives are to evaluate the safety and tolerability, determine dose limiting toxicity (DLT) and maximum tolerated dose (MTD). Additionally, pharmacokinetics (PK) and preliminary efficacy will also be evaluated. **Results:** As of 31 Dec 2023, 59 pts (57 mCRPC, 1 bladder cancer and 1 ureteral carcinoma) were enrolled at 7 DLs (1 pt at 0.03 mg/kg, 3 pts each at 0.06, 0.08, 0.10 mg/kg, 17 pts each at 0.12 mg/kg and 29 pts at 0.14 mg/kg, and 3 pts at 0.16 mg/kg). No DLTs, no drug-related deaths were observed. Enrolled mCRPC pts received a median 9 prior systematic antitumor drugs (median 2 prior chemotherapy, 72.9% pts had received chemotherapy, and median 4 new hormonal agents). Median age was 67.5 (range 57, 78). Median PSA was 82.2 ng/ml (range 0.006, 2995ng/ml) at baseline. 89.8% pts have an ECOG score of 1 or 2. Most treatment-related adverse events (TRAEs) were grade 1 or 2, ≥ grade 3 TRAEs mainly includes neutrophil decrease (29.5%), WBC decrease (19.7%), lymphocyte decrease (11.5%). Among 7 efficacy evaluable pts with mCRPC per RECIST v1.1 at 0.14 mg/kg or higher dose levels, best overall response (BOR) of 3 PR and 4 SD were observed, with ORR 42.9%, DCR 100%. Overall median radiographic progression-free survival (rPFS) was 9.2 months (95%CI, 5.0-NA) in 28 evaluable (who have at least one tumor assessment after study treatment) mCRPC pts per RECIST1.1 and PCWG3. C_{max} and AUC_{0-t} of CBP-1018 and free MMAE increased with dose, and the $t_{1/2}$ of CBP-1018 was ranged from 0.54 to 1.15 h in different dose cohorts, respectively. Accumulation, C_{max} and AUC_{0-t} of CBP-1018 were not observed. **Conclusions:** CBP-1018 was well-tolerated at DLs of 0.03-0.16 mg/kg Q2W with no DLTs. MTD was not reached. Promising preliminary efficacy ORR and rPFS were observed, supporting a further investigation in large scale clinical trial for mCRPC patients. Yehui Shi and Hai Huang is the corresponding author. Kaiwen Li and Junyan Wu contributed equally to this work. Clinical trial information: NCT04928612. Research Sponsor: Coherent Biopharma.

Patient-reported outcomes (PROs) for rezvilutamide versus bicalutamide in combination with androgen-deprivation therapy (ADT) in high-volume, metastatic, hormone-sensitive prostate cancer (mHSPC): An analysis of the CHART randomized, open-label, phase 3 trial.

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Background: In the CHART trial, rezvilutamide plus ADT significantly improved radiographic PFS and OS compared with bicalutamide plus ADT in patients with high-volume mHSPC (Gu et al., Lancet Oncol 2022). Here, we report the PRO results from the CHART trial. **Methods:** Eligible patients were men ≥18 years old with high-volume mHSPC and without previous chemotherapy or other localized treatment for prostate cancer. Patients were randomly assigned (1:1) to receive ADT plus either rezvilutamide (240 mg) or bicalutamide (50 mg) orally once daily. PROs were exploratory endpoints and were assessed in all randomized patients by using the Brief Pain Inventory-Short Form (BPI-SF) and Functional Assessment of Cancer Therapy-Prostate (FACT-P). PROs were collected within 7 days prior to the first dose, on Day 1 of each cycle (28 days) in Cycles 2–12, once every 2 cycles in Cycles 13–36, once every 4 cycles afterwards, and on Day 30 after the last dose. **Results:** Between Jun 28, 2018, and Aug 6, 2020, a total of 654 patients were randomly assigned to receive either rezvilutamide plus ADT (n=326) or bicalutamide plus ADT (n=328). The data cutoff for this PRO analysis was Feb 28, 2022, and the median follow-up was 29.3 months (IQR 21.0–33.3). Baseline pain scores and functional status scores were comparable between the two study groups. The median time to progression of pain (both intensity and interference) was not reached in either group. The 25th percentile for the time to average pain progression was 25.8 months (95% CI 14.8–31.4) in the rezvilutamide plus ADT group and 11.7 months (95% CI 8.7–22.1) in the bicalutamide plus ADT group (HR 0.79, 95% CI 0.58–1.08; p=0.133). Patients in the rezvilutamide group exhibited a longer time to pain interference progression compared to the bicalutamide group (25th percentile, 20.2 months [95% CI 12.9–31.3] vs 10.2 months [95% CI 7.4–11.1]; HR 0.70 [95% CI 0.52–0.93]; p=0.015). Regarding functional status, the time to deterioration of the FACT-P total score was prolonged in the rezvilutamide plus ADT group compared to the bicalutamide plus ADT group (25th percentile, 12.8 months [95% CI 7.4–20.3] vs 6.0 months [95% CI 4.6–9.2]; HR 0.66, 95% CI 0.50–0.86; p=0.002). Additionally, the rezvilutamide plus ADT group exhibited delayed deterioration in all FACT-P subscale scores compared to the bicalutamide plus ADT group. **Conclusions:** Rezvilutamide plus ADT demonstrated superiority over bicalutamide plus ADT in delaying pain progression and functional status deterioration in high-volume mHSPC. Clinical trial information: NCT03520478. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Fractionated docetaxel (D) and radium 223 (Ra223) in metastatic castration-resistant prostate cancer (CRPC): A modular phase I trial.

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Background: Disease progression following novel hormonal therapy in CRPC remains bone-dominant and D-responsive. D + Ra223 would be a logical combination but myelosuppression is dose-limiting. Prior combinations have required a reduction in dose intensity (DI) in both agents. Fractionated schedules of D Q2weekly (DQ2) have comparable activity to D 75mg/m^2 Q3weekly with mitigated myelosuppression. We hypothesized that a fractionated schedule of DQ2 with standard Ra223 dosing would be feasible while preserving DI. **Methods:** Subjects had progressive bone-metastatic CRPC, ECOG PS 0-2, and no bulky visceral disease. Design was phase I, 6+6, dose escalation plus expansion with 28-day cycles. DQ2 was given in a 4-week lead-in, then with Ra223 every 4 weeks. Dose-level (DL) 1: D 40mg/m^2; if neutropenia, then 1a: D 40mg/m^2 with G-CSF on Day 16, 2a: D 50mg/m^2 with G-CSF on Day 16. Up to 6 cycles of the combination were given. Primary objective was the feasibility and maximum tolerated DL explored (MTD). Secondary objectives included PSA response, ORR, PFS, OS, and quality of life. **Results:** 43 patients (pts) enrolled including 34.9% non-white pts and 76.7% with ≥ 4 bony mets. 8 dropped out during the D lead in (1 each neutropenia, stroke, failure to thrive, anorexia/fatigue, thrombocytopenia, infusion reaction and 2 hospitalized for other reasons). At DL1, 2 of 3 had DLT (both neutropenia). No DLT occurred at DL1a (n=5) or DL2a (n=5). MTD was DL2a. 22 subjects enrolled to expansion cohort at DL2a. Of the 35 pts treated with D + Ra223, adverse events of interest listed in the table. No febrile neutropenia, fractures, or G5 toxicity were seen. 19/35 completed all 6 cycles of combination therapy. PSA50 response was seen in 18 (51.4%) and PSA90 in 9 (25.7%) pts. Of 31 pts with evaluable data, best response (RECIST 1.1) was 1 CR, 5 PR, 23 SD, 2 PD. Median PFS was 50.0 weeks (95% CI: 37.3-86.1) and OS was 86.1 weeks (95% CI: 60.0-130.9). 10 pts progressed exclusively in nodal/visceral metastases compared to 6 in bone only. Quality of life measures remained stable on study. **Conclusions:** Utilizing a D lead-in strategy, combination DQ2 and Ra223 was feasible and well tolerated, with a favorable PFS and evidence of preferential control of osseous metastases. Dose-intensity for both docetaxel and Ra223 was preserved and comparable to the FDA-approved dose-schedules for each of the single agents. The lead-in design and use of G-CSF contributes significantly to the feasibility. Clinical trial information: NCT03737370. Research Sponsor: Bayer HealthCare.

Adverse events of interest.

Adverse Event	Grade 1-2	Grade 3	Grade 4
Anemia	20 (57.1%)	2 (5.7%)	0 (0%)
Diarrhea	17 (48.5%)	1 (2.8%)	0 (0%)
Fatigue	26 (74.3%)	2 (5.7%)	0 (0%)
Febrile Neutropenia	————	0 (0%)	0 (0%)
Lymphopenia	22 (62.9%)	10 (28.5%)	3 (8.5%)
Neuropathy	14 (40%)	0 (0%)	0 (0%)
Neutropenia	12 (34.3%)	7 (20%)	2 (5.7%)
Thrombocytopenia	22 (31.4%)	0 (0%)	0 (0%)

5050 Poster Session

Association of tumor genetics with outcomes in patients (pts) with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) treated with ^{177}Lu-PSMA-617.

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Background: ^{177}Lu-PSMA-617 is approved for the treatment (tx) of mCRPC. Though tx is associated with improved survival, not all pts experience a benefit. Acquired resistance is common and some pts have intrinsic resistance. There is a lack of data on genomic markers that could aid in selecting pts for tx. In this study, we aim to characterize molecular predictors of benefit to ^{177}Lu-PSMA-617. **Methods:** We used the retrospective Prostate Cancer Precision Medicine Multi-Institutional Collaborative Effort (PROMISE) clinical-genomic database (n=2100). The primary endpoint was to investigate the association of genomic alterations with a ≥50% PSA decline (PSA50) from baseline following ^{177}Lu-PSMA-617. Associations were assessed using Wald-chi square test and Cox regression in multivariable analysis. Secondary endpoints included clinical progression-free survival (PFS) and overall survival (OS). **Results:** We identified 115 pts with PSMA PET+ mCRPC treated with ^{177}Lu-PSMA-617 who had commercial genetic sequencing prior to tx (median age 72 yrs, 25% non-white). Median number of prior lines for mCRPC was 3 with 71 pts (62%) receiving >1 androgen receptor signaling inhibitor (ARSI) and 55 pts (48%) receiving >1 taxane; 11 pts (9%) received ARSI with ^{177}Lu-PSMA-617. Overall, the PSA50 was 49% with median OS and PFS of 14.0 and 7.6 months (mos), respectively. In pts with a PSA50, median OS and PFS were 22.6 and 11.6 mos, respectively, vs 11.2 and 5.6 mos for those without a PSA50. Genetic alterations associated with PSA50 are in the table. PSA50 was 48% in pts with (n=32) vs 49% in pts without DDR alterations (n=83). PSA50 was 44% in pts with tumor suppressor gene alterations (TSGa) (*PTEN*, *p53*, *RB1*) (n=68) vs 56% in pts without (n=47). Median PFS was 7.6 vs 7.3 mos for pts with and without any TSGa (p=0.90), and median OS was 12.2 mos vs 22.6 mos for pts with and without TSGa (p=0.004). Of the 43 pts with AR alterations, 8/15 (53%) with LBD mutations, 10/27 (37%) with AR amplification, and 0/1 with AR-V7 had a PSA50. *FGFR*, *CDK12* and *MYC* alterations were enriched in individuals without a PSA50 (75-83%). **Conclusions:** We demonstrate that *CDK12*, *MYC* and *FGFR* alterations were associated with a lower PSA50 with ^{177}Lu-PSMA-617. Larger cohorts should be investigated for confirmation, as biomarkers to inform relative benefit of tx could be useful in prioritizing options for mCRPC. Research Sponsor: None.

	TP53 n=48	AR n=43	TMPRSS2 n=21	PTEN n=17	CDK12 n=10	BRCA1 n=4	BRCA2 n=8	MYC n=6	FGFR n=8	ATM n=6	SPOP n=4
PSA Response	23/48	18/43	10/21	8/17	2/10	2/4	5/8	1/6	2/8	4/6	2/4
	48%	42%	48%	47%	20%	50%	63%	16%	25%	67%	50%
No PSA Response	25/48	25/43	11/21	9/17	8/10	2/4	3/8	5/6	6/8	2/6	2/4
	52%	58%	53%	53%	80%	50%	38%	83%	75%	33%	50%
p-value	1.0	0.23	1.0	1.0	0.09	1.0	0.48	0.20	0.27	0.43	1.0

5051 Poster Session

Molecular and clinical correlates of high PSMA/*FOLH1* mRNA expression in primary and metastatic prostate cancer (PC).

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Background: The *FOLH1* gene encodes prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein that is expressed in PC cells. PSMA is a target for diagnostic imaging and treatment in PC. We utilized a database of molecularly profiled PC tumors to evaluate correlates of high *FOLH1* mRNA expression. **Methods:** NextGen sequencing of DNA (592-gene/whole exome) and RNA (whole transcriptome) was performed on PC specimens (n=7,558) through Caris Life Sciences. *FOLH1*-High/Low expression was defined as above/below median RNA transcripts per million (TPM). Androgen receptor (AR), neuroendocrine (NEPC), MAPK, and T-cell inflamed RNA signature scores were calculated. Tumor cell PD-L1+ expression (≥2+, ≥5%; SP142) was assessed by IHC. Overall survival (OS) and time on treatment (TOT) were calculated from time of diagnosis or therapy start. **Results:** Specimens were derived from the prostate gland (n=4495, 59.5%), lymph nodes (n=858, 11.4%), bone (n=568, 7.5%), liver (n=359, 4.7%), urinary tract (n=340, 4.5%), lung (n=116, 1.5%), and other metastatic sites (n=822, 10.9%). Relative to the prostate (390.9 TPM), *FOLH1* mRNA expression varied by metastatic site, with highest expression in lymph nodes (518.2 TPM, $p<0.001$) and lowest expression in lung (209.7 TPM, $p<0.001$) and liver metastases (143.1 TPM, $p<0.001$). Higher *FOLH1* expression significantly correlated with presence of AR-V7 variants (18% vs 15%) and *ASXL1* (6% vs 3.9%) alterations, and fewer alterations in *FOX1A* (7.9% vs 10.6%), *APC* (4% vs 10.3%), *PIK3CA*(3.1% vs 6.4%), *CTNNB1* (3.1% vs 4.8%), and *PIK3R1* (0.7% vs 2%). High *FOLH1* expression positively associated with AR signaling score, MAPK activation, and T-cell inflammation, and negatively correlated with NEPC signaling (all $p<0.001$). Tumors with high *FOLH1* expression were more frequently PD-L1+ (3.9% vs 2.2%, $p<0.01$). Among primary tumors, OS was similar between *FOLH1* high and low groups; however, among metastatic tumors, OS was improved in patients (pts) with high *FOLH1* expression compared to low expression (96.3 vs 87.9 months, HR 0.82 95% CI 0.73-0.92). There was no difference in TOT among pts receiving ARSIs, taxanes, or PARPi. Among 149 pts that received 177Lu-PSMA-617, there was a trend towards improved TOT in *FOLH1*-high (n=78) versus -low (n=71) tumors (HR 0.76, 95%CI 0.55-1.05). **Conclusions:** This is the largest combined genomic, transcriptomic and survival outcomes analysis of PSMA (*FOLH1*) expression in PC. In PC, greater *FOLH1* mRNA expression was associated with higher AR signaling scores and AR-V7 expression, and fewer mutations in the Wnt and PI3K pathways. *FOLH1*-high pts showed greater T cell inflammation and PD-L1 expression, and lower NEPC signaling. High *FOLH1* expression was associated with greater OS among patients with metastatic tumors, with a trend towards improved outcomes to 177Lu-PSMA-617. Such pts may benefit from distinct therapeutic strategies. Research Sponsor: None.

PLATIPARP: A phase 2 study of induction docetaxel and carboplatin followed by maintenance rucaparib in treatment of patients with mCRPC with homologous recombination DNA repair deficiency.

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Background: Genes involved in homologous recombination DNA repair (HR) are inactivated in ~25% of patients with metastatic castration-resistant prostate cancer (mCRPC). Inactivation of HR has been associated with sensitivity to DNA damage by platinum chemotherapy and PARP inhibitors (PARPi). While both drug classes have shown efficacy, resistance and/or cumulative dose-limiting toxicities are inevitably observed. Here, we report results from a single-center phase 2 study investigating whether induction chemotherapy (IC) with docetaxel and carboplatin followed by maintenance PARPi would provide prolonged disease control. **Methods:** Patients with mCRPC tumors harboring a pathogenic alteration in an HR gene, who had received prior taxane and/or androgen receptor pathway inhibitor (ARPI), but not prior PARPi were eligible. Patients received IC with 4 cycles of docetaxel 60mg/m^2 with carboplatin AUC 5 IV q21 days, followed by the PARPi rucaparib 600mg BID continuously as maintenance therapy until disease progression or unacceptable toxicity. The primary endpoint was clinical/radiographic progression free survival (PFS) compared to a historical control of 9.1 months with PARPi alone without prior platinum. 20 patients provided ~90% power to determine whether this treatment lowered risk of progression with a hazard ratio of 0.5 (implying PFS of 18.2 months), based on a 1-sided 1-sample log-rank test. Secondary endpoints included PSA_{50} response rate, safety, and overall survival. Post-hoc subgroup analysis was performed for the BRCA complex group (alterations in *BRCA1*, *BRCA2*, and *PALB2*) and for those refractory to IC. **Results:** 18 patients were enrolled between 2018 and 2021. Under-enrollment occurred due to loss of manufacturer support for rucaparib prior to study completion. 11/18 (61%) of patients had ≥2 prior ARPI, and 9/18 (50%) had previously received docetaxel. HR genes included on study were *ATM* (7), *BRCA1* (3), *BRCA2* (8), *PALB2* (1), *FANCA* (1) and *CHD1/SPOP* (1) with three tumors harboring two alterations. Clinical outcomes for the overall cohort and key sub-groups are reported in the table. 6/18 (33%) patients experienced grade ≥3 adverse events, including one patient with grade 4 thrombocytopenia. **Conclusions:** IC followed by maintenance rucaparib did not significantly increase PFS in patients with HR alterations compared to historical control. Results were more encouraging in the BRCA complex group. IC refractory patients were not rescued by subsequent PARPi, suggesting overlapping mechanisms of resistance when platinum is used prior to PARPi. Clinical trial information: NCT03442556. Research Sponsor: None.

Group	PSA_{50}	PFS (months)	OS (months)
Overall	12/18 (67%)	8.1 (6.5- NR)	18 (12.8 – NR)
BRCA complex	8/12 (67%)	17.7 (7.5 – NR)	26.9 (14.0 – NR)
Other HR	4/6 (67%)	6.7 (5.8 – NR)	13.2 (10.9 – NR)
Refractory to IC	0/6 (0%) *(with subsequent rucaparib)*	5.9 (4.9 – NR)	11.2 (7.7 – NR)

Real-world comparative effectiveness and cardiovascular safety of enzalutamide versus abiraterone amongst older men diagnosed with metastatic castration-resistant prostate cancer.

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Background: Abiraterone and enzalutamide are frequently used in treating metastatic castration-resistant prostate cancer (mCRPC), and their use has expanded to castration-sensitive and non-metastatic settings. The objective of this study was to compare real-world overall survival and risk of major adverse cardiovascular events (MACE) between initiators of abiraterone and enzalutamide in a cohort of older adult men with mCRPC. **Methods:** The Surveillance Epidemiology and End Results-Medicare database was leveraged to design a comparative observational study. Initiators of abiraterone or enzalutamide between 2011-2017 were identified, a period when both drugs were only approved for mCRPC. Propensity scores and inverse-probability-of-treatment weighting were used to balance measured confounders. MACE was defined as a hospitalization for myocardial infarction, heart failure, or ischemic stroke or transient ischemic attack. Hazard ratios were obtained from weighted Cox proportional hazards (mortality) and Fine-and-Gray models (MACE). **Results:** The study population consisted of 5,633 men 66 years of age and older diagnosed with mCRPC, of which 3,720 initiated abiraterone and 1,913 enzalutamide. The median age at initiation was 77. Compared to enzalutamide initiators, the overall survival was similar in patients initiating abiraterone at both one-year (mortality hazard ratio (HR) = 1.05; 95% CI: 0.95 – 1.17) and five-years of follow up (HR= 1.01; 95% CI: 0.95 – 1.08). The one-year risk of MACE was higher in abiraterone initiators (HR = 1.30; 95% CI: 1.01 – 1.67). The agents displayed similar effects on MACE when considering a five-year follow-up period after therapy initiation (Table). **Conclusions:** The long-term comparative effectiveness and cardiovascular safety of abiraterone and enzalutamide were similar, though a short-term increase in MACE was seen in abiraterone initiators, highlighting the importance of considering cardiovascular risk and cancer prognosis during therapy selection. Research Sponsor: None.

Outcomes in a propensity-score weighted population of older adult men diagnosed with mCRPC initiating abiraterone or enzalutamide between 2011-2017.

	Abiraterone (n = 3,720) Percentage (95% CI)	Enzalutamide (n = 1,913) Percentage (95% CI)	Measures of Contrast (Abiraterone vs. Enzalutamide)	
			Percentage Point Difference (95% CI)	HR (95% CI)
Overall survival				
1-year	67.1 (65.6, 68.7)	67.9 (65.7, 70.1)	-0.8 (-3.5, 1.9)	1.05 (0.95, 1.17)
5-year	16.2 (15.0, 17.4)	16.0 (14.3, 17.8)	0.1 (-2.0, 2.3)	1.01 (0.95, 1.08)
MACE risk				
1-year	5.9 (5.1, 6.7)	4.5 (3.5, 5.4)	1.4 (0.2, 2.7)	1.30 (1.01, 1.67)
5-year	12.2 (11.0, 13.3)	12.6 (11.0, 14.3)	-0.4 (-0.2, 1.5)	1.04 (0.88, 1.23)

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event.

Real-world baseline treatment patterns and overall survival (rwOS) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with olaparib in the United States.

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Background: Olaparib is one of the first targeted therapies for pts with mCRPC. Real-world data on treatment patterns prior to receiving olaparib are limited in mCRPC pts with homologous recombination repair gene mutation (HRRm). This study describes real-world novel hormonal agent (NHA) use by clinical setting prior to receiving olaparib in mCRPC and rwOS in pts with HRRm mCRPC treated with olaparib monotherapy. **Methods:** HRRm+ pts with confirmed mCRPC diagnosis, age ≥21 years, treated with olaparib monotherapy (post May 19, 2020) and prior to abiraterone or enzalutamide were abstracted from electronic medical records in the ConcertAI Oncology Dataset with PC diagnosis between 1990 and 2023. HRR genes of interest were *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L.* Frequency of pts who progressed from metastatic hormone-sensitive PC (mHSPC) and from non-metastatic CRPC (nmCRPC) to mCRPC and treatment patterns prior to mCRPC were summarized. Kaplan-Meier analysis was used to describe the rwOS from the start date of earliest olaparib monotherapy treatment (index date). **Results:** A total of 144 mCRPC olaparib treated pts were identified [median age 73 years; any BRCAm including co-occurring HRRm 56.3%; White 73.6%; ECOG 0-1 at index 78.4%; Gleason ≥8 at index 66.7%]. Of the 144 pts, 80.5% of pts progressed from mHSPC, 11.8% of pts progressed from nmCRPC, and 7.6% of pts were identified in mCRPC setting. For pts who progressed from mHSPC, 62.1% were NHA-treated in the mHSPC setting. Overall, 43.8% initiated olaparib monotherapy in the first 2 lines of therapy after mCRPC diagnosis while 15.3% initiated olaparib in 5L+ (Table). Among pts diagnosed with mHSPC before mCRPC, olaparib was most frequently received in 2L (26.7%) and in 3L (22.4%). For mHSPC pts treated with NHA, olaparib was most frequently received in 2L (31.9%); in contrast, for mHSPC pts that were NHA-naïve, olaparib was most frequently received in the 5L+ (29.5%). The overall median rwOS from olaparib initiation was 16.5 (95% CI: 12.4, 21.1) months; and 20.3 (95% CI: 14.7, 26.8) and 12.9 (95% CI: 10.9, 16.9) months, respectively, for pts with and without any BRCA mutations. **Conclusions:** This real-world analysis indicates many mCRPC pts with HRRm are receiving several lines of therapy prior to olaparib, even when NHA are used prior to mCRPC. Earlier treatment with olaparib monotherapy may improve duration of therapy and overall survival. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and AstraZeneca UK Ltd, who are codeveloping olaparib.

Line of earliest olaparib monotherapy from time of mCRPC diagnosis.

Line of Therapy, n (%)	Overall N=144	mHSPC → mCRPC N=116	NHA Treated in mHSPC → mCRPC N=72	NHA Naïve in mHSPC → mCRPC N=44
1L	25 (17.4)	22 (19.0)	22 (30.6)	0 (0.0)
2L	38 (26.4)	31 (26.7)	23 (31.9)	8 (18.2)
3L	33 (22.9)	26 (22.4)	14 (19.4)	12 (27.3)
4L	26 (18.1)	21 (18.1)	10 (13.9)	11 (25.0)
5L+	22 (15.3)	16 (13.8)	3 (4.2)	13 (29.5)

Circulating tumour DNA fraction as a predictor of treatment efficacy in a randomized phase 2 trial of [^{177}Lu]Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel (TheraP ANZUP 1603).

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Background: The TheraP trial showed that for patients with PSMA-positive, non-FDG-discordant mCRPC progressing after docetaxel, LuPSMA significantly improved biochemical and objective response rates, progression-free survival (PFS), and quality of life compared to cabazitaxel. While subsequent studies nominated high PSMA SUVmean to inform patient prioritization for LuPSMA, limited genomic data exists to guide optimal selection of these two life-prolonging therapies. We present an exploratory analysis of ctDNA fraction (ctDNA%) in baseline samples from the TheraP trial. **Methods:** We analyzed 180 baseline blood samples from participants who received ≥1 cycle of protocol-assigned treatment. Plasma cell-free DNA and matched white blood cell DNA underwent targeted sequencing to estimate ctDNA%. Prespecified ctDNA% categories (<2%, 2-30%, and >30%) were associated with previously validated imaging thresholds (PSMA SUVmean ≥10 and FDG metabolic tumor volume [MTV] ≥200mL), rate of PSA reduction ≥50% (PSA50-RR), and PFS, using chi-square test, logistic regression and Cox regression, respectively. **Results:** ctDNA% was evaluable in 178 (99%) participants, with ctDNA ≥2% in 85%. Median ctDNA% was 28% in ctDNA≥2% samples, and balanced across treatment arms. The odds of a PSA50 response to LuPSMA vs cabazitaxel were significantly higher for men with ctDNA <2% (OR infinite, p=0.0067; PSA50-RR 100% vs 58%), with no difference at ctDNA >30% (OR 1.1, p=1.0; PSA50-RR 46% vs 44%). Higher ctDNA% was associated with shorter PFS in LuPSMA- but not cabazitaxel-treated patients (LuPSMA: HR 5.0, p<0.001 for ctDNA <2% vs >30%; cabazitaxel: HR 1.4, p=0.35 for ctDNA <2% vs >30%; interaction p=0.035). The predictive potential of ctDNA% was additive to PSMA SUVmean in LuPSMA-treated patients. Higher ctDNA % categories were enriched for patients with high FDG MTV and low PSMA SUVmean disease (Table). **Conclusions:** ctDNA% is a candidate predictive and prognostic biomarker for differential response to LuPSMA versus taxane chemotherapy in patients with molecular imaging-selected mCRPC progressing after docetaxel. Clinical trial information: NCT03392428. Research Sponsor: Partnership between ANZUP Cancer Trials Group and the Prostate Cancer Foundation of Australia (PCFA); Australian Nuclear Science and Technology Organisation (ANSTO); Endocyte Inc. (a Novartis Company); Movember; The Distinguished Gentleman's Ride; It's a Bloke Thing; CAN4CANCER; Prostate Cancer Foundation Challenge Award; Terry Fox New Frontiers Program Project Grant; Canadian Cancer Society Challenge Grant; ANZUP Synchrony Fellowship Award.

	LuPSMA (ctDNA Categories)			Cabazitaxel (ctDNA Categories)			LuPSMA (PSMA SUVmean and ctDNA Category)			
	<2% (n=17)	2-30% (n=42)	>30% (n=37)	<2% (n=12)	2-30% (n=38)	>30% (n=32)	≥10 + <2% (n=12)	<10 + <2% (n=4)	≥10 + ≥2% (n=22)	<10 + ≥2% (n=58)
PSA50-RR	100%	69%	46%	58%	42%	44%	100%	100%	86%	48%
Odds ratio (LuPSMA *vs* cabazitaxel)	<2%: OR infinite, p=0.0067 2-30%: OR 3.1, p=0.024 >30%: OR 1.1, p=1.0									
Median PFS (mo)	14	5.1	3.0	6.0	5.1	2.8	16	13	6.9	3.2
HR (95% CI)	Ref	3.0 (1.6-5.5)	5.0 (2.6-9.3)	Ref	1.1 (0.57-2.2)	1.4 (0.70-2.8)	Ref	1.4 (0.44-4.6)	2.7 (1.2-5.9)	5.0 (2.5-10)
FDG MTV ≥200mL	0%	24%	46%	0%	11%	56%				
p	<0.001			<0.001						
PSMA SUVmean ≥10	76%	36%	16%	33%	37%	16%				
p	<0.001			0.13						

BRCA1/2 reversion mutations (*BRCA*rev) in advanced prostate cancer in the absence of prior PARP inhibitor (PARPi) therapy.

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Background: In prostate cancer (PCA), *BRCA1/2* alterations confer sensitivity to PARPi; however, in cases other than PCA with homozygous *BRCA* deletions, somatic *BRCA*rev may restore *BRCA*function and mediate treatment resistance. In this study, we analyzed liquid biopsies of men with advanced PCA to (1) identify *BRCA*rev, (2) to determine the clinical context in which *BRCA*rev developed, and (3) to ascertain potential effect of prior chemotherapy on duration of PARPi response. **Methods:** *BRCA1/2*mutations were examined via liquid biopsies (FoundationOne Liquid CDx) during the course of clinical care for PCA patients during a 12-month period (from 01/2023 to 12/2023). Clinicopathological features and treatment history were extracted from medical records and/or treating oncologists' notes. **Results:** Among 416 PCA patients with detected *BRCA1/2* alterations, 25 (6.0%) patients harbored *BRCA*rev that were predicted to restore *BRCA* function. Ten of 25 (40%) patients had detailed clinical and treatment history available. In three of 10 (30%) patients, somatic *BRCA*rev were detected in the absence of prior PARPi therapy. All three PARP-naïve patients had been previously treated with chemotherapy (platinum or docetaxel) and radiation. Two patients had castration-resistant prostatic adenocarcinoma, while the third patient had de novo high-stage prostatic small cell neuroendocrine carcinoma without prior androgen deprivation. In all three PARP-naïve patients, multiple reversion mutations were detected per patient post-chemotherapy/radiation. Two of the three patients were predicted to have an original germline *BRCA2*alteration. The remaining 7 *BRCA*rev-positive patients (70%) had prior PARPi treatment (all Olaparib). In PARPi-treated patients, duration of PARPi treatment prior to identification of *BRCA*rev ranged from 5 to 24 months. 4 out of 7 PARPi-treated patients had received prior docetaxel, and duration of PARPi response was longer in chemo-naïve patients compared with those who had received prior docetaxel before PARPi (Mean: 18.6 vs 8.3 months, respectively). **Conclusions:** In men with *BRCA*-mutated PCA, chemotherapy and/or radiation may induce *BRCA*rev in the absence of PARPi therapy. Testing of post-chemotherapy or radiation patients for *BRCA*rev may be warranted prior to the start of PARPi therapy in patients with PCA. Our results support early PARPi therapy prior to radiation or chemotherapy as post-chemotherapy/radiation *BRCA*rev may potentially dampen the future success of subsequent PARPi strategies. Research Sponsor: None.

Clinicopathological features of PCA patients with *BRCA*rev in the absence prior PARPi therapy.

n	Original Mutation	PCA Type	Castration Resistant	Prior Chemo	Prior XRT
1	*BRCA2* T2542fs*9	NE	NO	YES, platinum	YES
2	*BRCA1 K459fs*15*	ACA	YES	YES, docetaxel + platinum	YES
3	*BRCA2 L2092fs*7*	ACA	YES	YES, docetaxel	YES

NE=neuroendocrine, ACA=adenocarcinoma, XRT=radiation.

Association of genomic alterations with clinical outcomes following lutetium-177-PSMA vipivotide tetraxetan in men with metastatic castrate-resistant prostate cancer.

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Background: Lutetium-177-PSMA vipivotide tetraxetan (Lu177) is approved for men with PSMA-positive metastatic castrate-resistant prostate cancer (mCRPC) previously treated with androgen receptor signaling inhibitors and taxane chemotherapy. The tumor genomic alterations conferring sensitivity or resistance to Lu177 are unknown. We investigated the association of genomic variants with clinical outcomes in men with mCRPC treated with Lu177. **Methods:** Somatic & germline DNA sequencing data were examined from men treated with ≥1 cycle Lu177 at The James Cancer Hospital of The Ohio State University from 3/2022 – 10/2023. Pathogenic variants from tissue or blood testing were identified. Sets of genes with similar biological function were annotated, including homologous recombination repair (HRR) genes (*BRCA1*, *BRCA2*, *ATM*, *CDK12*, *CHEK1*, *CHEK2*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*), established tumor suppressor genes (*TP53*, *RB1*, *PTEN*) and cell cycle genes (*CCND1*, *CCND3*, *CDK4*, *CDK6*, *CDK12*, *CDKN1B*, *CDKN2B*) associated with prostate cancer. The impact of genomic variants on PSA50 response (Chi-Square & Fisher's exact test), median overall survival (OS) and median progression-free survival (PFS) (Kaplan-Meier method) and OS or PFS (Cox proportional hazards model) was assessed. **Results:** Of 153 patients treated with Lu177, 120 underwent genomic sequencing: 109 had somatic testing (76 tissue-based, 33 blood-based), 50 had germline and 39 had both somatic & germline testing. Patients with amplification of cell cycle genes (n=8) had poorer OS of 5.1 months (mos.) vs 13.4 mos. for those without amplification (p=0.001, HR 4.26, 95% CI 1.79-10.11), and shorter PFS of 4.3 vs 7.4 mos. (p=0.027, HR 2.40, 95% CI 1.10-5.22). Patients with loss or mutation of HRR genes (n=32) had OS of 13.7 vs 12.2 mos. for those with no HRR alterations, but this was not significant (p=0.101, HR 0.57, 95% CI 0.29-1.12). No other genomic alterations were significantly associated with OS or PFS and none were associated with PSA50 response. The table lists the most frequently altered genes in PSA50 responders vs non-responders (differences not significant by Fisher's exact test). **Conclusions:** Genomic alterations warrant investigation in larger cohorts as prognostic and predictive biomarkers for Lu177 therapeutic response. Our data suggest that amplification of genes impacting cell cycle regulatory pathways may be of particular interest. Our findings support continued efforts to determine the impact of cyclin dependent kinase (CDK) 4/6 inhibitors for high-risk and metastatic prostate cancer, either alone or in combination with agents such as Lu177. Research Sponsor: National Cancer Institute; K12CA133250.

Frequently altered genes by PSA50 response (n=58 in each group).

	# Of Responders With Alteration	# Of Non-Responders With Alteration
TP53	23	18
AR	12	15
TMPRSS2-ERG	10	12
PTEN	8	11
DNMT3A	7	4
MYC	6	6
APC	3	7
BRCA2	5	5
ATM	4	5

Biomarker assessment and pharmacology of HP518, an AR PROTAC degrader from the phase 1 dose-escalation study in patients with metastatic castration-resistant prostate cancer (mCRPC).

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Background: HP518 is an oral PROteolysis TArgeting Chimera (PROTAC) protein degrader that degrades both wild-type AR and clinically relevant AR ligand-binding domain (LBD) mutants including L702H. To evaluate the safety, PK, and anti-tumor activity of HP518, and select a recommended phase 2 dose (RP2D), we conducted a first-in-human, Phase 1, open-label, multicenter, non-randomized, dose escalation study in pts with mCRPC. We report biomarker, pharmacology and efficacy data from this Phase 1 study. **Methods:** Pts with mCRPC with disease progression on at least 1 novel hormonal agent (NHA) and $\leq$ 1 line of chemotherapy received HP518 QD orally in sequential cohorts (25, 50, 100, 200, and 300, 400, 500 mg per day, Bayesian N-CRM design). Primary objectives were to assess HP518 safety and select the RP2D. Secondary objectives included evaluating the PK of HP518, PSA50 response and radiographic progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and Prostate Cancer Working Group 3 (PCWG3) criteria. Exploratory objectives were to evaluate AR expression in circulating tumor cells (CTCs) at the highest dose cohort before and after 12 weeks of treatment and genomic profile using cell-free DNA (cfDNA). **Results:** As of 29Jan2024, a total of 22 pts were enrolled. Overall, HP518 was well tolerated, with a favorable safety profile. No DLT, and a cumulative of ten SAE (1 related/9 unrelated) were observed. There were twelve Grade $\geq$3 treatment-emergent adverse events (TEAEs) in 6 pts treated up to 500 mg; no grade $\geq$4 TEAEs. The most common TEAE in all cohorts was grade 1 or 2 vomiting and nausea. PSA50 response was seen in 3 pts. 2 pts had confirmed partial responses (PR) per RECIST criteria. 2 pts received HP518 for $\geq$24 weeks including 1 pt with a durable PSA50 and PR response for 52 weeks. Following multiple oral doses of HP518, median peak plasma concentrations were observed at 3 -12h post-dose. Over the 5-fold dose range (100 to 500 mg), the increase in Cmax and AUC0-last was approximately dose proportional on day 1. A steady state was reached after day 56. ctDNA data were available from 19 pts, of which four patients were diagnosed with AR LBD mutations. Three LBD mut non-responder pts had low drug exposures. In addition, one AR LBD mut patient had high mutational burden suggestive of AR-independent resistance. cDNA and CTC analysis showed diverse molecular changes in the AR including four pts with AR-V7 splice variant as well as non-AR resistance patterns in most patients. **Conclusions:** HP518, a novel AR PROTAC degrader, demonstrated encouraging efficacy in mCRPC pts, with responses seen in patients with full-length AR, AR LBD mutations, and AR amplification. These data support further investigation of HP518 in mCRPC pts. Clinical trial information: NCT05252364. Research Sponsor: Hinova Pharma.

5059 Poster Session

Rezvilutamide (REZ) plus docetaxel (DOC) in patients (pts) with chemo-naïve metastatic castration-resistant prostate cancer (mCRPC) after progression on abiraterone (ABI).

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Background: Despite DOC is recommended for chemo-naïve mCRPC pts previously treated with novel hormone therapy, prognosis remains unfavorable. Herein we report the safety, PK, and preliminary efficacy of addition of REZ (a novel androgen receptor inhibitor) to DOC in chemo-naïve mCRPC pts who had progressed after ABI. **Methods:** This was a multicenter, 2-part, phase 2 study. Part 1 included a 3 + 3 dose escalation phase and a dose expansion phase. Eligible pts were enrolled to receive REZ (160/240 mg, PO, QD) plus DOC (75 mg/m^2, IV, D1, Q3W, up to 10 cycles [C]), followed by REZ monotherapy (240 mg, PO, QD). REZ was given continuously staring from C1D2. DOC was concurrent with prednisone (5 mg, PO, BID). Both dose levels of REZ were selected to be expanded. Primary endpoint of part 1 was safety. **Results:** As of Aug 31, 2023, 36 pts were enrolled (18 with REZ 160 mg plus DOC and 18 with REZ 240 mg plus DOC). In the REZ 160 mg plus DOC and REZ 240 mg plus DOC groups, rate of pts with ECOG PS of 1 was 83.3% and 61.1%, rate of pts with Gleason score $\geq$ 8 was 88.9% and 72.2%, rate of pts with >10 bone metastases was 66.7% and 44.4%, and median baseline prostate-specific antigen (PSA) level was 81.7 ng/mL (range: 2.7-5993.0) and 144.0 ng/mL (2.9-3720.0). No DLTs were reported. Treatment-related adverse events of grade $\geq$ 3 occurred in 32 (88.9%) pts (14 [77.8%] pts with REZ 160 mg plus DOC, and 18 [100.0%] pts with REZ 240 mg plus DOC), with the most common being decreased neutrophil count, decreased white blood cell count, and anemia. C2/C1 ratio of AUC_{0-24h} and C_{max} of DOC was 0.73 and 0.78 when combined with REZ 160 mg, while that was 0.58 and 0.68 when combined with REZ 240 mg, which indicated influence of CYP3A strong inducer REZ on CYP3A4 substrate DOC with stronger impact at REZ 240 mg. Rate of PSA response at week 12 was 75.0%, time to PSA progression was 10.5 mo (95% CI, 5.6-11.3), and radiological PFS was 13.8 mo (95% CI, 5.7-19.6) with REZ 160 mg plus DOC, while that with REZ 240 mg plus DOC was 60.0%, 14.1 mo (95% CI, 4.1-21.4), and 8.5 mo (95% CI, 5.6-not reached) (Table). **Conclusions:** REZ plus DOC was well tolerated with promising efficacy in chemo-naïve mCRPC pts who had progressed after ABI. Clinical trial information: NCT04603833. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy.

	REZ 160 mg plus DOC	REZ 240 mg plus DOC	Overall
Rate of PSA response at week 12*	12 (75.0)	9 (60.0)	21 (67.7)
Rate of PSA decline ≥50% from baseline§	14 (77.8)	13 (72.2)	27 (75.0)
Time to PSA progression, mo§	10.5 (5.6-11.3)	14.1 (4.1-21.4)	10.5 (5.6-14.1)
Radiological PFS, mo§	13.8 (5.7-19.6)	8.5 (5.6-NR)	10.9 (8.4-19.2)
OS, mo§	19.5 (12.9-27.4)	14.5 (9.9-19.9)	16.2 (12.9-22.5)
ORR#	2 (50.0)	0	2 (15.4)
DCR#	4 (100.0)	7 (77.8)	11 (84.6)

Data are n (%) or median (95% CI). *Assessed in pts with at least one PSA level measurement at week 12 and later; N was 16, 15, and 31. §Assessed in full analysis set; N was 18, 18, and 36. #Assessed in pts with baseline soft tissue lesions; N was 4, 9, and 13. NR, not reached.

5060 Poster Session

ODM-209, a CYP 11A1 inhibitor in patients with mCRPC: Results from the STESIDES phase 1 study.

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Background: ODM-209 is a novel, oral selective inhibitor of CYP11A1, that blocks production of all steroid hormones and precursors that may activate hormone receptor (e.g. androgen or estrogen) signaling pathways. It's mode of action is similar to ODM-208/MK-5684 currently in phase 3 clinical development in patients with metastatic castration resistant prostate cancer (mCRPC). We report the results of the first-in-man phase I STESIDES study (NCT03878823). **Methods:** STESIDES was a dose finding Phase 1 trial with a 3+3 design in patients with progressive mCRPC who had previously received ≥1 line of AR signalling inhibitor and ≥1 line of taxane-based chemotherapy. Four patients with ER-positive/HER2 negative (ER+/HER2-) breast cancer (BC) were also enrolled. ODM-209 was administered once or twice daily with glucocorticoid and mineralocorticoid replacement therapy and androgen deprivation therapy (in men with mCRPC). Endpoints included dose-limiting toxicities (DLTs), adverse events (AE's), pharmacokinetics, pharmacodynamics, PSA and RECIST response, and exploratory molecular profiling. Patients with and without androgen receptor ligand-binding domain(*AR*-LBD) activating mutations were included. **Results:** 38 patients (median age 67 yrs.) received ODM-209 in doses ranging from 10 to 20 mg/day. Of 34 patients with mCRPC, 18 (53%) had previously received both abiraterone and enzalutamide, and 18 (53%) patients both docetaxel and cabazitaxel; 19 patients (56%) had activating *AR*-LBD mutations detected at baseline. All 4 BC patients had ESR1 mutations. Steroid hormone concentrations were mostly undetectable on treatment as expected. Patients generally tolerated the treatment well. The most commonly reported AE's were fatigue (53%) and peripheral oedema (34%). Adrenal insufficiency was recorded in 4 patients (11%), of which 2 were considered serious, 1 case being a DLT in a patient with BC at 15 mg/day. Hyponatremia (21%) and hyperkalemia (16%) were also common and used as an indication to increase corticosteroid replacement dose. In patients with mCRPC serum testosterone was undetectable (limit of detection 0.2 ng/dL) in almost all patients in all dose groups at Day 8 and remained so at 16 weeks. 10 (29%) patients with mCRPC achieved a PSA decline of ≥50%, being 9/19 (47%) and 1/15 (7%) in patients with and without *AR*-LBD mutations respectively. 3/11 (27%) evaluable patients with mCRPC achieved a partial response by RECIST (1 in an *AR*-LBD wild-type patient). No responses were seen in patients with BC. The median duration of treatment was 4.8 and 3.7 months in mCRPC patients with and without activating *AR*-LBD mutations. **Conclusions:** Phase 1 results of ODM-209 suggest activity in heavily pre-treated patients with mCRPC particularly in those with activating AR-LBD mutations, with expected on-target AE's. Similar findings were recently reported with ODM-208/MK-5684 (NEJM Evidence 2023). Clinical trial information: NCT03878823. Research Sponsor: Orion Corporation.

5061 Poster Session

Phase 1 trial of mevrometostat (PF-06821497), a potent and selective inhibitor of enhancer of zeste homolog 2 (EZH2), in castration-resistant prostate cancer (CRPC).

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Background: Mevrometostat (M; PF-06821497) is a potent and selective small molecule inhibitor of EZH2. Dose exploration of M in combination with enzalutamide (E) plus androgen deprivation therapy showed a manageable safety profile and preliminary evidence of objective response (OR), decline in prostate-specific antigen (PSA) to ≥50% of baseline (PSA_{50}), and peripheral pharmacodynamic (PD) modulation in patients (pts) with CRPC in part 2A of a phase 1/2 study (NCT03460977; Schweizer, ESMO 2022, 488P). We report longer term follow up from the dose escalation cohort of M+E in CRPC. **Methods:** This is an open-label, phase 1/2 study of M (orally, 150-1250 mg twice daily) + E (160 mg daily) in adult pts with CRPC who had received prior abiraterone (A) and/or E and had evidence of cancer progression per Prostate Cancer Working Group 3 (PCWG3) criteria at entry. The primary endpoint was safety. Pharmacokinetics, radiographic progression-free survival (rPFS), PSA_{50}, and OR by PCWG3 were also assessed. Dose/response relationship of M on-target H3K27Me3 PD modulation in whole blood and tumor biopsies and circulating tumor DNA mutational profiling were exploratory endpoints. **Results:** As of November 2, 2023, 47 pts had received ≥1 dose of study treatment. Median (interquartile range) duration of follow up was 9.7 (2.0-22.8) months (mo). Median (range) age was 70 (53-87) years. Overall, 57.4% of pts had received prior A, 74.5% had received prior E and 48.9% had received prior taxane therapy. As of data cut, 18 events were observed (14 progression events and 4 deaths). Median (95% CI) rPFS was 17.0 (6.3, not estimable [NE]) mo in the total population; 17.1 (6.2, NE) mo for pts who received prior A (without E) (n=12), and 11.7 (4.2, NE) mo for pts who received prior E (± A) (n=35). Confirmed PSA_{50} (95% CI) was observed in 14.9% (7.0, 31.4) of pts. In 22 pts with baseline measurable disease, OR rate (95% CI) was 27.3% (10.7, 50.2), including 1 complete and 5 partial responses. Geometric mean (95% CI) H3K27Me3 reduction was -75% (-93, -11) for M+E at 1250 mg M (twice daily) in tumor-paired biopsies (n=6). Durable antitumor activity was observed in both post-A (without E) and post-E (± A) pts with and without androgen receptor and/or TP53 mutations. Adverse events (AEs) led to treatment discontinuation in 9 (19.1%) pts. The most common treatment-emergent AEs (TEAEs) considered related to M were diarrhea (42.6%), dysgeusia (42.6%), and anemia (36.2%). Grade ≥3 TEAEs considered related to M were reported in 17.0% of pts. Serious TEAEs related to M were observed in 6.4% of pts. No treatment-related deaths were observed. **Conclusions:** M+E shows promising activity in both post-A (without E) and post-E (± A) pts with CRPC with evidence of tumor PD modulation and with a manageable AE profile. Further investigation of M+E in pts with CRPC is warranted. Clinical trial information: NCT03460977. Research Sponsor: Pfizer Inc., and Astellas Pharma Inc. provided enzalutamide for this study.

Race and decisional conflict about genetic testing in patients with advanced prostate cancer.

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Background: Guideline recommended genetic testing in advanced prostate cancer (PC) is underutilized and not always accepted by patients (pts). We assessed attitudes and decisional conflict (DC) surrounding genetic testing associated with subsequent test completion, and differences between white and nonwhite pts. **Methods:** Eligibility for this prospective single institution study included pts with N1 or M1 PC who had not yet completed genetic testing. Upon informed consent, pts were given a 24-question survey using a Likert scale of 0 (strongly agree) to 4 (strongly disagree) to assess attitudes toward genetic testing including a validated assessment of DC. DC and DC subscores (range 0-100, with 100 being highest DC) were calculated from subsets of survey responses. Self-identified race was obtained from the EMR. Two-group comparisons between white and nonwhite pts, and between those who completed genetic testing and who did not, were conducted with SAS v9.4 software using Fisher's exact test for categorical variables and Wilcoxon rank sum test for Likert scale survey questions and DC score variables. **Results:** Of 42 enrolled pts (21 white, 17 black, 1 Asian, 3 declined), 22 (52.4%) completed genetic testing. Compared to white pts, nonwhite pts expressed more concern about test result privacy (mean = 1.72 v 2.95, p = 0.002), test results being used for non-healthcare purposes (1.78 v 3.00, p = 0.003), and trying unproven treatments (1.72 v 2.67, p = 0.01). Nonwhite pts felt more external pressure in decision-making compared to white pts (0.67 v 0.29, p = 0.04). No significant differences were appreciated in completion of testing, DC, or any subscore between racial groups. Compared to pts who did not complete testing, those who completed testing were more likely to report they knew which options were available (0.73. v 1.25, p = 0.05), knew the benefits of each option (0.77 v 1.30, p = 0.04), knew the risk and side effects of each option (0.95 v 1.50, p = 0.05), were clear about which benefits matter most to themselves (0.73 v 1.37, p = 0.02), and were clear about the best choice for themselves (0.73 v 1.35, p = 0.02). DC (28.59 v 18.11, p = 0.03) was higher in pts who did not complete testing, along with uncertainty (31.25 v 19.32, p = 0.02) and informed (31.25 v 20.45, p = 0.03) subscores. No differences were seen in values clarity, support, or effective decision subscores. **Conclusions:** In our study, nonwhite pts expressed greater concern about privacy, data misuse, and trying unproven treatments. Those who did not complete testing had more DC with greater uncertainty about knowledge and decision making. These findings will help direct targeted interventions to increase knowledge, trust, and decisional certainty about genetic testing in pts with advanced PC. Ongoing studies will assess the impact of these interventions on rates of testing completion at our institution. Research Sponsor: None.

Matching-adjusted indirect comparisons (MAICs) of talazoparib plus enzalutamide (TALA+ENZA) versus olaparib plus abiraterone and prednisone/prednisolone (OLAP+AAP) for first-line (1L) therapy in patients with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair mutations (HRRm)/BRCAm.

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Background: Poly-ADP ribose polymerase inhibitors (PARPi) in combination with a novel hormonal therapy (NHT) have shown benefit for the 1L treatment of mCRPC in an all-comers population as well as HRRm and BRCAm subpopulations (TALA+ENZA [TALAPRO-2; NCT03395197] and OLAP+AAP [PROpel; NCT03732820]). In the absence of head-to-head studies, their comparative efficacy is unknown. The relative efficacy of TALA+ENZA (n=200 HRRm; n=71 BRCAm) vs OLAP+AAP (n=111 HRRm; n=47 BRCAm) in these subpopulations were estimated using MAICs for radiographic progression-free survival (rPFS) based on blinded independent central review and overall survival (OS). **Methods:** Unanchored MAICs were conducted using individual patient data from TALAPRO-2 Cohort 2 (data cutoff [DCO]: 03/10/22 [rPFS/OS]) and published summary level data from PROpel (DCO: 30/07/21 [rPFS]; 12/10/22 [OS]). To align across the two trials, patients from TALAPRO-2 with specific HRRm/BRCAm (co-occurring or standalone) that were not assessed in PROpel were removed from the dataset for each analysis. TALAPRO-2 patients were also matched based on PROpel's eligibility criteria and characteristics were adjusted for key prognostic factors identified in the literature and clinical expertise including prior taxane chemotherapy in castration sensitive prostate cancer (CSPC), visceral metastasis, bone only metastasis, Eastern Cooperative Oncology Group score, prostate-specific antigen levels, Gleason score, BRCA1 and BRCA2. **Results:** After the removal of patients with specific gene mutations not assessed in PROpel and those who received prior NHT in CSPC, 157 and 64 patients remained in the TALA+ENZA arm for HRRm and BRCAm, respectively. The comparative effect estimates for rPFS and OS are presented in the Table. None of the results were statistically significant. **Conclusions:** These analyses demonstrate numerically favorable results for TALA+ENZA compared to OLAP+AAP highlighting its therapeutic potential in 1L mCRPC for patients with HRRm and BRCAm. Limitations include inability to adjust for all characteristics and biases due to unobserved trial differences. Research Sponsor: None.

TALA+ENZA (TALAPRO-2 Cohort 2) vs OLAP+AAP (PROpel).

Outcome	HRRm	BRCAm
rPFS		
HR (95% CI)	0.654 (0.420, 1.020)	0.813 (0.342, 1.930)
OS		
HR (95% CI)	0.666 (0.407, 1.087)	0.966 (0.380, 2.451)

HR $<$ 1.0 indicates the comparison favors TALA+ENZA.

Biomarkers associated with outcomes from KEYLYNK-010: Pembrolizumab (pembro) plus olaparib (ola) versus next-generation hormonal agent (NHA) in previously treated metastatic castration-resistant prostate cancer (mCRPC).

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Background: Pembro + ola did not significantly improve rPFS or OS vs NHA in unselected patients (pts) with previously treated mCRPC in the phase 3 KEYLYNK-010 study (NCT03834519). Here, we present the results of prespecified biomarker analyses with respect to rPFS or OS. **Methods:** Pts were randomly assigned 2:1 to pembro + ola or NHA. PD-L1 combined positive score (CPS) was measured by IHC (22C3 pharmDx); HRRm, BRCAm, *TP53*, *PTEN*, *SPOP*, *ATM*, *CDK12*, TMB, and MSI were analyzed in tissue samples using FoundationOne CDx or ctDNA using FoundationOne Liquid CDx; AR-V7 was analyzed using Epic Sciences' CTC assay. Associations (continuous scale) with outcomes were evaluated using adjusted Cox proportional hazards regression, and 1- (pembro + ola) and 2-sided (NHA) *P* values were calculated; significance was prespecified at $\alpha < .05$. For biomarkers with sufficient sample size for subgroup analysis, rPFS and OS HRs were evaluated for pembro + ola vs NHA. **Results:** Of 782 treated pts, PD-L1 was evaluable in 730 (pembro + ola, 490; NHA, 240); HRRm, BRCAm, *TP53*, *PTEN*, *SPOP*, *ATM*, and *CDK12* in 718 (pembro + ola, 489; NHA, 229); TMB in 414 (pembro + ola, 275; NHA, 139); MSI in 316 (pembro + ola, 210; NHA, 106); and AR-V7 status in 544 (pembro + ola, 367; NHA, 177). In the biomarker-evaluable population, 28% had HRRm, 10% had BRCAm, 45% had *TP53*m, 34% had *PTEN*m, 8% had *SPOP*m, 7% had *ATM*m, 7% had *CDK12*m, 4% were TMB-H (≥10 mut/Mb), 2% were MSI-H, and 13% were AR-V7 positive. For pembro + ola, positive associations were only observed between PD-L1 CPS and rPFS ($P = 0.034$) and between HRRm and BRCAm and rPFS (adjusted $P = 0.003$ and < 0.001, respectively). No associations were observed for NHA (all $P > 0.05$). rPFS and OS HRs for pembro + ola vs NHA by biomarker status are shown (Table), with notable results observed for AR-V7 status. **Conclusions:** For pembro + ola, PD-L1 CPS had a weak positive association with rPFS, while HRRm and BRCAm had strong positive associations with rPFS; these biomarkers did not correlate with NHA outcomes. We observed a potential benefit with pembro + ola over NHA (for rPFS and OS) in AR-V7–positive mCRPC pts, which requires validation. Clinical trial information: NCT03834519. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	n Pembro + ola; NHA	rPFS, HR (95% CI)	OS, HR (95% CI)
PD-L1 CPS			
<1	363; 191	1.01 (0.81-1.26)	0.96 (0.75-1.21)
≥1	127; 49	0.87 (0.56-1.36)	0.80 (0.52-1.24)
HRRm			
Mut	141; 57	0.63 (0.43-0.91)	0.90 (0.59-1.39)
WT	348; 172	1.19 (0.94-1.51)	0.95 (0.75-1.21)
BRCAm			
Mut	53; 22	0.43 (0.23-0.83)	0.57 (0.28-1.17)
WT	436; 207	1.10 (0.89-1.36)	0.96 (0.77-1.19)
TP53			
Mut	226; 96	0.96 (0.72-1.28)	0.83 (0.62-1.10)
WT	263; 133	1.00 (0.76-1.32)	0.91 (0.68-1.24)
PTEN			
Mut	169; 77	1.19 (0.83-1.69)	1.03 (0.72-1.46)
WT	320; 152	0.87 (0.68-1.10)	0.82 (0.63-1.07)
AR-V7			
+ve	51; 20	0.47 (0.24-0.91)	0.41 (0.22-0.78)
-ve	316; 157	1.05 (0.82-1.34)	1.04 (0.79-1.35)

HRs adjusted for baseline ECOG PS + measurable disease + prior NHA.

5065 Poster Session

Development of a machine learning model to predict overall survival results from randomized clinical trials of patients with metastatic prostate cancer.

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Background: Overall survival (OS) remains the gold standard endpoint for clinical trials in metastatic prostate cancer (metPC) yet requires extensive follow-up. We sought to develop a model utilizing short term ($\leq$ 4 months) prostate specific antigen (PSA) kinetic data to predict the OS readout from phase 3 clinical trials, with the goal of accelerating readout time of trials for patients (pts) with metPC. **Methods:** Clinical and PSA data were obtained from 7 metPC trials: 6 randomized, double-blind, phase 3 trials (TITAN, COU-AA-301, COU-AA-302, LATITUDE, ACIS, and MAGNITUDE), and one multicenter, phase II trial (GALAHAD). We developed 18 PSA kinetic variables from the first 4 months of enrollment including: 50% decline in PSA (PSA50), 90% decline in PSA, PSA=0.1, and PSA=0.2 within 1, 2, 3, and 4 months; and slope and base of the exponential fit of PSA over the first 4 months on study). To balance pt and disease characteristics, TITAN, COU-AA-301, and ACIS were used to train the intermediate endpoint, with remaining studies held out as an external testing cohort. A random 60/40% split of the pooled pt-level data was performed as a sensitivity analysis. Adaptive least absolute shrinkage and selection operator (aLASSO)-based Cox proportional hazards models were applied to select previously identified prognostic baseline clinical variables with and without PSA kinetic variables most predictive of OS on five-fold cross validation. Performance with and without PSA kinetics was assessed using C-index, integrated Brier score (IBS), and time-dependent area under the receiver operating characteristic curve (tAUC) at 12, 24, 36, and 48 months. **Results:** The study included 6,451 pts with median follow-up of 22 months and 85,785 PSA values. aLASSO selected Eastern Cooperative Oncology Group performance status, disease extent, lactate dehydrogenase, albumin, hemoglobin, PSA, and alkaline phosphatase as baseline variables for the prognostic comparator model. In the model including PSA kinetics, aLASSO identified PSA50 at 4 months, PSA0.1 at 1 month, and PSA slope as kinetics providing additional intra-treatment information to improve prediction of OS. The model with PSA kinetics showed improved performance on the test trials: C-index (0.72 vs. 0.66), IBS (0.158 vs. 0.173), and tAUC (0.84, 0.78, 0.78, and 0.76 vs. 0.78, 0.71, 0.69, and 0.65 at times 12, 24, 36, and 48 months, respectively; $p < 0.05$.) Sensitivity analysis using a random split of the pooled pt-level data supported the importance of PSA50 at 4 months and PSA slope. **Conclusions:** Data from 6,451 mPC pts enrolled on prospective clinical trials were used to develop a machine learning model which included kinetic PSA data and predicted the long-term OS readout in Phase 3 trials with just the first four months of data. This model will be validated in independent data sets comprised of other completed phase 3 trials. Research Sponsor: Prostate Cancer Foundation; 22CHAS02.

A phase 1b dose escalation study of FOR46, a novel antibody-drug conjugate targeting a tumor-specific epitope of CD46, in combination with enzalutamide (Enza) in patients with metastatic castration resistant prostate cancer (mCRPC).

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Background: FOR46 is an MMAE-containing antibody-drug conjugate (ADC) targeting a tumor-specific conformational epitope on the extracellular domain of CD46 on prostate cancer and other cancer tissues in a lineage independent fashion. A prior phase 1, first-in-human trial of FOR46 demonstrated encouraging preliminary activity in mCRPC. In pre-clinical models, androgen receptor blockade with enzalutamide enhances CD46 epitope expression and achieves additive activity in combination with the CD46 ADC. We sought to evaluate the combination of FOR46 plus enza in mCRPC patients (pts). **Methods:** Pts with mCRPC with progression on ≥ 1 androgen receptor pathway inhibitor (ARPI) were enrolled. No prior chemotherapy for mCRPC was allowed. A 3+3 dose escalation design was utilized with a starting dose of FOR46 of 1.8 mg/kg adjusted body weight (ABW) in combination with enza 160 mg/day. Dose escalation was explored with and without prophylactic granulocyte colony-stimulating factor (G-CSF) support. The primary endpoint was determination of the maximally tolerated dose (MTD) of FOR46 in combination with enza. A baseline CD46-directed PET imaging probe utilizing the same antibody backbone as FOR46 (^{89}Zr-DFO-YS5) was obtained in a subset of pts. **Results:** Seventeen pts were enrolled. Median age was 71 years (range 58 – 91) and median PSA was 43.8 ng/mL (range 2.1 – 379.6) at study entry. Twelve pts (70.6%) had ≥ 2 lines of prior ARPI. The median duration of treatment was 5.0 months (range 1– 18). Dose-limiting toxicities (DLTs) included grade 4 neutropenia at a dose of 2.1 mg/kg without G-CSF (n = 2), grade 4 hyponatremia at 2.4 mg/kg (n = 1), and grade 3 elevated transaminases at 2.4 mg/kg (n = 1). The MTD of FOR46 was established at 2.1 mg/kg ABW, with primary G-CSF prophylaxis, in combination with enza 160 mg/day. Grade ≥ 3 treatment-related adverse events (trAEs) were observed in 29.4% of pts. The most common trAEs of any grade were fatigue (n = 11, 64.7%), peripheral sensory neuropathy (n = 8, 47.1%), elevated transaminases (n = 3, 17.6%), alopecia (n = 4, 23.5%), decreased appetite (n = 7, 41.2%), neutropenia (n = 3, 17.6%), and weight loss (n = 3, 17.6%). Grade 2 neuropathy was observed in 2 patients (11.8%). Preliminary anti-tumor activity was observed with PSA declines in 13/16 (81.3%) of evaluable pts, and a disease control rate (stable disease ≥ 6 months) of 41.2%. ^{89}Zr-DFO-YS5 demonstrated tumor uptake on whole body PET with pharmacokinetics typical for an IgG radiopharmaceutical. **Conclusions:** In combination with enza, the established MTD of FOR46 with primary G-CSF prophylaxis was safe and demonstrated preliminary evidence of efficacy. ^{89}Zr-DFO-YS5 PET demonstrates tumor-specific uptake and will be employed in the ongoing Phase 2 portion of the study as a potential predictive biomarker of response. Clinical trial information: NCT05011188. Research Sponsor: None.

5067 Poster Session

Site versus central read discrepancy rates in PCWG3 evaluation for progression.

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Background: Prostate Cancer Working Group-3 Criteria (PCWG3) is the standard for determining radiographic response assessments in Prostate Cancer (PC) Clinical Trials. PCWG3 accounts for soft tissue and bone responses by following RECIST and evaluation of metastatic bone disease, respectively. In PC, the determination of progressive disease (PD) by bone metastases is often challenging due to increased osteoblastic activity during drug treatment known as flare phenomenon. To account for this, PCWG3 uses the 2+2 rule during the flare window and requires persistence of bone lesions over a specified period. Protocols often require blinded independent central review (BICR) verification of PD (VOP) where sites request BICR confirm site suspected radiographic PD (rPD). This is often a challenge as BICR radiologists are required to follow the strict PCWG3 requirements for PD. Previous studies have shown a 32% site vs. central discordance in RECIST trials, yet there is limited data for PCWG3. Due to the complexity of PCWG3, we hypothesized that site vs central discordance is greater than that of RECIST. Thus, we aimed to examine site vs central discordance for PD by PCWG3 by analyzing archived data on site requested radiographic VOP. **Methods:** Aggregate data from metastatic PC trials requiring BICR VOP by PCWG3 was collected and retrospectively analyzed. Of the 6537 patient data reviewed, 3685 patients had at least one site requested VOP. For these patients with site suspected progression, a comparison between site submitted VOP requests and the BICR outcome of PD or non-PD was used for determination of discordance. The data was further categorized based on the number of times the site submitted a request and when BICR verified PD. **Results:** Analyses showed 50.91% of patients had BICR verified PD at the time of initial site request. The remaining 49.09% of patients had at least one instance of non-PD before PD was determined by BICR. For 33.3% of patients, central PD was never verified by BICR. In the remaining patients with VOP requests, 11.78% had verified PD following one Non-PD result, 4.03% had verified PD following two or more non-PD results. **Conclusions:** BICR verified rPD serves as an important endpoint in PC trials yet our analysis shows almost half of initial patient VOP requests from the site were not verified centrally. This is greater than the established discordance in RECIST trials and warrants further investigation. For over 15% of patients who did not have verified PD by BICR on the first request, PD was verified in a subsequent request. We postulate that these discrepancies are due site misinterpretation of PCWG3 or sites requesting VOP when insufficient time has passed to meet the persistence requirements. In addition, PCWG3s requirement for lesion persistence may differ from clinical practice in the assessment of PD. This preliminary analysis provides vital insight into site vs central discordance in BICR confirmation of PD in PC trials. Research Sponsor: None.

Plasma tumour DNA dynamics and circulating subclones patterns in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with cabazitaxel in a prospective biomarker trial (NCT03381326).

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Background: Liquid biopsies enable non-invasive detection of circulating biomarkers for disease monitoring and treatment resistance interrogation. We aimed to study circulating tumour DNA (ctDNA) and its early changes during treatment to identify biomarkers of resistance to cabazitaxel in mCRPC patients (pts). We also designed and validated a Circulating Subclonality Index (CSI) to capture subclonal events in plasma and correlate with outcomes. **Methods:** mCRPC pts (N=104) candidate for cabazitaxel were enrolled in a prospective biomarker multicentre trial. Plasma was collected at baseline (BL), prior to cycle 3/4 (C3) and at progression (PD) and analyzed using a bespoke prostate cancer capture panel (PCF_SELECT [Orlando et al, NAR Cancer 2022]). ctDNA fraction was calculated using allele specific quantitation of hemi-deletions. We optimised PCF_SELECT to use non-integer copy numbers (CN) as a sub-clonality measure of circulating clones. CSI was defined as the proportion of CN-altered genes (derived from CLONETv2 output) where the CN value of either allele had a distance >0.1 from the nearest integer value. Primary outcome measures were overall survival (OS) and progression-free survival (PFS). Medians and [95% CI] are reported. **Results:** Early ctDNA dynamics (change from BL to C3) strongly associated with outcomes: pts with increasing ctDNA levels had the shortest OS (7.5 months (mo), HR 4.6 [2.1-10.3], p<0.0001) compared to pts with decreasing ctDNA (15.7 mo, HR 2.4 [1.3-4.4], p=0.0015) and pts with no detectable tumour at either timepoint (29.9 mo). Pts with early ctDNA increase had a higher risk of PD (OR 14.1 [3.5-44.5], p<0.0001), and ctDNA dynamics were independently related to OS (HR 6.6 [3.5-12.6], p<0.0001] and PFS (HR 7.6 [3.8-15.2], p<0.0001). Median CSI proved to be a robust statistical value for outcomes. Pts with lower BL CSI had shorter OS (7.8 [4.0-10.0] vs 12.1 [9.7-15.7] mo, HR 2.0 [1.1-3.5], p=0.011) and PFS (2.7 [2.3-4.4] vs 5.6 [4.6-7.3] mo, HR 1.9 [1.1-3.4], p=0.013) compared to those with higher CSI. BL CSI was independently related to PFS (HR 2.1 [1.2-3.7], p=0.014). A significant CSI decrease was observed upon cabazitaxel PD compared to BL (p=0.003). **Conclusions:** Early ctDNA dynamics identified pts with worse outcomes during cabazitaxel. Lower subclonality, representative of fewer circulating subclones, was observed at PD and associated with shorter PFS. This suggests that a treatment-resistant clone, associated with a lower index of subclonality, dominates in ctDNA. Clinical trial information: NCT03381326. Research Sponsor: ESMO (European Society of Medical Oncology); Sanofi Genzyme.

Dynamic androgen receptor alterations (ARa) ctDNA profiles and clinical outcomes in metastatic prostate cancer (mPC).

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Background: The AR plays a pivotal role in PC pathogenesis and ARa, including ligand binding domain mutations and amplifications, can evolve under the selective pressure of androgen deprivation therapy and androgen receptor signaling inhibitors (ARSi). Next-generation sequencing of circulating tumor DNA (ctDNA) enables non-invasive, longitudinal monitoring of AR dynamics in patients (pts) undergoing systemic therapies. This study aims to explore the dynamic changes in ctDNA profiles, particularly focusing on the AR gene and its association with clinical outcomes. **Methods:** We utilized GuardantINFORM, a clinical-genomics database containing de-identified ctDNA test results and commercial payer-claims data. Eligible pts had a diagnosis of mPC and underwent ctDNA testing pre (within 3 months prior to initiation) and post (within 3 months of discontinuation prior to initiating subsequent treatment) ARSi, poly ADP-ribose polymerase inhibitors (PARPi), and taxane chemotherapy. The primary endpoint was to characterize changes in molecular alterations pre- and post-therapy. Secondary endpoints included overall survival (OS), time to treatment discontinuation (TTD), and time to next treatment (TTNT) for pts receiving with ctDNA testing within 3 months prior to 1L ARSI for mCRPC. **Results:** From a database of 21,682 pts with PC, 145 had ctDNA collected pre/post ARSI, 54 pre/post PARPi, and 115 pre/post taxane chemotherapy. We observed increased ARa across the three treatment groups (%pre/%post): ARSi (17/35), PARPi (39/43), and taxanes (44/58) (Table). In the ARSi group, most common (%pre/%post) ARa included AR amplifications (11/23), AR T878A (5/9), AR L702H (2/6) and AR H875Y (0.7/1.4). In the PARPi group, the most prevalent (%pre/%post) ARa comprised AR amplifications (24/32), AR L720H (15/15), AR T878A (11/9) and AR F877L (2/6). In the taxane group, notable (%pre/%post) ARa consisted of AR amplifications (33/44), AR L702H (4/10), AR H875Y (3/9) and AR T878A (7/8). 1294 pts had ctDNA testing prior to 1L ARSi for mCRPC and were included in the outcomes analysis. Pts with ARa showed worse TTD (2.8 vs 4.3, $p<0.0001$), TTNT (6.9 vs 4.8, $p<0.0001$) and (OS (15.3 vs 49.3, $p<0.0001$). **Conclusions:** Our study elucidates evolving changes in AR in mPC using ctDNA profiling. We observed an increase in ARa following ARSi, PARPi, and taxane treatment in mPC. Furthermore, our findings highlight associations between ARa and clinical outcomes, emphasizing the potential for personalized treatment strategies in mPC pts based on molecular profiling. Research Sponsor: None.

Dynamic *ARa* in ctDNA.

(%)	Gene	Prevalence Pre-Tx (%)	Newly Detected Post Tx (%)	No Longer Detected Post Tx (%)	Prevalence Post Tx (%)
ARSi	AR AMP	11	17	-5	23
	AR T878A	5	6	-1	9
	AR L702H	2	5	-1	6
PARPi	AR AMP	24	11	-4	32
	AR L702H	15	4	-4	15
	AR T878A	11	0	-2	9
Taxanes	AR AMP	33	18	-7	44
	AR L702H	4	6	-1	10
	AR H875Y	3	7	-1	9

METRADS-P vs. RECIST/PCWG criteria to detect disease progression in metastatic castration-resistant prostate cancer (mCRPC).

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Background: Radiographic Progression-free survival (rPFS) derived from Computer Tomography (CT) and Bone Scan (BS) using Prostate Cancer Working Group (PCWG) criteria is utilized as an intermediate clinical endpoint for overall survival (OS) benefit in mCRPC. Whole Body MRI (WBMRI) is emerging as a potentially superior response biomarker, allowing a more accurate assessment of bone marrow and soft tissue disease. We have now compared the performance of previously reported WBMRI criteria (MET-RADS-P) with PCWG criteria as a response biomarker for mCRPC, and this with overall survival (OS). **Methods:** We retrospectively analysed imaging data from mCRPC patients that 1) discontinued therapy based on PCWG criteria; 2) had contemporaneous WBMRI, CT, and BS at time-points according to PCWG. Soft tissue lesions were classified according to RECIST1.1 both on CT and WBMRI; bone lesions were classified on BS using PCWG criteria as non-PD (non-progressive disease), PD-U (PD unknown) & PD (progressive disease) and on WBMRI using MET-RADS-P as non–PD (subclassified as partial response-PR & stable disease-SD) & PD, for each imaging time-point. We calculated % agreement between MET-RADS-P and PCWG across all time-points. Median PFS as per PCWG (rPFS) and METRADS-P (mPFS) and median OS according to METRADS-P response at 12 weeks was estimated by Kaplan Meier. **Results:** 100 cases (91 subjects received 100 lines of treatment, 100 baseline imaging & 216 follow-up imaging assessments). For soft tissue disease, RECIST 1.1 and WBMRI assessments were concordant at 201 of 216 time-points (93.1%); the discordance was related to superior detection of local disease and liver metastases on WBMRI. Bone metastases assessments showed agreement in 37.5% time-points, with details as follows (% over BS category): 1) Negative BS (13 time-points): WBMRI 69.2% negative, 15.4% PR, 15.4% as PD; 2) Non-PD BS (154 time-points): WBMRI non-PD 51% (34.4% PR, 17.5% SD), 48.1% PD; 3) PD-U BS (40 time-points): WBMRI PD 90%; Non-PD 10% (1pt FLARE & 3pt with subsequent concordant PD). At time of PD-U, 30 out of 40 pt (75%) discontinued treatment due to RECIST PD (24/40) & clinical progression (6/40). 4) PD confirmatory BS (9 time-points) : WBMRI 100%PD. Median rPFS by PCWG was 4.9 months (m) (95%CI: 3.8-5.7); the median mPFS by MET-RADS-P was 2.8 months (2.6-3.9), with overall progression rate of 70% and 94% respectively. Non-PD by WBMRI at 12-weeks associated with longer OS when compared with PD by MRI (median OS: 17.9m (14.2-22.6) vs 14.4m (9.6-17.0) (crude log-rank test 0.0059). **Conclusions:** Regarding soft-tissue disease, MET-RADS-P detects progression earlier than RECIST in 4.2% time-points, while for bone metastases it detects progression earlier than PCWG at 51.9% of timepoints. WBMRI can better classify BS non-PD patients in PR, SD and PD. Response evaluation based on WBMRI is a prognostic factor in mCRPC. Research Sponsor: National Institute for Health and Care Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, and by the Royal Marsden Cancer Charity; Prostate Cancer UK (PCUK).

The effect of ACEi/ARB on survival outcome of patients with mCRPC treated with abiraterone.

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Background: Androgen deprivation therapy (ADT), such as Abiraterone Acetate (AA), has emerged as a standard treatment for metastatic prostate cancer (mPCa). However, long-term ADT treatment may increase the incidence of cardiovascular adverse events, such as hypertension, which are a common cause of death in patients receiving ADT. Therefore, it is crucial to select appropriate antihypertensive drugs that effectively manage blood pressure and improve overall survival (OS) in these patients. **Methods:** This study conducted a secondary analysis of the COU-AA-301 and COU-AA-302 trials, which were multicenter double-blind randomized controlled trials (RCTs) to evaluate the efficacy of AA in combination with prednisone and ADT compared to prednisone plus ADT alone in patients with metastatic castration-resistant prostate cancer (mCRPC). Patients were retrospectively assessed and stratified based on the concurrent medication including angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB) or not. OS and progression-free survival (PFS) were assessed using the Kaplan-Meier method and log-rank test. Multivariable Cox regression analysis was performed to determine the independent correlation of ACEi/ARBs with OS and PFS. Statistical significance was defined as $P<0.05$. **Results:** In COU-AA-301, the use of ACEi/ARB medications showed a significant association with improved OS (16.4 vs. 14.2 months, $p<0.001$) and PFS (3.1 vs. 2.9 months, p=0.002) in AA arm. After adjusting for baseline factors, ACEi/ARB medications were still found to reduce the risk of death (HR 0.72, 95% CI 0.56-0.91) and disease progression (HR 0.81, 95% CI 0.69-0.96). Similarly, in COU-AA-302, ACEi/ARB medications were associated with prolonged OS (37.4 vs. 31.9 months, p=0.003) and PFS (20.3 vs. 14.7 months, p=0.002) in AA arm. By adjusting for baseline factors, ACEi/ARB medications remained significantly associated with lower risk of death (HR 0.70, 95% CI 0.56-0.88) and disease progression (HR 0.70, 95% CI 0.55-0.88). In the placebo group, ACEi/ARB medications demonstrated improved OS only in COU-AA-301 (13.7 vs. 10.6 months, p=0.021). However, this trend did not reach statistical significance after adjusting for baseline factors (HR 0.76, 95% CI 0.55-1.03). Furthermore, the use of ACEi/ARB medications did not confer any PFS benefits in COU-AA-301 and failed to show both PFS and OS benefits in COU-AA-302. **Conclusions:** The use of ACEi/ARB medications has shown promise in improving OS and PFS in mCRPC patients treated with AAP. However, it is important to acknowledge the inherent limitations of post-hoc analysis, and therefore, further validation through prospective clinical trials is warranted. Research Sponsor: None.

Overall survival from PANTHER: A multicenter trial of apalutamide, abiraterone acetate plus prednisone in Black and White patients with metastatic castration-resistant prostate cancer (mCRPC).

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Background: ACIS was an international phase III trial comparing apalutamide (A) plus abiraterone acetate and prednisone (AAP) to AAP in patients (pts) with mCRPC. Recognizing that lack of diversity in clinical trials is a major challenge to real-world translation of outcomes, we purposely designed to PANTHER to oversample Black pts compared to our catchment area demographics to estimate clinical outcomes among Black and White pts with mCRPC, accrued in parallel, single arm cohorts and treated with A+AAP. Here we report the long term radiographic progression-free survival (rPFS) and overall survival (OS) for both cohorts. **Methods:** This parallel cohort multicenter study treated androgen receptor pathway inhibitor naïve mCRPC pts with oral apalutamide (240 mg/d), abiraterone (1000 mg/d) and prednisone (10 mg/d) (AAAP) continuously until disease progression, unacceptable toxicity or 2 years, at which point patients were switched to standard of care. The primary endpoint is rPFS; secondary endpoints were to estimate (OS) and best PSA response among Black and White pts, separately. The target number of rPFS events was 26 per group. Exploratory endpoints included safety and correlative biomarkers of outcome by race and ancestry. **Results:** Between July 2017 and January 2021, we enrolled 43 Black and 50 White pts from 8 sites. Key baseline prognostic factors for the Black and White cohorts, respectively included: Gleason score 8-10 (56%; 56%), KPS 70-80% (26%; 18%), median age (67; 72), median PSA 15.20; 17.56), median time from diagnosis to enrollment (4.6 years; 3.3 years), visceral metastases (23.7%; 18.0%), prior docetaxel (33%; 44%). At the time of the abstract submission, there were 22 and 40 rPFS events, and 20 and 35 deaths in Black patients and White pts, respectively. Median follow up was 56 months (95% CI 50, 62) and 62 months (95% CI 56, NR) for Black and White pts, respectively. 24 months rPFS rate was 61% (95% CI 49, 78) and 38% (95% CI 27, 54) for Black and White pts, respectively. 36 months OS rate was 68% (95% CI 55, 83) and 50% (95% CI 37, 66) for Black and White pts, despite discontinuing study medications at 2 years and switching to standard of care. **Conclusions:** We hypothesize that treatment with the combination of A+AAP may result in clinical efficacy in Black men with mCRPC. Further prospectively powered studies of dual androgen receptor pathway inhibition with AAP among Black men with advanced prostate cancer are needed to determine the potential clinical benefits in this understudied population. Clinical trial information: NCT03098836. Research Sponsor: Janssen Pharmaceuticals.

5073 Poster Session

Race and association between ADT and adverse events.

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Background: Many prior studies have linked androgen deprivation therapy (ADT) for prostate cancer (PC) with adverse events such as cardiac events and osteoporosis. Whether these associations differ by race is unknown. **Methods:** We performed a retrospective population-level analysis to assess the association between ADT (specifically GnRH agonist) use and time to cardiovascular events, bone fracture, new osteoporosis diagnosis, or time to composite event (i.e., the first of any of cardiovascular, bone fracture, or osteoporosis events) in the Veterans Affairs Health Care System (VA) as a function of race. We identified 790,916 patients from 2001-2021 who were diagnosed with PC and treated with ADT or no ADT. Given small numbers, patients treated with other forms of ADT including bilateral orchiectomy or GnRH antagonists were excluded. Patients were also excluded if they were missing race/ethnicity. Data were stratified by race/ethnicity including: Non-Hispanic White (White) 598,574, Non-Hispanic Black (Black) 145,267, Hispanic 30,139 and Other 16,936. Univariable and multivariable Cox proportional hazards models were used to test the association between ADT as a time-dependent covariate and time to the given event across all patients and as a function of race. **Results:** On multivariable analysis among all patients, ADT was associated with increased risk of cardiovascular events (HR 1.16, 95% CI 1.15- 1.17, $p<0.001$), bone fractures (HR 1.59, 95% CI 1.55-1.62, $p<0.001$), osteoporosis (HR 2.73, 95% CI 2.65-2.80, $p<0.001$), and composite event (HR 1.29, 95% CI 1.27-1.30, $p<0.001$). When stratified by race, ADT remained significantly associated with all outcomes in all races (all $p<0.001$). Compared to White men, among Black men, the HRs for ADT were slightly lower for cardiovascular events (1.09 vs. 1.18), bone fracture (1.35 vs 1.65), and composite event (1.19 vs 1.31), but slightly higher for osteoporosis (3.16 vs 2.64). HRs in Hispanics and Other races were very similar to those in White men. **Conclusions:** Consistent with many prior studies, we found that ADT was associated with increased risk of cardiovascular events and bone complications. Though risks differed slightly among Black men, overall differences were small. These findings demonstrate that ADT is associated with adverse cardiovascular and bone complications regardless of race. Better means to reduce ADT-associated risks are needed across all races. Research Sponsor: Sumitomo Pharma Inc; Pfizer Inc; U.S. National Institutes of Health; T32 HL116273.

Final results of a phase I/II dose-escalation study of fractionated dose ^{177}Lu-PSMA-617 for progressive metastatic castration resistant prostate cancer (mCRPC).

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Background: PC commonly expresses PSMA and has dose-responsive radiosensitivity. ^{177}Lu-based radioligands usually use an empiric dosing regimen. This 1st dose-escalation study of ^{177}Lu-PSMA-617 employed a dose-dense fractionation schedule intended to allow delivery of higher total doses to overcome radioresistance due to repopulation. Here, we report mature results of the study. **Methods:** Progressive mCRPC following > 1 potent ARPI (e.g., abi/enza) and chemo (or unfit/refuse taxane) without limit of # prior therapies provided adequate organ function and ECOG PS 0-2. Treatment: single cycle of fractionated dose ^{177}Lu-PSMA-617 on D1 and D15. In Ph I dose-escalation, patients (pts) received one cycle of 7.4 - 22 GBq followed by Simon 2-stage Ph II at 22.2 GBq. PSMA expression was not required for treatment, but pre- and post-treatment ^{68}Ga-PSMA11 PET/CT and/or ^{177}Lu-PSMA-617 SPECT done. Primary efficacy by PSA changes with 2ndary outcomes with CT/bone scans, PSMA PET, circulating tumor cell (CTC; CellSearch) counts, plasma DNA (PCF_SELECT), and survival. **Results:** Between 1/2017 – 2/2021, 50 pts treated with median PSA 164.3, 35 (70%) CALGB (Halabi) poor risk. 47 (94%) bone, 38 (76%) nodal, 12 (24%) lung, 5 (10%) liver mets (4 additional pts with PSMA PET+ liver mets not apparent on CT). 29 (58%) with prior >2 ARPI, 29 (58%) with >1 chemo, 14 (28%) with Ra-223, 2 (4%) with ^{177}Lu-J591. 27 (54%) treated at 22 GBq. No dose-limiting toxicity during Ph I. 38 (76%) with any PSA decline, 27 (54%) with >50% PSA. Median rPFS 8.3 mo [5.6-16.7], and OS 15.7 mo [10.9-20.6]. Of 17 RECIST measurable, 6 (35.3%) responded, 7 (41.2%) stable, 4 (23.5%) progressed. Of 31 with paired CTC counts, 16 (52%) decreased, 5 (16%) were stable; 10 (32.3%) converted to favorable/undetectable. Plasma DNA with high allele-specific ploidy and *AR*copy number gain associated with OS (univariate). Treatment emergent adverse events (TEAE): 32 (64%) dry mouth, 22 (44%) pain flare, 22 (44%) fatigue, 19 (38%) nausea, 15 (30%) anemia, 15 (28%) thrombocytopenia (plts), 9 (18%) neutropenia (ANC). All TEAEs restricted to grade (Gr) 1-2 except 6 (12%) with Gr 3 anemia, 2 (4%) Gr 3/4 plts, 1 (2%) Gr 3 ANC. TEAE incidence and Gr were not related to dose. On multivariable analysis, ^{177}Lu dose administered (p=0.09), CALGB risk (p=0.04), prior chemo (p=0.009), associated with OS; dose (p=0.1), CALGB risk (p=0.2), and AR copy number (p=0.2) associated with PSA50 decline. Baseline PSMA imaging (by imaging score or SUVmax) was not associated with OS or response. **Conclusions:** A single-cycle of fractionated-dose 177Lu-PSMA-617 is safe. Despite no pre-selection for PSMA expression, most had PSA decline with favorable PFS and OS compared to historical controls and similar to PSMA-selected targeted radionuclide studies administering multiple cycles in a less dose-intense approach. Clinical trial information: NCT03042468. Research Sponsor: Weill Cornell Medicine; Prostate Cancer Foundation; U.S. Department of Defense; W81XWH-17-PCRP-IA; U.S. National Institutes of Health; ULI RR024996.

Hematologic toxicity in ^{177}lu-PSMA-617 treatment for mCRPC: Unraveling the impact of PSMA PET bone tumor volume (PSMA-bTTV).

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Background: Lutetium-177 prostate-specific membrane antigen (^{177}Lu-PSMA-617) is a life-prolonging treatment approved by the FDA in metastatic castration-resistant prostate cancer (mCRPC), at a very late stage when there frequently reduced bone marrow reserve. We aim to report the incidence of hematologic toxicity during treatment and potential risk factors in a single-center study. **Methods:** This retrospective single-institution case series included mCRPC patients who underwent at least one cycle of ^{177}Lu-PSMA-617 treatment between June 2022 and January 2024. Hematological parameters were documented at baseline, 3 weeks after each treatment, and before each subsequent treatment administration. Then, we captured the nadir values for each parameter during treatment. Hematologic toxicities were assessed using the Common Terminology Criteria for Adverse Events v5.0, with Grades 3 and 4 considered significant. Multivariable logistic regression analyses were conducted to investigate the association between hematological adverse events and baseline characteristics including PSMA-bTTV, measured by semi-automatic contouring of the PSMA-expressing whole-body bone metastases on pre-treatment PSMA PET. **Results:** Our study included 138 mCRPC patients (median age: 73y, prior chemotherapy: 92%, prior radiation: 43.5%, bone involvement: 89.1%), who underwent a median of 3 cycles (IQR: 2-5) of ^{177}Lu-PSMA-617 treatment. At baseline, 8 (5.8%) patients had grade 3 anemia, 2 (1.4%) patients had grade 3 leukopenia, and 1 (0.7%) patient had grade 3 thrombocytopenia. Nadir values during treatment indicated that 23 (16.7%) had grade 3 anemia, 5 (3.6%) had grade 3 leukopenia, and 11 (8%) had grade 3 and 4 thrombocytopenia. Multivariable analysis of predisposing factors for hematologic adverse events showed that the PSMA-bTTV was significantly associated with occurrence of any grade ≥3 hematologic toxicity, anemia, and thrombocytopenia after adjusting for other baseline clinical variables (Table). **Conclusions:** Over 1 in 5 patients with mCRPC experienced significant hematologic adverse events during treatment with ^{177}Lu-PSMA-617. Bone tumor volume is a possible risk factor for developing significant hematologic toxicity. Research Sponsor: None.

Multivariable analyses of potential risk factors and associated odds-ratios for development of grade ≥3 hematologic toxicity.

	Any			Anemia			Leukopenia			Thrombocytopenia		
Variables	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
Age	1	0.9-1.1	0.9	1	0.9-1	0.4	1.1	0.9-1.3	0.3	1	0.9-1.1	0.8
Number of chemotherapy regimens	1.4	0.8-2.4	0.3	1.5	0.8-2.7	0.2	1.1	0.2-4.4	0.9	1.2	0.5-2.9	0.7
Prior radiation	2.3	0.8-6.6	0.1	1.8	0.6-5.6	0.3	2.6	0.3-25.7	0.4	2.7	0.5-13.3	0.2
Renal impairment	0.7	0.1-3.6	0.6	1.3	0.3-6.9	0.8	-	-	-	-	-	-
PSMA-bTTV	1.1	1.05-1.2	<0.001	1.1	1-1.2	<0.001	1.1	1-1.2	0.08	1.1	1.1-1.2	0.001
^{223}Radium	2	0.6-6.7	0.3	1.2	0.3-4.7	0.8	10.1	1-102.9	0.051	2.9	0.5-15.8	0.2

Rapid and deep prostate-specific antigen (PSA) response to apalutamide plus ADT and survival in metastatic castration-sensitive prostate cancer (mCSPC) in real world practice in the US (OASIS Project).

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Background: Apalutamide (APA) in combination with androgen-deprivation therapy (ADT) is an effective life-prolonging treatment option for mCSPC. Early and deep PSA responses are response indicators in metastatic castration-resistant PC that have been associated with improved clinical outcomes in patients with PC. APA+ADT has been shown to induce early and deep PSA responses. We evaluated correlations between PSA and long term clinical outcomes in adults with mCSPC in real world practice. **Methods:** This retrospective, observational cohort study used the ConcertAI RWD 360 prostate cancer dataset to evaluate correlations between PSA and long term clinical outcomes in adults with mCSPC who initiated treatment with APA+ADT. All patients with newly diagnosed mCSPC from 1 Jan 2018 to 30 Sept 2022 were enrolled and followed up until 31 Mar 2023. Correlations between time to 50% and 90% declines in PSA (PSA50 and PSA90), and time to undetectable PSA (≤0.2 ng/mL) and 24-month OS were evaluated. Adjusted Hazard ratios (aHRs) were estimated using multivariate Cox proportional hazard models adjusted for age, comorbidities, BMI, baseline PSA. **Results:** 183patients with mCSPC who initiated APA+ADT treatment and had monthly PSA testing were included in the analysis; mean (SD) age 73 years (8), baseline PSA 34 (81). Mean (SD) duration of follow up was 18 m (10). Overall, 116 patients (63%) reached undetectable PSA over the follow-up period and 24-month OS was 68%. OS was significantly higher when patients achieved undetectable PSA, PSA90 and PSA50 within 3 months after initiating APA+ADT (24-month survival rate, 87%, 84% and 80%, respectively) compared with patients who did not reach these levels during the follow-up period (Table). The aHR was 0.15 (95% CI 0.05–0.47; p<0.001) in patients who reached undetectable PSA within 3 months compared with not yet reached. The aHR was 0.27 (0.12–0.65; p<0.01) in patients with onset of undetectable PSA beyond 3 months compared to not reached. **Conclusions:** Rapid and deep PSA decline was strongly associated with better overall survivalin patients with mCSPC initiated on APA+ADT. Research Sponsor: Janssen Global Services, LLC.

Multivariate analysis of overall survival by PSA kinetics in patients with mCSPC treated with APA+ADT.

PSA Response		N	Survival Rate at 24 Months	aHR (95% CI)	P-value
Undetectable PSA	<3 months	67	87%	0.15 (0.05–0.47)	<0.001
	>3 months	49	80%	0.27 (0.12–0.65)	<0.01
	Not reached	67	57%	Reference	
PSA90	<3 months	69	84%	0.1 (0.035–0.3)	<0.0001
	>3 months	35	77%	0.27 (0.1–0.7)	<0.01
	Not reached	79	65%	Reference	
PSA50	<3 months	124	80%	0.16 (0.061–0.4)	<0.0001
	>3 months	24	77%	0.32 (0.11–0.97)	<0.05
	Not reached	35	54%	Reference	

Prognostic validation of a digital pathology-based multi-modal artificial intelligence (MMAI) biomarker in patients with metastatic hormone-sensitive prostate cancer (mHSPC) from the CHAARTED trial (ECOG-ACRIN EA3805).

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Background: The ArteraAI MMAI prognostic biomarker leverages histopathology images and clinical data to risk stratify patients (pts) with localized prostate cancer. This study aimed to validate the MMAI biomarker in mHSPC. **Methods:** The validation cohort included a subset of pts from the CHAARTED phase III randomized trial with known age at diagnosis, baseline PSA, T-stage, and available histopathology images. Baseline characteristics were compared to examine the balance between included and excluded patients. Using the existing MMAI model, scores were generated, and prognostic ability was evaluated for overall survival (OS) in Cox proportional hazard model. Four defined prognostic groups based on tumor volume (high (HV) vs. low (LV)) and metastatic stage at diagnosis (M1 vs. M0) were included: 1. M0LV, 2. M0HV, 3. M1LV, 4. M1HV. These clinical groups were evaluated using multivariable analysis (MVA) which included MMAI risk group and treatment. **Results:** A subset of the CHAARTED patient population had evaluable digital histopathological images, allowing inclusion in this study (N=456/790, 57.7%), of which 370 (81.1%) were classified as MMAI-high and 86 (18.9%) as MMAI-intermediate/low risk. Data were available from 394/456 pts for classification into M0LV (N=57), M0HV (N=29), M1LV (N=66), or M1HV (N=242). MMAI-high proportion among groups were 56.1%, 69.0%, 86.4% and 92.6%, respectively. Median follow-up of the censored patients was 4.1 (IQR: 3.3-5.0) yrs. The estimated 5-yr OS across MMAI high, intermediate, and low groups was 39%, 58%, 83%, respectively (log rank p=<0.001). On MVA, the MMAI-high risk group model associated with OS (HR: 1.77 (95% CI: 1.10-2.84) p=0.02) adjusting for treatment arm, volume status, and stage at diagnosis (Table 1). When compared to M0LV, HV subgroups were also associated with OS on MVA. **Conclusions:** The ArteraAI MMAI model was found to be prognostic for OS among men with mHSPC in CHAARTED. This effect persisted when controlling for treatment, metastatic burden, and metastatic status at diagnosis. On MVA, M0HV and M1HV also maintained prognostic value. This analysis is exploratory in nature, to be followed by development of a model optimized for advanced prostate cancer. Research Sponsor: Artera, Inc.; National Cancer Institute.

Multivariable cox proportional hazard model with Walt test p-values.

Endpoint	Variable	MVA* HR (95% CI)	P value
OS	MMAI-High vs. non-High	1.77 (1.10-2.84)	0.02
	ADT + Docetaxel vs. ADT	0.86 (0.65-1.12)	0.26
	M0HV vs. M0LV	2.60 (1.34-5.05)	0.005
	M1LV vs. M0LV	1.33 (0.71-2.48)	0.37
	M1HV vs. M0LV	2.49 (1.48-4.18)	<0.001

*Controlled for MMAI, treatment, and volume (high vs low) + stage (M0 vs M1 at diagnosis).

Treatment outcomes for patients with Ga68-PSMA-PET prostate cancer (PC) with or without conventional imaging correlates.

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Background: The high sensitivity of PSMA PET/CT in pts with PC has created a new advanced disease space (PSMA+/CT-) with stage migration. Treatment outcomes and optimal management remain largely unstudied for these pts. **Methods:** Pts with metastatic castration sensitive PC identified during standard of care PMSA PET/CT imaging (Ga68 gozetotide/PSMA-11) were reviewed retrospectively at UTSW and stratified by whether a CT lesion correlates to a PSMA avid lesion (SUVmax >2.5): PSMA+/CT- vs PSMA+/CT+ groups. The primary objective was PSA Progression Free Survival (PFS) and time to castration resistance (TTCR) between cohorts. The secondary objective was TTCR in pts with PSMA+/CT- disease based on exposure to androgen deprivation therapy (ADT) alone or with AR-targeted therapy (ARTT intensification). Cohorts were compared using a two-sample t-test or a chi-square test; survival analysis was conducted using Kaplan-Meier and Cox proportional hazards regression. **Results:** Overall,135 pts were included; of whom 122 received ADT (PSMA+/CT- [n=73] vs PSMA+/CT+ [n=49]) and 13 PMSA+/CT- pts received localized treatment only. PSMA+/CT- and PSMA+/CT+ pts had comparable median age at diagnosis and similar racial distribution. The median follow-up was 19 months. In pts who received ADT, the PSMA+/CT- group had a lower median PSA (1.3 vs 14 ng/ml, *P*=0.0002), a lower rate of de-novo metastatic disease (30% vs 55%, p=0.0082) and ADT+ ARTT use (59% vs 88%, p=0.0006) compared to the PMSA+/CT+ group. Median therapy duration was similar. In pts receiving ADT, the median PSA PFS in the PSMA+/CT- group was not reached (NR) versus 37 months in the PSMA+/CT+ group. After adjusting for known prognostic factors, PSMA+/CT- lesions were significantly associated with a better PSA PFS and TTCR (Table). In pts with PMSA+/CT- receiving ADT alone (n=30) vs ADT+ARTT (n=43), only 1 patient progressed to castration resistance. After adjusting for prognostic factors, pts with PSMA+CT- disease who received ADT had a better PSA PFS [HR 0.1 (0.02-0.45)] compared to those who received localized therapy only (n=13). **Conclusions:** Pts with PSMA+CT- PC vs pts with PSMA+/CT+ PC have better prognosis and outcomes, with low rates of PSA progression and castration resistance. Localized therapy alone is likely insufficient for these pts, and ARTT intensification to improve longer term outcomes needs prospective studies through ongoing trials. Research Sponsor: None.

	PSA PFS			TTCR		
Variable	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
PSMA + CT- lesion (Univariable)	0.24	0.08-0.74	0.013	0.06	0.0077-0.44	0.006
PSMA + CT- lesion (Multivariable)	0.21	0.05-0.85	0.029	0.04	0.004-0.34	0.004
PSA at baseline	1	0.99-1	0.97	1	0.99-1	0.9
Bone mets	1.27	0.39-4.11	0.69	0.54	0.17-1.7	0.29
Received ADT+ARTT	0.39	0.14-1.1	0.08	0.64	0.25-2.5	0.48
De-novo disease	1.5	0.53-4.28	0.43	0.8	0.25-2.5	0.69
Gleason score (≥8)	0.57	0.2-1.5	0.27	1.59	0.48-5.2	0.44

Prognostic implications of PSA levels at 7 months in metastatic hormone-sensitive prostate cancer treated with enzalutamide: Landmark analysis of ENZAMET (ANZUP 1304).

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Background: ENZAMET (NCT02446405) showed that enzalutamide added to testosterone suppression (TS) with or without docetaxel improves overall survival (OS) compared with TS plus standard non-steroidal anti-androgen (NSAA) in patients with metastatic hormone-sensitive prostate cancer (mHSPC). We assessed PSA levels in ENZAMET participants at 7 months after randomization to determine correlations with OS. In *CHAARTED*, participants with mHSPC high volume disease (HV), 20% achieved PSA ≤ 0.2 with ADT (androgen deprivation therapy) alone versus 44% with low volume disease (LV) and for HV with ADT + Docetaxel, 36% achieved PSA ≤ 0.2 vs 64% with LV. **Methods:** Participants were included if they were followed for at least 7 months after randomization, and had availability of PSA and outcome data. Landmark analysis at 7 months used prognostic classifiers as previously identified in *SWOG 9346* and *CHAARTED* of PSA ≤ 0.2 and > 0.2 at 7 months after initiation of therapy. **Results:** The total number of ENZAMET participants (pts) with PSA at 7 months of ≤0.2ng/mL was 646 of 1125 (57%): 271/562 (48%) in the NSAA arm versus 375/563 (67%) in the ENZA arm. Five-year OS for TS + NSAA (±Doc) arm PSA ≤ 0.2 = 71% vs PSA > 0.2 = 36% and for TS + ENZA (±Doc) arm PSA ≤ 0.2 = 74% vs PSA > 0.2 = 43%. The % of pts with PSA levels at 7 months ≤0.2ng/mL and corresponding 5-year OS outcomes by key prognostic groups (HV vs LV) ± docetaxel is shown (Table). In comparison with *CHAARTED* in those with HV, 37% achieved PSA ≤ 0.2 with ADT alone versus 61% with LV which increased to 55% for HV and 79% for LV respectively with addition of enzalutamide. In those with HV treated with ADT + D 39% achieved PSA ≤ 0.2 vs 58% with LV increasing to 60% for HV and 74% for LV respectively with addition of enzalutamide. **Conclusions:** A PSA nadir of ≤0.2 at 7 months is associated with a longer OS regardless of treatment and prognostic group (HV vs LV). Enzalutamide increased the rate of achievement of PSA <0.2 for all groups. Clinical trial information: NCT02446405. Research Sponsor: Astellas; Cancer Council Australia; The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).

PSA response and 5-year OS by disease volume in both arms ± docetaxel.

	TS + NSAA		TS + ENZA		TS + Doc + NSAA		TS + Doc + ENZA	
Disease volume	**PSA ≤0.2ng/mL**	**PSA >0.2ng/mL**	**PSA ≤0.2ng/mL**	**PSA >0.2ng/mL**	**PSA ≤0.2ng/mL**	**PSA >0.2ng/mL**	**PSA ≤0.2ng/mL**	**PSA >0.2ng/mL**
High Volume:								
% (No./Total No.)	37 (111/301)	63 (190/301)	55 (167/301)	45 (134/301)	39 (70/179)	61 (109/179)	60 (108/180)	40 (72/180)
% 5-yr OS (95% CI)	66 (58, 76)	33 (26, 41)	62 (55, 70)	36 (28, 46)	60 (50, 73)	38 (29, 49)	55 (46, 66)	40 (30, 54)
Low Volume:								
% (No./Total No.)	61(160/261)	39 (101/261)	79 (208/262)	21(54/262)	58 (41/71)	42 (30/71)	74 (54/73)	26 (19/73)
% 5-yr OS (95% CI)	75 (68, 82)	42 (33, 54)	83 (78, 89)	58 (46, 74)	65 (51, 84)	51 (35, 73)	79 (69, 91)	73 (55, 96)

Validation of a digital pathology-based multimodal artificial intelligence model in oliogmetastatic castration-sensitive prostate cancer, including in patients from the STOMP and ORIOLE phase II randomized clinical trials.

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Background: Oligometastatic castration-sensitive prostate cancer (omCSPC) is a state of limited metastatic disease. Randomized trials have demonstrated improvements in progression-free survival in patients with omCSPC treated with metastasis-directed therapy (MDT). However, clinical outcomes remain heterogenous and response to MDT is variable, raising the need for prognostic/predictive biomarkers. A multimodal artificial intelligence (MMAI) biomarker (ArteraAI Prostate Test) was recently trained using data from patients with localized prostate cancer and found to be prognostic. Here, we evaluated this biomarker in omCSPC. **Methods:** We performed an international multi-institution retrospective review of 221 men with omCSPC who were evaluated with MMAI scoring. The primary objective was to compare overall survival (OS) between patients with high- and low-MMAI score (stratified by median score). OS was defined as the time from diagnosis of omCSPC to death of any cause, calculated with the Kaplan-Meier method and compared using the log-rank test and Cox regression. The secondary objective was to evaluate MMAI score as predictive for MDT treatment effect in a subset of patients enrolled in the STOMP and ORIOLE randomized clinical trials. Given too few OS events for this subset, we evaluated MMAI for metastasis-free survival (MFS), defined as time of randomization to development of a new metastasis or death of any cause and analyzed using Cox regression. An interaction test was performed between treatment arm and MMAI score. **Results:** Median follow-up of the surviving patients was 38.0 months. Patients with high MMAI (>0.527) were found to have higher PSA (5.8 vs 2.9, p=0.005), higher Gleason score (68.2% vs 38.8% Grade Group ≥4, p<0.001), more likely to have *de novo* metastatic disease (28.2% vs 8.1%, p<0.001), and more likely to have bone metastases (55.5% vs 39.6%, p=0.019). Patients with a high MMAI had a significantly worse OS (HR=4.38, 95% CI=1.24-15.56; p=0.022) with a median OS of 108.4 mo. vs "not reached" (p=0.012). In the STOMP and ORIOLE subset (N=51; median follow-up=61 months), MMAI was not prognostic for MFS (HR=1.24, 95% CI=0.64-2.43, p=0.52). MMAI however was predictive for MDT benefit as patients with high (HR=0.32, 95% CI=0.12-0.90; p=0.03), but not low (HR=1.59, 95% CI=0.63-4.04; p=0.33) MMAI demonstrated improvement in MFS when treated with MDT (p-interaction=0.02). **Conclusions:** We have shown for the first time that the ArteraAI MMAI biomarker is prognostic for OS in patients with omCSPC. Further, MMAI appears to be predict benefit of MDT with high MMAI demonstrating a greater improvement in MFS following MDT over observation. Further work in validating these findings is warranted to allow for greater personalization in the management of patients with omCSPC. Research Sponsor: None.

Correlation of body mass index (BMI) with survival outcomes in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC): Analysis of patient (pt)-level data from SWOG 1216 study.

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Background: Obesity has been associated with improved survival outcomes in metastatic castration-resistant prostate cancer (PMID: 34226662). However, association of obesity with survival has not been reported in mHSPC setting. Herein we report the correlation of BMI with survival outcomes from patient level data from phase III study, SWOG 1216 which randomized pts with mHSPC in 1:1 to ADT + bicalutamide or ADT + orteronel. **Methods:** Inclusion: all pts treated on SWOG 1216 study with available BMI. Overall survival (OS) was summarized by median survival and its 95% confidence interval (CI). Multivariate analysis for OS was conducted using Cox proportional hazard model with categorized BMI as a continuous variable, and adjusted for treatment arm, disease burden, Gleason score, log 2 PSA, age and Zubrod performance status. All analysis was conducted using R v4.2.1. **Results:** Of 1279 pts, 12 were underweight, 252 had normal BMI, 958 were overweight and 57 were obese. Median age was 67.8 (IQR: 61.9, 73.9) years, no visceral metastases (88%) and baseline log2 median PSA of 4.89 (IQR: 3.27, 6.76). All four BMI cohorts had similar age, Gleason score, extensive disease burden, liver metastases and treatment allocation ($p>0.05$). Differences in baseline PSA and Zubrod performance status were observed between BMI cohorts ($p<0.05$). The OS (in years) in underweight, normal, overweight and obese cohorts was 1.8, 4.4, 6.5 and 4.8 for bicalutamide arm and 2.8, 5.7, not reached (NR) and NR for orteronel arm, respectively. After adjusting for prognostic variables, multivariate analysis confirmed that high BMI is associated with better OS (HR=0.82, 95% CI: 0.68-0.98; p=0.029) (Table). **Conclusions:** Our results show that as categorized BMI increased, the risk of death decreased in pts with mHSPC. These data warrant external validation in other randomized phase III studies and can help counseling and prognostication of patients with mHSPC in the clinic. Funding: NIH/NCI grants CA180888, CA180819, and in part by Millennium Pharmaceuticals (Takeda Oncology Company). Clinical trial information: NCT01809691. Research Sponsor: None.

Multivariate cox proportional hazard model for OS.

Variable	HR	95% CI	p-value
BMI (categorized continuous)	0.82	0.68 - 0.98	0.029
Treatment (orteronel vs bicalutamide)	0.87	0.72 - 1.04	0.12
Extensive disease (yes vs no)	1.93	1.59 - 2.34	<0.001
Gleason score (≥8 vs <8)	1.24	1.02 - 1.51	0.027
Log 2 PSA	1.08	1.04 - 1.12	<0.001
Age	1.01	1.00 – 1.02	0.3
Zubrod performance status (0-1 vs ≥2)	2.63	1.79-3.86	<0.001

PROact: A prospective phase II study to evaluate olaparib plus abiraterone and prednisone combination therapy in patients with metastatic hormone sensitive prostate cancer with HRR gene mutation.

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Background: Approximately 10% - 15% of patients with metastatic hormone sensitive prostate cancer (mHSPC) harbor loss-of-function mutations in homologous recombination repair (HRR) genes. Although olaparib plus abiraterone and prednisone has significantly prolonged overall survival in metastatic castration resistant prostate cancer patients, there is a lack of evidence regarding the efficacy and safety of this combination therapy in patient with mHSPC. Here, we report the interim analysis results of PROact study, the first phase II trial to evaluate the effects of olaparib plus abiraterone and prednisone in mHSPC patients with HRR gene mutation. **Methods:** This was a single center, single arm, phase II trial (NCT05167175) conducted in male patients with mHSPC who had at least one HRR gene mutation (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD 51C, RAD51D*and *RAD54L*) as determined by tissue-NGS. Patients were administered olaparib 300 mg BID plus abiraterone 1000 mg QD and prednisone 5 mg QD. Previous treatment with new hormonal agent (NHA) was not allowed. The primary endpoint was 1-year radiographic progression-free survival (rPFS) rate per PCWG3-modified RECIST 1.1 by investigator assessment. The secondary endpoint included prostate-specific antigen (PSA) response rate, objective response rate (ORR), and adverse events. **Results:** Between May 19, 2022 and Dec 8, 2023, a total of 30 patients were enrolled and administered combination therapy. All the patients had *de novo* mHSPC, and the median age was 68 (range 49-85), with a median PSA of 166 ng/mL at baseline. A total of 7 HRR mutations were identified, included *BRCA2* (n=11), *CDK12* (n=8), *ATM*(n=6), *PALB2* (n=2), *CHEK2* (n=2), *RAD51B* (n=2) and *RAD51D* (n=1). As of Jan 29, 2024, the median follow-up was 7.1 months. In the 30 patients who had PSA response evaluated, PSA50 response rate achieved 100% (30/30), and the PSA90 response rate was 96.7%(29/30). In the 12 patients who had RECIST assessment, the objective response rate was 91.7% (11/12). Two achieved complete response, nine obtained partial response, and one had stable disease. The treatment was well tolerated, with 7(23.3%) patients experienced ≥grade 3 treatment-related adverse events (TRAEs). Common TRAE was anemia. **Conclusions:** This was the first trial to show efficacy and an acceptable safety profile of olaparib plus abiraterone and prednisone in mHSPC patients with HRR mutation. Data of primary endpoint of 1-year rPFS will be reported in the due time. Clinical trial information: NCT05167175. Research Sponsor: AstraZeneca; CHIATAI TIANQING; Chosen Med.

Post-progression survival of patients with metastatic hormone-sensitive prostate cancer (mHSPC) who received darolutamide or placebo: Post hoc analysis of ARASENS.

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Background: Darolutamide (DARO) is a structurally distinct and highly potent androgen receptor pathway inhibitor (ARPI). In ARASENS (NCT02799602), the addition of DARO to androgen-deprivation therapy (ADT) and docetaxel (DOC) significantly reduced the risk of death by 32.5% in patients (pts) with mHSPC, despite most placebo (PBO) pts (75.6%) receiving subsequent therapy. DARO also delayed time to progression to metastatic castration-resistant prostate cancer (mCRPC; median, not reached vs 19.1 months for PBO), resulting in a longer time in mHSPC, which is associated with improved quality of life vs mCRPC. We report post-progression subsequent anticancer therapies and related survival from ARASENS. **Methods:** Pts with mHSPC were randomized 1:1 to DARO 600 mg twice daily or PBO in addition to ADT + DOC. After treatment discontinuation, pts entered active and long-term survival follow-up periods during which assessments included subsequent therapies and survival outcomes. Post-progression survival was defined as time from first subsequent therapy to death using Kaplan-Meier estimates. **Results:** Of 1305 treated pts (DARO n=651; PBO n=654), 315 receiving DARO and 495 receiving PBO entered follow-up. Of these, 57% (n=179) and 76% (n=374), respectively, received subsequent therapy; abiraterone and enzalutamide were the most frequent first subsequent therapy (Table). In the DARO arm, 90% of first subsequent therapies were ARPI or chemotherapy. Minimal difference was observed in post-progression survival between subsequent therapies, suggesting subsequent therapy with another ARPI does not provide further survival benefit vs non-ARPI options (mainly chemotherapy). In contrast, in the PBO arm where the majority (78%) received first subsequent therapy with an ARPI, a survival benefit was observed vs non-ARPI subsequent therapies (median, 23.0 vs 13.5 months). **Conclusions:** DARO+ADT+DOC increased overall survival vs PBO+ADT+DOC and also delayed time to progression to mCRPC. DARO pts had similar survival with all post-progression therapies. Pts receiving PBO+ADT+DOC quickly progressed to mCRPC and treatment with an ARPI in ARPI-naïve pts improved survival. Clinical trial information: NCT02799602. Research Sponsor: Bayer.

First subsequent anticancer therapy in ARASENS.

	Darolutamide (N=651)	Placebo (N=654)
No. of patients who entered active/long-term follow-up*	**315**	**495**
No. (%) of patients with subsequent anticancer therapy†	**179 (56.8%)**	**374 (75.6%)**
Abiraterone acetate	83 (46.4%)	193 (51.6%)
Enzalutamide	29 (16.2%)	97 (25.9%)
Abiraterone acetate/enzalutamide	***112 (62.6%)***	***290 (77.5%)***
Cabazitaxel	26 (14.5%)	26 (7.0%)
Docetaxel	26 (14.5%)	45 (12.0%)
Cabazitaxel/docetaxel	***52 (29.1%)***	***71 (19.0%)***
Radium-223	10 (5.6%)	8 (2.3%)

*Includes 1 patient who did not enter follow-up but received subsequent therapy.
†5 patients in each arm received sipuleucel-T, lutetium-177 PSMA-617, or apalutamide.

EMBARK post hoc analysis of sexual activity (SA) patient-reported outcomes (PROs) in patients (pts) who were sexually active or interested in sex at baseline (BL).

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Background: In EMBARK (NCT02319837), enzalutamide (ENZ) + leuprolide (L) or ENZ (ENZ mono) delayed metastasis-free survival vs placebo (P) + L while maintaining high quality of life (QoL) in high-risk biochemically recurrent nonmetastatic hormone-sensitive prostate cancer. SA (a composite score from European Organization for Research and Treatment [Tx] of Cancer QoL Questionnaire-Prostate 25 [QLQ-PR25]) was better preserved with ENZ mono vs P + L with no difference between ENZ + L vs P + L. To better understand effect on SA in relevant subgroups, we examined SA in pts who were sexually active or interested in sex at BL. **Methods:** QoL was assessed (BL, every 12 weeks) until metastasis/death. Cox regression was used to examine time to confirmed deterioration (TTCD) (confirmed at next visit) defined by one category change for sexual interest, activity, satisfaction, erectile function, and feeling like a man using QLQ-PR25 and FACT-P items (Table).Intent-to-treat analysis was applied. **Results:** Among pts interested in sex (n=694) or sexually active (n=437) at BL, TTCD in QLQ-PR25 SA domain, items 50 (interest), 51 (activity), GS7 (satisfaction), and BL5 (erectile function) were significantly delayed with ENZ mono vs P + L. In contrast, TTCD in BL5 (erectile function) was shorter with ENZ + L vs. P + L (Table). **Conclusions:** Among pts who were interested in sex or sexually active at BL, ENZ mono better preserved SA vs P + L in terms of SA domain, interest, activity, satisfaction, and maintaining erection. Adding ENZ to L had no impact on interest, activity, or satisfaction but may adversely affect erectile function, though differences in the median TTCD were clinically non-significant (0.06 months [1.8 days] and 0.09 months [2.7 days] in pts interested in sex and sexually active at BL, respectively). Clinical trial information: NCT02319837. Research Sponsor: This study was funded by Astellas Pharma Inc. and Pfizer Inc., the co-developers of enzalutamide.

	Interested in sex at BL (n=694)					Sexually active at BL (n=437)				
	median months			HR [95% CI]		median months			HR [95% CI]	
	ENZ + L	ENZ mono	P + L	ENZ + L vs P + L	ENZ mono vs P + L	ENZ + L	ENZ mono	P + L	ENZ + L vs P + L	ENZ mono vs P + L
QLQ-PR25 SA	2.96	5.59	2.96	1.08 [0.89, 1.32]	0.75 [0.61, 0.92]	2.86	5.45	2.89	1.10 [0.86, 1.40]	0.69 [0.54, 0.90]
50: ***To what extent were you interested in sex?***	5.42	8.48	5.55	1.04 [0.85, 1.28]	0.70 [0.57, 0.87]	2.99	11.10	5.52	1.02 [0.78, 1.32]	0.65 [0.49, 0.85]
51: ***To what extent were you sexually active (with/ without intercourse)***	2.89	8.18	2.96	1.14 [0.89, 1.47]	0.67 [0.51, 0.87]	2.89	5.72	2.96	1.15 [0.90, 1.47]	0.69 [0.54, 0.90]
FACT-P										
GS7: ***I am satisfied with my sex life***	5.55	11.07	5.39	0.82 [0.60, 1.12]	0.57 [0.41, 0.80]	3.25	8.44	2.96	0.79 [0.56, 1.12]	0.59 [0.41, 0.85]
P5: ***I am able to feel like a man***	16.59	14.16	14.00	1.00 [0.80, 1.26]	1.03 [0.82, 1.29]	13.73	13.77	14.00	1.17 [0.88, 1.54]	1.08 [0.81, 1.43]
BL5: ***I am able to have and maintain an erection***	2.83	5.55	2.89	1.55 [1.15, 2.08]	0.66 [0.48, 0.90]	2.83	5.55	2.92	1.74 [1.24, 2.43]	0.68 [0.48, 0.97]

CI: confidence interval; HR, hazard ratio.

Prognostic value of baseline circulating tumor DNA (ctDNA) tumor fraction (TF) in metastatic hormone-sensitive prostate cancer (mHSPC).

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Background: In mHSPC, CHAARTED-defined disease volume and prior local definitive therapy are prognostic factors. These factors are imperfect and may not capture the clinical heterogeneity in mHSPC. Thus, new prognostic biomarkers are needed. ctDNA is a promising tool given the ease of obtaining genomic data and ctDNA TF. Although ctDNA has been well studied in metastatic castration-resistant prostate cancer (mCRPC), the prognostic value of ctDNA in mHSPC is unknown. **Methods:** We present a multi-center, non-interventional, prospective study of ctDNA in patients (pts) with newly diagnosed mHSPC. ctDNA was collected at baseline (prior to androgen deprivation therapy [ADT]), on mHSPC therapy (1 month [mo] and/or 6-7 mo after), and at mCRPC. Specimens were processed using the FoundationOne Liquid CDx assay (324 genes). Kaplan-Meier and Cox regression models were used to measure clinical endpoints including overall survival (OS) and time to mCRPC (TTCRPC). **Results:** Between January 2018 and August 2023, 73 pts were enrolled, of whom 56 had baseline ctDNA successfully processed. Median age was 72 years (interquartile range [IQR]: 66-76). 77% were White; 16% were Black. Most (68.5%) had de novo metastatic disease; 31.5% had recurrent disease. Median pre-ADT PSA was 38.0 ng/mL (IQR 15.2-175.0). CHAARTED high volume (HV) disease was present in 73%. Common metastatic sites were bone (80%) and lymph nodes (66%). All were treated with ADT, 19% of whom had ADT alone. Most (63%) had an androgen receptor signaling inhibitor (ARSI) or docetaxel (6%) added; 12% had triplet therapy (ADT with ARSI and docetaxel). Baseline detectable TF (TF+) was present in 35/56 (62.5%); 21/56 (37.5%) had baseline undetectable TF (TF-). Frequent gene alterations were *TP53*(39%), *PTEN* (23%), and *TMPRSS2*(16%). Pts with baseline TF+ had a median OS (mOS) of 37 mo vs not reached (NR) (HR 2.57, 95% CI 0.55-11.93, p=0.2) and median TTCRPC (mTTCRPC) of 15 mo vs NR (HR 2.07, 95% CI 0.75-5.71, p=0.2) compared to pts with baseline TF-. In subgroup analysis of pts with HV disease, mOS was 37 mo with baseline TF+ vs NR with TF- (HR 2.77, 95% CI 0.35-22.23, p=0.3); mTTCRPC was 12 mo vs 18 mo (HR 1.56, 95% CI 0.44-5.49, p=0.5). In pts with low volume disease, a similar observation with mTTCRPC was found in TF+ vs TF- (14 mo vs NR, HR 1.7, 95% CI 0.23-12.0, p=0.6). Among 30 pts with on-treatment samples, TF+ during therapy had a mOS of 37 mo vs 61 mo (HR 2.67, 95% CI 0.69-10.35, p=0.2) and mTTCRPC of 12 mo vs 52 mo (HR 1.75, 95% CI 0.68-4.47, p=0.2) compared to TF-. **Conclusions:** Pts with mHSPC and baseline TF+ appear to have a quantitative but not statistically significant worse OS and TTCRPC compared to pts with TF- regardless of disease volume. Inclusion of additional pts and longer follow-up may validate whether ctDNA can improve treatment decision making in mHSPC. Further work looking at TF threshold (>10% vs <10%) is ongoing. Research Sponsor: Foundation Medicine, Inc.; Prostate Cancer Foundation; U.S. National Institutes of Health; 5P50CA186786.

Abiraterone with discontinuation of gonadotropin-releasing hormone (GnRH) analogues in patients (pts) with metastatic prostate cancer (PC): A single arm, phase II study.

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Background: Abiraterone acetate (AA) is approved in metastatic PC. AA inhibits CYP17, required for androgen biosynthesis. A first in human trial suggested that AA monotherapy was inadequate to maintain castrate testosterone (T) in non-castrate men and AA development required continued GnRH analogues. However, T recovery is often delayed post GnRH analogue cessation; the need for their ongoing use to maintain castrate T with AA use is unclear and studies are limited. We present a single arm, phase II trial of pts with metastatic PC treated with AA+Prednisone (AAP) after GnRH discontinuation. **Methods:** We conducted a single arm, phase II study for pts with metastatic PC treated with AAP with GnRH analogue discontinuation. Entry criteria required metastatic PC treated with AAP and GnRH analogue & baseline T of <50 ng/dl without previous orchiectomy. After enrollment AAP was continued with GnRH analogue discontinuation. Primary endpoint was the pt proportion with castrate T (<50 ng/dl) at 6 months. Secondary endpoints included time to LH normalization, PSA response, radiographic progression-free survival (rPFS) and overall survival (OS). T, PSA & LH levels were monitored at 12-week intervals. We used descriptive statistics to assess the time to non-castrate testosterone levels, LH normalization time & mean T, LH & PSA levels at each monitoring timepoint. **Results:** We enrolled 31 pts; 27 were evaluable at 6 months. Median age was 69 years. Race/Ethnicity included 21 (68%) non-Hispanic black (68%) and 10 (32%) Hispanic pts. Sixteen (52%) had castration-resistant disease as AAP indication. Mean duration of ADT and AAP prior to enrollment were 29.1 (3-204) and 9.2 (1-38) months, respectively. Median follow up was 28 months. At 6 months, 25/27 (92%) patients had castrate T as did 22/26 (85%) at 12 months, 18/23 (78%) at 18 months, 16/22 (73%) at 24 months and 11/17 (65%) at 30 months. There were no treatment discontinuations due to toxicity Mean T, LH and PSA values at timepoints are reported. rPFS and OS will be reported later. **Conclusions:** Pts with metastatic PC treated with AAP after GnRH analogue discontinuation often remain castrate with AAP monotherapy even 30 months after GnRH analogue cessation. Phase III trials showing benefit of AAP required continued GnRH analogue; this small phase II study does not change standard of care but does suggest that further evaluation of AAP monotherapy may be warranted; AAP without use of GnRH inhibitors successfully suppressed T levels. Further randomized clinical trials are needed to assess the role of AAP monotherapy without GnRH analogues in metastatic PC. Clinical trial information: NCT03565835. Research Sponsor: None.

Timepoints	Mean T levels (ng/dl)	Mean LH levels (mIU/mL)	Mean PSA levels (ng/mL)
Baseline	1.15	0.31	1.03
6 months	2.95	15.9	1.15
12 months	4.3	22.3	1.69
18 months	6.31	19.2	0.96
24 months	6.4	18.1	1.12
30 months	6.6	16.6	0.4

Resources to address challenges in first-line treatment intensification in metastatic castration-sensitive prostate cancer (mCSPC): A discrete choice experiment.

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Background: Althoughfirst-line treatment intensification (TI) (i.e., androgen-deprivation therapy with chemotherapy, novel hormonal therapies, or both) is recommended in mCSPC guidelines, it is used in <1/3 of patients. Phase 1 of the IMPLEMENT study used an implementation science approach to identify barriers to and facilitators of TI. Phase 2 of IMPLEMENT aimed to prioritize these factors and identify resources to increase TI. **Methods:** A discrete choice experiment was developed for 300 US-based physicians (150 oncologists, 150 urologists) who manage mCSPC. It included 6 descriptions of potential resources to help with TI decisions, based on results from Phase 1. Respondents selected from pairs of resource sets the set they perceived as most helpful across 12 scenarios. We analyzed responses using a mixed-effects logistic regression model and calculated a coefficient of helpfulness for each resource to identify those with the strongest impact on physicians' decisions. Coefficients were required to have a minimum value of zero, as resources would be optional. **Results:** Overall, physicians preferred decision support tools and databases of post-treatment options. Urologists found decision support tools most beneficial (coefficient of helpfulness 3.27; 95% CI 2.90-3.64), while oncologists preferred post-treatment databases (2.58; 95% CI 2.29-2.89) and clinical trial summaries (2.41; 95% CI 2.13-2.69). Tools to reduce administrative burden and information on outcomes of earlier vs later TI were not considered as helpful compared to other resources and across specialties. **Conclusions:** There were key differences between specialties in the helpfulness of resources, indicating substantial variability in clinical practice needs. These findings provide a clear path to develop concrete, specialty-tailored tools to increase guideline-concordant treatment of mCSPC. Research Sponsor: Astellas Pharma Inc; Pfizer Inc.

Resource Description	Associated Theme	Coefficient of Helpfulness*, mean (95% CI)
Decision support tool linking patient characteristics to first-line treatment options	Patient Assessment	1.91 (1.56, 2.31)
Database of post-treatment options after progression on TI	Anticipated Regret	1.73 (1.48, 2.01)
Summaries of key mCSPC clinical trial data	Knowledge of TI Outcomes	1.15 (0.92, 1.42)
Cross-specialty mCSPC treatment guidelines	Divergent Roles Between Specialties	0.64 (0.53, 0.77)
Information comparing clinical outcomes of first-line vs later TI in mCSPC	Disease Progression	0.35 (0.29, 0.43)
Tools to reduce administrative burden	Cost & Financial Toxicity	0.21 (0.17, 0.27)

*Coefficients >1: above average utility; <1: below average utility. Logit model accuracy: 72%.

Whole exome correlates in metastatic hormone sensitive prostate cancer (mHSPC): Results from E3805 CHAARTED.

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Background: The landscape and clinical impact of genomic variants in mHSPC are incompletely understood. We have shown that deleterious germline *BRCA2* alterations (alts) associate with shorter time to castration resistant prostate cancer (TTCRPC) on androgen deprivation therapy (ADT), but not on ADT plus docetaxel (ADT+D) (ASCO 2023). Somatic variation from tissue of patients (pts) with mHSPC is not well characterized and may influence therapeutic outcomes. **Methods:** We performed whole exome sequencing of HSPC specimens obtained at initial diagnosis and germline DNA from whole blood from pts in the CHAARTED trial (NCT00309985) of ADT vs ADT+D. Somatic single nucleotide variants (SNV) and allele-specific copy number alts (CNAs) were identified, including estimation of tumor mutational burden (TMB) and copy number burden (CNB). Prognostic effects were evaluated in both arms. Loss of selected tumor suppressor genes was defined by monoallelic or biallelic loss. TTCRPC and overall survival (OS) were estimated by Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated by Cox models. **Results:** After quality control, 68 tumor-normal cases were analyzed. The majority of pts had synchronous(51.5%) and high volume (58.8%) disease. Most frequent somatic SNVs were *TP53* (33.8%), *PTEN* (7.4%), *PIK3CA* (5.9%) and *SPOP* (5.9%). *AR* amplification was uncommon (4.4%), however frequent *MYC* gain (60.3%) was seen as well as monoallelic deletion of *NKX3-1*, *TP53*, *PTEN* and *BRCA2*. Whole genome doubling occurred in 14.7%. Median TMB and CNB were 4.7 mut/Mb and 9.1%, respectively. CNB was elevated in synchronous (p=0.01) and high volume (p=0.046) disease. CNB greater than median was associated with shorter TTCRPC in the overall cohort (HR 2.06, 95%CI 1.13-3.75, p=0.015) and ADT+D arm (HR 2.98, 95%CI 1.17-7.58, p=0.016). The effect in the overall cohort was reduced after adjustment for volume and presentation (HR 1.72, p=0.091). A compounding effect of *PTEN* and *TP53* alts was seen in the ADT arm where median TTCRPC for wild-type (WT), 1-gene hit, 2-gene hit was 19.6 mos, 8.5 mos, 6.3 mos, respectively. The median OS of WT vs 1-hit/2-hit loss was 47.1 mos vs 26.8 mos (HR 2.05, 95% CI 0.90-4.68, p=0.087). Similar differences in TTCRP and OS by *PTEN*/*TP53* status were not observed with ADT+D. **Conclusions:** The genomic landscape of mHSPC is characterized by frequent alts in putative drivers known to be enriched in mCRPC (Table). We observed a low rate of genomic instability and AR amplification/mutation similar to non-metastatic HSPC. Concordant with the STAMPEDE trial, greater CNB confers a higher risk of progression. Combined tumor suppressor gene alts associate with prognosis in mHSPC, which may differ by therapy intensification. Research Sponsor: None.

Frequency (%) of recurrent and pathogenic genomic alts.

	TCGA-M0	CHAARTED-mHSPC	SU2C-mCRPC
AR	1	4	63
TP53	8	35	53
PTEN	17	16	40
PIK3CA	2	6	5
SPOP	11	6	8
MYC	7	9	13
BRCA2	3	9	13

A phase II trial of enzalutamide (Enz) with 5-alpha reductase inhibitors (5-ARI) as an androgen deprivation therapy (ADT)–sparing approach for older men with castration-sensitive prostate cancer (CSPC).

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Background: Older men with prostate cancer who have aging-related conditions are at high risk for adverse events (AEs) from ADT. 5-ARI inhibit the conversion of testosterone to dihydrotesterone and could be synergistic with Enz. In this phase II study, we evaluated Enz and Dutasteride (Dut) or Finasteride (Fin) in lieu of ADT for older men with CSPC who are at risk of AEs from ADT. **Methods:** Eligible patients were ≥65 years (y); deemed "not fit" by geriatric assessment (GA) or at high risk for side effects from ADT as determined by the treating physician; had metastatic (M1) or non-metastatic (M0) CSPC with a PSA doubling time ≤9 months and testosterone >50ng/dl. Enz 160 mg daily and Dut 0.5mg daily or Fin 5mg daily were administered until disease progression per Prostate Cancer Clinical Trials Working Group 2 guidelines. The primary study endpoint is PSA progression free survival (PFS). Key secondary endpoints include time to PSA nadir, absolute PSA nadir and evaluation of safety and toxicity of study treatments per CTCAE V4.0. **Results:** 43 men enrolled in the study. At study entry, subjects had the following baseline characteristics: median age was 78 y (range 66-94); 93% had ECOG 0-1; 63% had M1 CSPC with 30% of them having high volume disease per CHAARTED criteria; 23% had Gleason ≥ 8 CSPC; median PSA was 11.4 ng/ml (2-145), and median testosterone level was 342 ng/dl (56-639). Baseline GA at study entry showed that 18.6% had Instrumental Activity of Daily Living impairment; 9.8% had recent falls; 52.4% had Short Physical Performance Battery impairment; 40.5% had Older American Resources and Services (OARS) physical health and 31% had OARS medical social support impairments; 11.6% had Geriatric Depression Scale impairments; 65.9% had either Blessed Orientation-Memory-Concentration or Montreal Cognitive Assessment impairments; and 34.9% had Vulnerable Elders Survey-13 impairments. At a median follow-up of 5.9 y, 23 pts (53%) remained on study treatment and the median PSA PFS has not been reached for the entire group. The median time to PSA nadir was 8.1 months, with median PSA nadir at 0.02 ng/ml (range 0-2.75) and 98% having ≥90% PSA decline. The five most common any grade AE was fatigue (88%), gynecomastia (72%), hot flashes (42%), hypertension (40%), and falls (37%). No subject had treatment-related Grade 4 or 5 AEs. Four (9.3%) subjects withdrew treatment, 21% held treatments and 30.2% reduced dose of treatment due to AEs. **Conclusions:** The combination treatment with Enz and Dut/Fin appears to have clinical efficacy for older patients with CSPC who are at high risk for AEs from ADT. Clinical trial information: NCT02213107. Research Sponsor: Astellas Pharma Global development and Pfizer.

Association of androgen receptor gene expression signature and *ARV7*with clinical outcome in metastatic hormone-sensitive prostate cancer.

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Background: The androgen receptor (AR) plays a predominant role in prostate cancer (PC) biology and it represents a cornerstone of PC treatment strategies, including androgen deprivation therapy (ADT) and androgen receptor selective inhibitors (ARSI). However, the androgen receptor splice variant 7 (*ARV7*) has emerged as a biomarker for resistance to AR target therapies. In this study we aim to investigate a signature of AR-regulated genes and the *ARV7* in a cohort of metastatic hormone-sensitive prostate cancer (mHSPC) patients (pts). **Methods:** This is a multicenter retrospective biomarker study performed in mHSPC pts treated with ADT, ADT+Docetaxel (D) and ADT+ARSI (abiraterone/enzalutamide). A customized panel of 184 genes was tested in from FFPE tumor samples by nCounter platform (Nanostring Technologies). AR signature was comprised of 31 AR-related genes. Single-sample GSEA (ssGSEA) was used to calculate a gene-set enrichment score per patient. RNA expression levels were correlated with castration resistance-free survival (CRPC-FS) (primary endpoint) and overall survival (OS) by Kaplan Meier and multivariate Cox modeling. Analyses were performed with R software (v.4.3.2). **Results:** A total of 326 pts were included: 93 treated with ADT, 125 with ADT+D, and 108 with ADT+ARSI. Baseline PSA was 44 ng/ml (range 0.2–7448), Gleason score was $\geq$ 8 in 72.7% of pts, 15.3% had visceral metastasis, 64.6% had high volume disease and 77.9% were de novo stage IV disease. Median follow-up was 39.5 months (m) (95%CI 4.4–223.5). Median time to CRPC was 21.7 m (95%CI 19.4–25.9) and median OS 49.1 m (95%CI 43.9–57.1). Among the 326 pts, 108 (33.1%) were classified as high AR signature, while 81 of them (24.8%) were considered high *ARV7*. High AR signature expression levels were associated with less frequency of visceral metastasis (p=0.01) and high *ARV7*expression correlated with higher Gleason scores (p=0.009). High AR signature expression independently correlated with longer CRPC-FS (33 vs 19.3 m; HR 0.7, p=0.011). Considering AR signature individual genes as continuous variables in the multivariate analysis, the high expression of four genes was independently associated with longer CPRC-FS: *KLK3* (HR 0.9, p=0.024), *KLK2* (HR 0.9, p=0.027), *CD200* (HR 0.8, p=0.028), and *GNMT* (HR 0.9, p=0.013). Besides, the high expression of these genes was independently associated with longer OS: *KLK3* (HR 0.8, $p<0.001$), *KLK2*(HR 0.9, p=0.014), *CD200*(HR 0.8, p=0.014), *ACSL3*(HR 0.8, p=0.015), and *PTGER4* (HR 0.8, p=0.04). Focusing in the *ARV7*gene, a high expression of *ARV7* was independently associated with shorter OS (43.2 vs 52.2 m; HR 1.4, p=0.028). **Conclusions:** High expression of the AR signature correlates with a better prognosis in mHSPC pts, while high expression of *ARV7*is associated with adverse clinical outcomes. This may be useful as a potential biomarker to personalize treatment strategies. Research Sponsor: None.

Impact of alterations in tumor suppressor genes (TSG-alt) on survival outcomes in patients (pts) with de novo metastatic castration-sensitive prostate cancer (dn-mCSPC) receiving androgen deprivation therapy (ADT) with androgen receptor pathway inhibition (ARPI) or docetaxel.

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Background: TSG-alt have been associated with poor survival in the mCRPC setting (PMID: 31061129) and in the mCSPC setting from small single institution cohorts (PMID: 34294873). However, large studies evaluating their impact on survival outcomes with ADT intensification in mCSPC setting are lacking. Herein, we evaluate the impact of TSG-alt on outcomes in a large real-world patient population with dn-mCSPC receiving ADT treatment (Rx) with ARPI or docetaxel. **Methods:** This study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine Prostate Cancer clinical-genomic database (FH-FMI CGDB), with de-identified data originating from approximately 800 US cancer clinics. Inclusion criteria: dn-mCSPC, tissue biopsy within 90 days of diagnosis, and initiation of ARPI or docetaxel + ADT within 120 days of diagnosis. Time to castration-resistance (TTCR) and overall survival (OS), indexed from metastatic diagnosis, were evaluated with Cox proportional hazards models adjusted for baseline prognostic factors (PSA, Gleason score, age, ECOG, hemoglobin, alkaline phosphatase, and albumin). OS risk intervals were left truncated to date of comprehensive genomic profiling report to adjust for immortal time bias. **Results:** Of 5356 pts in FH-FMI CGDB, 571 met inclusion criteria. Of these, 321 received ADT + ARPI and 250 ADT + docetaxel. Pts with pathogenic TSG alt were: 214 *TP53* (37%), 154 *PTEN* (27%), and 37 *RB1* (6%). Results are summarized in Table. **Conclusions:** In this real-world analysis, alt*RB1* and alt*TP53* had worse OS than their respective wild-type (wt) counterparts with both ARPI and docetaxel whereas alt*PTEN* had similar OS with ARPI and Docetaxel in dn-mCSPC pts. Based on these results, *RB1* and *TP53* may represent prognostic biomarkers guiding treatment selection and clinical trial enrollment in dn-mCSPC and may assist with counseling and prognostication. Research Sponsor: None.

Adjusted Hazard ratios for TTCR and OS (adjusted for baseline PSA, Gleason score, age, ECOG, hemoglobin, alkaline phosphatase and albumin).

Gene	ARPI TTCR aHR (95% CI, p)	Docetaxel TTCR aHR (95% CI, p)	ARPI OS aHR (95% CI, p)	Docetaxel OS aHR (95% CI, p)
alt*RB1* vs wt*RB1*	3.58 (2.04-6.29, <0.01)	0.77 (0.38-1.57; 0.47)	4.03 (2.30-7.10; <0.01)	2.85 (1.56-5.21, <0.01)
alt*TP53* vs wt*TP53*	1.60 (1.16-2.22, <0.01)	1.15 (0.86-1.52, 0.36)	1.62 (1.12-2.34, 0.01)	1.47 (1.03- 2.08, 0.03)
alt*PTEN* vs wt*PTEN*	0.96 (0.67-1.38, 0.83)	0.92 (0.67-1.26, 0.62)	1.01 (0.66-1.54, 0.95)	0.91 (0.63-1.32, 0.62)

aHR: adjusted hazard ratio.

Comparison of outcomes with docetaxel or ARPI combination therapy for metastatic hormone-sensitive prostate cancer (mHSPC) by volume of disease.

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Background: Combination therapy has improved treatment of metastatic hormone sensitive prostate cancer (mHSPC). Doublets include androgen deprivation therapy (ADT) plus docetaxel (DOC) or the androgen receptor pathway inhibitors (ARPIs) abiraterone, enzalutamide, apalutamide, or darolutamide. There have been no large clinical trials that compare DOC to ARPIs in mHSPC. This study evaluates overall survival and time to castration-resistance in patients with de novo (synchronous) mHSPC in the Veterans Health Administration treated with combination therapy. **Methods:** Veterans were identified with initial diagnosis of 'distant' prostate cancer. All veterans had ADT initiated within 4 months of diagnosis and followed until September 2023. First combination therapy with DOC from 7/2016-6/2021 or ARPI from 7/2017-6/2021 were included if initiated within 4 months after ADT. Volume of disease was determined from chart review and castration-resistance (mCRPC) by a combination of natural language processing and administrative data. Real-world progression-free survival (rwPFS) was determined as time to mCRPC or death. Kaplan-Meier time to event analyses and Cox proportional hazard modeling with age, Black race, Charlson comorbidity index, prostate specific antigen, body mass index, and weight change in the year prior was used for analyses. **Results:** 1,226 patients with de novo mHSPC were identified with median age of 71.5 years and 349 (28.6%) were Black. High volume disease was identified in 929 (76.0%) and low volume in 293 (24.0%). DOC was used in 341 (27.9%) and ARPIs in 881 (72.1%). Veterans with high volume disease had shorter overall survival (OS) than low volume (23.8 vs. 64.1 months, $p<0.001$). Overall, there was no difference in OS between DOC and ARPI (36.4 vs. 38.9 months, p=0.68), however DOC was associated with a shorter rwPFS (16.5 vs 22.1 months, $p<0.001$). In high volume disease, there was no difference in OS between DOC and ARPI (33.8 vs. 32.5 months, p=0.68), however DOC was associated with a shorter rwPFS (14.9 vs 19.2 months, p=0.002). In a multivariable model of patients with high volume disease, there was no difference in OS observed between initial treatment with DOC and ARPIs (aHR 0.83, 95% CI 0.69-1.00). **Conclusions:** In veterans with de novo mHSPC, no difference in OS were observed between combination treatment with DOC or ARPI in patients with low or high-volume mHSPC. ARPIs were associated with longer progression free survival. Due to a lack of clinical trials comparing DOC and ARPI therapy, these data may guide selection of combination therapy for mHSPC. Research Sponsor: Prostate Cancer Foundation; U.S. Department of Defense; W81XWH-22-1-0602.

Time in months to rwPFS or death in veterans with synchronous mHSPC.

	Low Volume n=293		High Volume n=929	
Treatment	**rwPFS (mos)**	**Overall Survival (mos)**	**rwPFS (mos)**	**Overall Survival (mos)**
ADT+docetaxel n=341	24.3	64.5	14.9	33.8
ADT+ARPI n=881	41.9	67.4	19.2	32.5
Total n=1226	37.3	64.5	17.2	33.0

Therapeutic strategy for targeting recurrent oncogenic kinase gene fusions in prostate cancer.

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Background: Prostate cancer is known to be the second leading cause of death for men in the United States. Studies so far have indicated androgen signaling to be a crucial pathway in prostate cancer progression. The primary goal of this study was to profile and sort the oncogenic kinase gene fusions by their clinical and genetic characteristics. We also sought to identify molecular alterations of the androgen receptor (AR), including fusions, AR variants, and co-occurring pathogenic variants including mutations, amplifications, and deletions. **Methods:** We performed molecular profiling with WES and WTS of 8377 prostate cancer tumor tissue and metastatic tumor specimens. Targeted NGS evaluating single nucleotide alterations, copy number alterations, and fusions was performed on these specimens. **Results:** Our studies identified that out of 8377 tumor samples 128 harbored recurrent, oncogenic kinase fusions (1.5%). Amongst all the kinase gene fusion cases BRAF (0.8%) had the highest number of fusions followed by FGFR2 (0.2%), AKT3 (0.2%) and RAF (0.1%). All BRAF & RAF1 fusions functioned as 3` partners and retained the kinase domain. For fusions involving FGFR2 and AKT3, they participated as both 5' and 3' partners, retaining the kinase domain. We then characterized the fusions based on their concordant mutational status with high frequency of TP53 (23.3%) and PI3KCA (9.2%) mutations. We next examined AR status due to its pivotal role in prostate cancer progression and found that AR pathogenic mutations only accounted for 4.2% of the total number of fusion cases. For BRAF fusion targets, it was noted that very few AR point mutations (W742C and H875Y), known to cause resistance to AR antagonists, associated with it. Other fusions targets like FGFR2, AKT3 and RAF1 also harbored very few co-occurring pathogenic mutations in AR. Another constitutively active variant of androgen receptor that lacks the androgen binding domain is ARv7 is observed in 15.6% of cases. **Conclusions:** Prostate cancer has been very difficult to treat, and first line of treatment so far has mainly included androgen related therapy and chemotherapy. However, our studies reveal the presence of recurrent gene fusions in prostate cancer that may likely play a crucial role in tumor progression. BRAF had the highest number of kinase fusion cases followed by FGFR2, AKT3 and RAF1. Interestingly for cases with BRAF fusions, it was observed that it retained the kinase domain, harbored no AR fusions or alterations and had very few co-occurring mutations. Similarly other fusions targets like FGFR2, AKT3 and RAF1 also had very few AR mutations and 79 % of kinase fusions retained the kinase domain. Our data suggests that the fusion targets may be functioning in an AR independent mechanism, mediated by constitutively active kinase domain present in these fusions. Repurposing kinase inhibitors in combination with AR inhibitors might be a new therapeutic opportunity. Research Sponsor: None.

Sexual health outcomes in sexual minority vs. heterosexual men after prostate radiotherapy.

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Background: The impact of prostate cancer treatments on sexual health outcomes in sexual minority men (SMM), especially in those who engage in receptive anal intercourse (RAI), remains an underrepresented area of scientific investigation. Additionally, limited data exist on differences between treatment-related sexual dysfunction in SMM and heterosexual men (HET). **Methods:** We conducted an exploratory retrospective analysis of a cohort of sexually active cancer survivors with intact prostates who were seen at least 6 months post-radiotherapy (RT), completed androgen deprivation therapy (ADT), and presented for follow-up between 6/2022 and 8/2023. Patients self-reported sexual orientation, gender identity, sex at birth, sexual behaviors, and PROMIS SexFS scores for orgasm ability, orgasm pleasure, sexual satisfaction, and anal discomfort domains. Average PROMIS scores were compared to the U.S. general population of adult men normative standard scores and between subgroups with mean differences [MD] and t-tests. We considered MD $>$ 3 points to be clinically meaningful. SHIM scores were dichotomized to erectile dysfunction ($<$16) and function ($>$17), and analyzed with logistic regression at baseline, 1-, and 2-years post-RT. **Results:** Of eligible HET and SMM, 39% HET (n=57/145) and 68% SMM (n=21/31) were sexually active with a partner (p=0.005); including 15 (71%) SMM who reported engaging in RAI. Overall, 8% were treated with brachytherapy, 46% external beam radiotherapy, and 46% both; 14% of patients received ADT. Median age was 66 years (interquartile range [IQR]: 61, 71), and median time to survey was 1.3 years (IQR: 0.9, 3.3). The cohort reported worse orgasm function (MD: 3.3, [95% CI: 0.9, 4.7], p$<$0.01), orgasm pleasure (MD: 7.2, [95% CI: 5.3, 9.1], p$<$0.001), and satisfaction (MD: 3.4, [95% CI: 1.9, 4.9], p$<$0.001) compared to norms. Very few demographic or outcome differences were observed between SMM and HET. SMM were more likely to be single (71%) than HET (33%, p$<$0.005). No differences in erectile function were observed between HET and SMM engaging in insertive intercourse. However, sexually active SMM engaging in RAI reported clinically meaningful differences in orgasm ability (MD: 3.5, [95% CI: -2.9, 9.9], p=0.1), orgasm pleasure (MD: 6.3, [95% CI: 5.2, 9.2], p=0.05), and anal discomfort (MD: 9.0, [95% CI: -0.9, 18.9], p=0.06) but not in satisfaction compared to norms. No clinically meaningful differences were observed by radiation modality. **Conclusions:** Prostate RT impacts sexual function in HET and SMM. However, the distinct health concerns of SMM and the unique functional anatomy involved in RAI underscore the need for prostate cancer clinicians and researchers to include RAI in sexual outcomes, collect data specific to SMM, and develop targeted interventions for this historically neglected cohort. Research Sponsor: Conquer Cancer, the ASCO Foundation.

5095 Poster Session

Clinical characteristics and treatment patterns of patients with high-risk localized prostate cancer (HR LPC) treated with radical prostatectomy (RP) and perioperative hormonal therapy (HT) in Japan, South Korea, and Taiwan.

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Background: Data on HR LPC patients treated with RP and perioperative HT is lacking in the Asia-Pacific (AP) region. Thus, this study aimed to describe the real-world clinical characteristics and treatment patterns of this group of patients in Japan, South Korea, and Taiwan. **Methods:** A retrospective observational study was conducted, utilizing data from chart review at five sites in Japan and data from electronic medical records of three medical centers in Korea and a multi-hospital system in Taiwan. Eligible patients were adults ≥18 years who were newly diagnosed with prostate cancer between 1 January 2015 and 30 June 2017 and had exactly one high-risk feature as per NCCN prostate cancer guidelines: cT3a; Gleason Grade Group 4 or 5; prostate-specific antigen (PSA) >20 ng/mL. Patients also received RP during the same period and had ≥3 months neoadjuvant HT and/or ≥6 months adjuvant HT. Data on clinical characteristics and treatments were collected. Patient data till 30 June 2022 was included, where possible. Considering differences in data collection methodology and clinical practice, data for Japan were reported separately from Korea and Taiwan. **Results:** There were 354 newly diagnosed HR LPC patients across sites in Japan and 677 newly diagnosed HR LPC patients across sites in Korea and Taiwan. Of these patients, 72.6% (n=257) of patients in Japan and 72.4% (n=490) of patients in Korea and Taiwan received RP. A total of 72 (20.3%) HR LPC patients in Japan and 33 (4.9%) HR LPC patients in Korea and Taiwan who received RP and perioperative HT were eligible for inclusion into this study. In the Japan cohort, 95.8% (n=69) of patients received neoadjuvant HT with RP and the median duration of neoadjuvant HT was 7.1 months. In the Korea and Taiwan cohort, 93.9% (n=31) of patients received adjuvant HT with RP and the median duration of adjuvant HT was 11.2 months. The median duration of follow-up was 11.7 months and 71.8 months in the Japan cohort and Korea and Taiwan cohort, respectively. The median age of patients was 73.5 years in the Japan cohort and 67.8 years in the Korea and Taiwan cohort. In both cohorts, majority of patients had cT3a (Japan: 44.4%; Korea and Taiwan: 42.4%) and one-third (33.33%) of patients had Gleason grade group 4 or 5 at LPC diagnosis. The median PSA at LPC diagnosis was 9.3 ng/mL in the Japan cohort and 11.1 ng/mL in the Korea and Taiwan cohort. **Conclusions:** This study revealed that while the proportion of HR LPC patients receiving RP was similar within the AP region, clinical practice on the use of perioperative HT differed. The proportion of HR LPC patients receiving RP in the AP region was higher compared to the United States in 2013 (42.0%). Globally, studies on the use of perioperative HT as part of a multi-modal therapy are ongoing to discover an optimal strategy for the management of HR LPC patients. Research Sponsor: Johnson & Johnson International (Singapore) Pte. Ltd.

Immunologic effects of B cell depletion on T cells in high-risk prostate cancer.

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Background: High-risk prostate cancer (HR-PCa) remains one of the leading causes of cancer-related death. Previous studies reported that a high density of immunosuppressive B cells in HR-PCa resection specimens was found to correlate with biochemical failure. In this context, a single arm prospective study assessing neoadjuvant rituximab, an anti-CD20 monoclonal antibody used to deplete B cells, was previously conducted on patients with HR-PCa eligible for radical prostatectomy ("PROTUX"). Here, we performed deep TCR sequencing to elucidate the impact of B cell depletion on T cells in prostate cancer patients. **Methods:** A single arm study enrolled patients with HR-PCa to receive neoadjuvant rituximab prior to radical prostatectomy (NCT: 01804712). Patients were treated with rituximab 375 mg/m^2 once weekly for 4 treatments followed by prostatectomy within 14 days of the final treatment of rituximab. A matched cohort of patients with HR-PCa who underwent prostatectomy without any prior therapy were used as controls. Specimens from 14 patients were retrieved and genomic DNA was isolated using a QIAamp DNA FFPE Advanced UNG kit. TCR sequencing was performed with Adaptive Biotechnologies using the Ultradeep TCRB v4b assay. Data were then analyzed using the Adaptive immunoSEQ Analyzer. Groups were compared using a Mann-Whitney U test. Statistical analysis and graphing were done in Prism 10 and R. **Results:** We observed that patients treated with rituximab had higher TCRb productive clonality (0.080 vs 0.026, p = 0.03). Strikingly, the calculated number of T cells present in prostatectomy samples was significantly greater in patients receiving rituximab compared to controls (1.18 cells/ng DNA input vs 0.10 cells/ng, p = 0.002). Maximum productive frequency and the cumulative frequency of the top 10 clones were not significantly different between the two cohorts. However, we found that the T cells from patients who received rituximab had longer TCRb CDR3 regions (proportion CDR3 ≥16 amino acids of 0.232 vs 0.197, p = 0.007), suggesting a less antigen-experienced phenotype. **Conclusions:** Using specimens from a clinical trial assessing the use of neoadjuvant rituximab in HR-PCa, we found that B cell depletion can significantly affect T cell infiltration, clonality, and phenotype. Given the increasing appreciation for crosstalk between T cells and B cells in mediating anti-tumor immune responses, these findings suggest a context dependent role of B-cells in patients with HR-PCa. Clinical trial information: NCT01804712. Research Sponsor: None.

Impact of pre-treatment MRI capsular involvement and extraprostatic extension on metastasis free and overall survival in localized prostate cancer.

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Background: Multiparametric magnetic resonance imaging (mpMRI) is not currently included in prostate cancer (PC) staging. The purpose of this study was to test the association between mpMRI detected prostate capsule involvement and extraprostatic extension (EPE) with metastasis free survival (MFS) and overall survival (OS) in patients treated for localized PC. **Methods:** Patients treated for localized PC between 2000-2021 from the Veterans Affairs Prostate Data Core having an mpMRI prior to definitive treatment were identified. MRI reports were assessed for minor or significant capsule abutment (defined as greater than or equal to 1.5 cm of capsule contact or radiologist's mention of long segment abutment), extracapsular extension (ECE), seminal vesicle invasion (SVI), or adjacent organ invasion (OI). mpMRI findings' impact on MFS by multivariable Fine-Gray competing-risks regression and OS by Cox regression were assessed. **Results:** Overall, 2,933 patients were included. Most pre-treatment mpMRIs (85%) occurred after 2016. 1,238 (42%) patients were Black. 569 (19%) patients had palpable disease. Median follow-up was 5 years. The 5-year cumulative incidence of metastasis was 10% (95% confidence interval (CI) 9-11%) and death was 7% (95% CI 6-9%). There were 643 (22%) patients with minor capsule abutment, 212 (7%) with significant capsule abutment, 281 (10%) with ECE, 103 (4%) with SVI, and 25 (1%) with OI. After controlling for age, race, prostate specific antigen level, grade group, clinical tumor stage, and treatment, the presence of significant capsule abutment, ECE, SVI, and OI were independently associated with MFS, but minor capsule abutment was not. On multivariable analysis controlling for the same factors, EPE (ECE, SVI, or OI) was associated with worse OS. **Conclusions:** In a modern, real-world cohort of localized PC patients from the largest integrated health system in the United States, significant capsule abutment and EPE on mpMRI are independently prognostic of MFS, but minor capsular abutment is not. EPE is associated with inferior OS. Given its independent prognostic value for MFS and association with OS, mpMRI should be more widely available to PC patients. Studies are ongoing to define its role as a standard staging tool. Research Sponsor: None.

MRI Finding	Hazard Ratios (95% Confidence Intervals)	
Metastasis-Free Survival	**Overall Survival**	
No capsule abutment	Reference	Reference
Minor capsule abutment	0.72 (0.50-1.04)	
Significant capsule abutment	2.18 (1.53-3.11)	0.64 (0.36-1.14)
ECE	1.49 (1.05-2.12)	1.43 (1.05-1.95)
SVI	3.17 (2.15-4.69)	
OI	4.85 (2.51-10)	

Independent blinded validation of an AI-based digital histology classifier for prostate cancer recurrence and metastasis risk prediction.

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Background: Artificial intelligence (AI) tools which identify pathology features from digitized whole slide images (WSI) of prostate cancer (CaP) generate data to predict risk of disease recurrence and metastasis. PathomIQ and ISMMS have developed an AI-enabled prognostic test, PATHOMIQ_PRAD, which predicts risk of biochemical recurrence (BCR) and distant metastasis (DM) using WSIs. The objective of this study was to evaluate the clinical validity of PATHOMIQ_PRAD using a retrospective clinical cohort at Cleveland Clinic. We also compared the test's performance to Decipher, an established genomic risk classifier. **Methods:** We conducted a retrospective PATHOMIQ_PRAD analysis of CaP WSIs of patients who underwent prostatectomy at Cleveland Clinic from 2009-2022 and did not receive any adjuvant therapy before BCR. 263 patients in the cohort received definitive treatment with radical prostatectomy and had a median follow-up of 50 months. Of these patients, 65 patients had BCR, and 14 patients developed DM as of last follow up. WSIs were de-identified, anonymized, and patient outcomes were blinded during the study. Patients were stratified into high-risk and low-risk categories based on pre-determined thresholds for PATHOMIQ_PRAD scores (0.45 for BCR and 0.55 for DM). The Kaplan-Meier method with log-rank was used to compare biochemical recurrence-free survival (BCRFS) and metastasis-free survival (MFS). Multivariable Cox proportional hazards regression was used to identify factors associated with BCR. **Results:** The rate of BCRFS and MFS were associated with both PATHOMIQ_PRAD score (BCR: >0.45 vs. <0.45, p<0.0001; DM: >0.55 vs. <0.55, p<0.0001) and Decipher score (BCR: >0.6 vs. <0.6, p=0.0009; DM: >0.6 vs. <0.6, p=0.0095). All 14 patients who had DM during the follow up time had a high PATHOMIQ_PRAD score. Univariate analysis shows that PATHOMIQ_PRAD reliably identifies patients at risk of BCR (HR: 4.19, p< 0.0001), and had comparable prognostic performance to Decipher (HR: 2.83, p=0.0013). Multivariate analysis (Table) shows that there was an increased risk of BCR in both the high-risk PATHOMIQ_PRAD (HR: 3.58, p=0.0005) and Decipher (HR: 2.20, p=0.0159) groups relative to the low-risk groups, which suggests that combining the two tests may further improve risk stratification. **Conclusions:** These results show that PATHOMIQ_PRAD continues to demonstrate clinical validity in predicting risk of BCR and DM with favorable performance compared to a commonly used genomic classifier. PATHOMIQ_PRAD may identify patients for early treatment intensification, as well as inform clinical trial patient selection. Research Sponsor: PathomIQ Inc.

Multivariable regression for biochemical recurrence.

	HR	95% CI	p-value
PathomIQ Score >0.45 vs. <0.45	3.576	1.749-7.313	0.0005
Decipher Score >0.6 vs. <0.6	2.197	1.159-4.167	0.0159

Prognostic impact of residual cancer burden (RCB) on long-term outcomes after neoadjuvant (neo) androgen receptor pathway inhibitor (ARPI) and radical prostatectomy (RP) for high-risk localized prostate cancer (HRLPC): A pooled analysis of phase 2 trials.

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Background: 6 months (mths) of neo-ARPI prior to RP for HRLPC has shown promising results in a series of phase 2 trials, with 15-20% of patients experiencing pathologic complete response (pCR) or minimal residual disease (≤5mm residual tumor, MRD). However, longer-term outcomes and the prognostic impact of residual cancer burden (RCB) at RP has not been evaluated. **Methods:** Data from patients (pts) treated on 5 neoadjuvant trials evaluating 6mths of neo-ARPI (abiraterone [abi], enzalutamide [enza], abi+enza, abi+apalutamide) and androgen deprivation therapy (ADT) at our institution between 2006 to 2018 were pooled. All pts had central pathology review performed to evaluate pCR/MRD and RCB on the RP specimen. RCB was quantified as the calculated tumor volume adjusted for tumor cellularity. Metastasis-free survival (MFS) was defined as the time from RP to development of metastasis outside of the pelvis on CT, bone scan or MRI, or death from any cause, or censored at the date of last follow-up. Utilizing the Contal & O'Quigley method, the optimal cut-off value for RCB, distinguishing high- and low-risk groups for MFS, was determined based on the log-rank statistic. A dichotomous RCB cut-off was chosen between 5% and the 95% percentiles of the RCB distribution for patients with residual disease (RCB>0). Multivariate Cox proportional hazards model was used to quantify the association of RCB with MFS after adjusting for age, biopsy Gleason score, and clinical T stage. **Results:** 218 pts were evaluable, with a median age of 61yrs. 154 pts (71%) had Gleason 8-10 at biopsy, 42 (19%) had cT3-4 disease and 40 (18%) had a baseline PSA >20ng/mL. Overall, 170 (78%) were classified as NCCN high/very-high risk and 48 (22%) as unfavorable intermediate-risk. At RP, 117 pts (54%) had ypT3 and 23 (11%) had pN1 disease, while 24 pts (11%) had pCR and 24 (11%) had MRD; The median RCB was 0.05cm^3 (IQR 0.00-0.32). During a median follow-up of 5yrs, 45 pts (21%) developed metastases and 11 (5%) died; 5-yr MFS rate was 81% (95% CI 74-86). On multivariate analysis, a higher RCB was associated with poorer MFS (HR 1.26 [1.03-1.54]), along with cT3-4 disease (HR 3.86 [1.59-9.41]). RCB index categories were defined as RCB-0 (no residual disease [i.e. pCR]; n=23), RCB-1 (<84th percentile [<0.67cm^3]; n=153), and RCB-2 (≥84th percentile [≥0.67cm^3]; n=28). 5-yr MFS rates were 100%, 81% (72-87) and 59% (35-76) for pts with RCB-0, RCB-1 and RCB-2, respectively. **Conclusions:** 5-yr MFS rate with 6mths of neo-ARPI prior to RP for HRPLC was >80%. The depth of pathologic response was prognostic for MFS, with a 100% 5-yr MFS in patients achieving pCR. RCB could be used to guide intensified adjuvant strategies in pts with residual disease at RP after neo-ARPI. Expert pathology review of pts treated in this manner is crucial. Research Sponsor: None.

COBRA: Assessment of safety and efficacy of ^{64}Cu-SAR-bisPSMA in patients with biochemical recurrence of prostate cancer following definitive therapy.

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Background: Accurate staging of recurrent prostate cancer (PC) is essential to inform the best treatment strategy. Prostate-specific membrane antigen (PSMA) is used as an imaging target in PC. ^{64}Cu-SAR-bisPSMA may offer several advantages over the currently approved PSMA PET agents due to the bivalent structure of SAR-bisPSMA and longer half-life ($t_{1/2}$) of ^{64}Cu (12.7h), compared to the monovalent agents utilizing ^{18}F and ^{68}Ga ($t_{1/2}<2$h). Clinical/translational evidence has demonstrated higher tumor uptake (2-3x), prolonged retention and detection of additional PC lesions using ^{64}Cu-SAR-bisPSMA compared to approved PSMA agents. **Methods:** This was a phase I/II study assessing the safety and efficacy of ^{64}Cu-SAR-bisPSMA (200 MBq) in PC patients with biochemical recurrence (BCR) and negative or equivocal standard of care (SOC) imaging (NCT05249127). Patients underwent PET/CT on Day 0 and Day 1 (1-4h and 24±6h post-dose, respectively), interpreted by 3 blinded central readers. The PET/CT results were assessed against a Reference Standard (histopathology, SOC imaging, Prostate Specific Antigen response) that was determined by an independent, blinded, central expert panel. Efficacy endpoints included detection rate (DR) and positive predictive value (PPV). The intended change in PC treatment due to the ^{64}Cu-SAR-bisPSMA results was recorded. **Results:** Fifty-two patients were enrolled and imaged (32 completed the study). Only one adverse event was related to ^{64}Cu-SAR-bisPSMA (Grade 2 worsening of type II diabetes, resolved). The Day 0 DR range across the readers was 44–58% (95% CI 30.0–71.8), increasing on Day 1 to 58–80% (43.2–90.0). Pelvic lymph nodes, a common site of PC metastases, had a Day 0 PPV range of 71.4–87.5% (95% CI 29.0–99.7) and Day 1 of 50.0–61.5% (15.7–86.1). The relative decrease in Day 1 PPV was related to the challenges to obtain the reference standard for additional lesions identified on Day 1, where biopsy of all lesions was not feasible and due to the low sensitivity of current SOC imaging. Additional lesions were identified on Day 1 (82–153 vs. 53–80 on Day 0). The ^{64}Cu-SAR-bisPSMA imaging led to clinicians changing their intended treatment plans in approximately half of the patients (48%). **Conclusions:** This study showed that ^{64}Cu-SAR-bisPSMA is safe and effective in detecting PC lesions in patients with BCR. In patients with a negative or equivocal SOC scan, ^{64}Cu-SAR-bisPSMA identified lesions in up to 80% of patients. More lesions and more patients with a positive scan were identified on next-day imaging, a feature that currently approved PSMA tracers cannot offer. PET results led to clinicians changing the intended treatment plan in approximately half of the patients. Taken altogether, these findings have important clinical implications as the identification of lesions in BCR patients can inform different treatment pathways. Clinical trial information: NCT05249127. Research Sponsor: Clarity Pharmaceuticals Ltd.

5101 Poster Session

Intensification of ADT with enzalutamide in high-risk patients with biochemical relapse following radical prostatectomy undergoing salvage radiation: Initial results from RTOG 3506 (STEEL).

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Background: Patients with high-risk features who experience biochemical relapse (BCR) after radical prostatectomy (RP) benefit from the addition of androgen deprivation therapy (ADT) to salvage radiotherapy (SRT). We hypothesized that intensification of androgen receptor (AR) blockade with enzalutamide would improve SRT outcomes for high-risk patients. **Methods:** Post prostatectomy prostate cancer patients who have had BCR (PSA ≥ 0.2 ng/mL) with at least 1 high-risk feature (Gleason 8-10, seminal vesicle invasion, pN1, persistent PSA >0.1 ng/mL after RP, and PSA ≥ 0.7 ng/mL) were eligible. Patients were randomized 1:1 to 24 months of ADT with an LHRH analog (LHRHa) or intensified ADT comprised of LHRHa + enzalutamide. The primary endpoint was progression free survival (PFS) with progression defined as PSA ≥ 0.05 ng/mL or initiation of new therapy following SRT. The target accrual of 170 patients provided 80% power to detect a HR=0.65 using a one-sided logrank test with a type I error of 0.10. **Results:** Between April 2019 and August 2022, 188 patients were enrolled. The patient characteristics were well balanced between the two arms. Median age was 64 years. Nodal involvement (pN1), pT3a-b, and Gleason 9 were noted in 22%, 77%, and 52% of patients, respectively. Over 70% had > 1 aggressive feature. Median follow-up time at the time of this report was 15.8 months. Prostatic fossa and pelvic SRT were mandatory. Para-aortic radiotherapy (RT), and lymph node and prostatic fossa lesion RT boosts were left at the discretion of the radiation oncologist. PFS favored the enzalutamide-intensified arm (HR=0.72, 80% confidence interval [CI]:0.56-0.94, one-sided p=0.14). Grade 3 adverse events (AEs) related to treatment in the standard versus enzalutamide arms were 11 vs. 23%, while Grade 4 AEs were 4% vs. 1%, respectively. The most common AEs (all grades, >15%) included hot flashes, fatigue, diarrhea, and decreased lymphocytes. The grade 3+ AEs (>3%) included decreased lymphocytes and hypertension. The largest differences (>7%) in AEs included insomnia, decreased lymphocytes. Diarrhea was less frequent with enzalutamide (40% vs 54%). **Conclusions:** The addition of enzalutamide to standard ADT did not meaningfully increase toxicity. While there was a trend toward PFS benefit from intensification, it has not yet met statistical significance. Updates on PFS and other clinical endpoints including quality of life will be reported with longer follow-up. Clinical trial information: NCT03809000. Research Sponsor: RTOG Foundation in partnership with Pfizer/Astellas.

Germline gene-specific associations in a large prostate cancer cohort.

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Background: Identification of pathogenic germline variants (PGV) in patients (pts) with prostate cancer (PC) enables precision therapy and cascade testing. Equitable advances in precision PC management require more detailed understanding of gene-level associations. Herein we describe PC gene-specific demography in a large cohort of PC pts. **Methods:** Germline genetic testing (GGT) (Invitae Corp.) and insurance claims (Komodo Healthcare Map) data were linked for PC pts from 2015-2023. ICD/CPT codes were used to define PC personal and family history and disease stage (early-stage = codes for active surveillance or definitive local treatment; advanced = remaining pts). PC genes analyzed were those in NCCN PC guidelines with >100 PGV+ pts: *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *HOXB13* and mismatch repair (MMR) genes (*EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*). Two sample t-tests were used for age and chi-square tests were used for other variables, with a Bonferroni correction for *post hoc* analysis. **Results:** 14,979 pts had GGT: 68% with advanced disease (enriched for *BRCA2*) and 32% with early-stage. Mean diagnosis age was 64, and significantly younger for *ATM*/*BRCA2*/*HOXB13*+ pts($p<0.04$) (Table). *BRCA2*was the most common PGV but was not enriched in any clinician-reported race/ethnicity. *CHEK2*/MMR+ pts were more likely to be White (*post hoc* $p<0.001$). The Midwest had the highest frequency of PGV (12%). A lower proportion of *CHEK2*+ pts resided in the South (*post hoc* $p<0.001$). 26% of PGV+ pts had documented PC family history, which was significantly associated with *BRCA2*/HOXB13, and negatively correlated with MMR ($p<0.02$ for both). **Conclusions:** In this cohort of ~15,000 PC pts, gene-specific associations were detected that warrant further study. Three-quarters of pts with PGV had no claims for family PC history, highlighting the importance of GGT in all pts meeting criteria, independent of family history. Further analysis of linked data will assess real-world treatment decisions and outcomes by GGT result. Research Sponsor: None.

N (%)	Total Cohort 14979	*ATM* 260 (1.7)	*BRCA1* 115 (0.8)	*BRCA2* 438 (2.9)	*CHEK2* 328 (2.2)	*HOXB13* 136 (0.9)	MMR 178 (1.2)	No Germline Findings 7881 (53)
Mean age at diagnosis (yrs) (SD)	64.4 (9)	**63.5 (9)**	64.2 (11)	**63.7 (9)**	64.5 (9)	**62.2 (9)**	63.5 (10)	64.7 (9)
Black	1568 (11)	**11 (0.7)***	7 (0.4)	40 (2.6)	**11 (0.7)^**	15 (1)	**5 (0.3)^**	784 (50)
Hispanic	636 (4)	13 (2)	5 (0.8)	19 (4)	7 (3)	0	5 (0.7)	312 (49)
White	9930 (66)	176 (2)	75 (0.8)	290 (3)	**264 (3)^**	102 (1)	**140 (1)^**	5261 (53)
Northeast	3191 (21)	71 (2)	24 (0.8)	101 (3)	76 (2)	16 (0.5)	36 (1)	1760 (55)
Midwest	3506 (23)	72 (2)	39 (1)	117 (3)	102 (3)	41 (1)	50 (1)	1927 (55)
South	4470 (30)	64 (1)	30 (0.7)	128 (3)	**66 (2)#**	45 (1)	38 (0.9)	2390 (53)
West	3644 (24)	53 (2)	22 (0.6)	87 (2)	83 (2)	34 (0.9)	47 (1)	1712 (47)
Family history of PC	3728 (25)	62 (2)	19 (0.5)	**130 (4)**	83 (2)	**53 (1)**	**29 (0.8)**	1925 (52)

Bolded values are significant ($p<0.05$) compared to "no germline findings" group Only most common race/ethnicity categories included Significant post hoc: *Black; ^Black, White;#South.

Socio-economic disparities in prostate cancer hospitalizations and outcomes across the United States.

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Background: Socioeconomic class (SEC), measured by educational attainment, is recognized as a notable factor influencing outcomes in prostate cancer. This study evaluated the effects of income status on the prevalence, treatment, and hospitalization outcomes among men diagnosed with prostate cancer. **Methods:** The combined 2016–2020 nationwide inpatient sample database was queried for all hospitalizations for a primary diagnosis of prostate cancer using ICD-10-CM codes. Socioeconomic status was defined based on the Agency for Healthcare Research and Quality (AHRQ) median annual income index into the lowest SEC ($1–$49,999), the lower SEC ($50,000–$64,999), the high SEC ($65,000–$85,999), and the highest SEC ($≥86,000). Baseline characteristics were compared using Pearson's $\chi 2$ tests and the Kruskal-Wallis test for nominal and continuous variables. Outcomes of interest were hospitalization rates, treatment, and outcomes (including mortality, complications, and resource utilization). The adjusted odds ratios of the outcomes were assessed using a stepwise multivariable logistic regression, adjusted for age, sex, race, insurance status, illness severity, risk of mortality, and comorbidity burden. This was done using the All Patient Refined Diagnosis Related Groups (APR-DRG) metrics and the Charlson comorbidity index. **Results:** The study analyzed 244,520 hospitalizations for prostate cancer. The median age of the cohort was 64 years (interquartile range: 59–69 years). Most were white Americans (69.9%) and blacks (16.3%). Approximately 53,550 (21.9%) were in the lowest SEC, 58,196 (23.8%) were in the lower SEC, 61,619 (25.2%) in the high SEC, and 66,803 (27.3%) in the highest SEC. Hospitalizations in the highest SEC were younger than those in the lowest SEC (63.7 vs. 66.5; P<0.001). Hospitalizations in the lowest SEC were correlated with greater mortality (655, 1.2%; AOR: 1.43; 95% CI: 1.22-1.56; P=0.011) compared with those in the highest SEC (475, 0.7%; AOR: 0.86; 95% CI: 0.65-0.97; P<0.001). The highest SEC correlated with higher rates of prostatectomy (2,995, 4.5%; AOR: 1.29; 95% CI: 1.08-1.10; P<0.001), whereas the lowest SEC had lower rates (1,810, 3.4%; AOR: 0.52-0.98; P=0.008). The lower and lowest SECs had higher frequencies of chemotherapy (8.1% and 7.4%, respectively; P for all <0.001). SEC did not correlate with the likelihood of immunotherapy (P = 0.738), radiotherapy (P = 0.073), length of hospital stays (P = 0.283), or mean hospital costs (P = 0.582). Hospitalizations in the higher SECs had lower odds of erectile dysfunction (highest SEC, AOR: 0.83; 95% CI: 0.74-0.93; P = 0.001; and high SEC, AOR: 1.13; 95% CI: 1.02-1.24). **Conclusions:** Prostate cancer affects the younger demographics of patients with higher SECs. However, hospitalizations in patients with lower SECs present with more advanced disease and result in poorer mortality outcomes than those in patients with higher SECs. Research Sponsor: None.

Willingness of patients with biochemically recurrent prostate cancer (BCR) with positive 18F-dcfpyl PET/CT PSMA to monitor without treatment.

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Background: For patients that have a rising PSA and negative CT and bone scan after surgery or radiation, there are no therapies that have been shown to improve survival. This fact has not been changed by the approval of DCFPyL PET/CT PSMA, which can now define subclinical disease in patients with bone and CT scans that are otherwise negative. Treatment and outcome data in BCR is not equivalent to metastatic castration sensitive prostate cancer (mCSPC). Despite the lack of data for the optimal management for prostate cancer that is PSMA positive (ppBCR), many providers feel they must treat patients because patients are unwilling to monitor ppBCR over time. **Methods:** The NCI is currently accruing to a study (NCT05588128; goal n=250) designed to monitor patients with BCR to understand the evolution of PSMA imaging over time. Eligible patients have BCR and underwent definitive treatment (surgery and/or radiation therapy) > 6 months prior to enrollment. Required PSA minimum 0.5 ng/mL; Testosterone minimum 100 ng/dL. Baseline CT and Tc-99m bone scans must be negative. Initial PSMA assessments occur within 8 weeks of confirmed eligibility. Positive PSMAs will be repeated every 6 months and negative PSMAs are repeated every 12 months for up to 5 years. PSAs are collected every 3 months. Following each PSMA scan, patients are counseled on the results. Radiation and intermittent systemic therapies (for 6 months or less) are allowed on this trial. **Results:** 57 patients have enrolled on the study and have been evaluated with PSMA PET thus far. Median PSA value at enrollment is 3.65 ng/mL (range, 0.5-71.6 ng/mL). Median PSA doubling time is 11.3 months (range, 1.2-132.4 months). Median patient age is 71 years (range, 54-92 years old). Self-reported race/ethnicity as follows: 75% White, non-Hispanic, 12% Black, non-Hispanic, 3.5% White, Hispanic, 3.5% Other, Hispanic, 2% Asian, 4% Unknown. Of the first 57 patients enrolled who have had PSMA PET scans, 52 patients (91%) were found to have positive findings. Among these, 49 patients (94%) with ppBCR elected to monitor their disease until the next scan. **Conclusions:** This study (NCT05588128) is the first prospective trial to monitor ppBCR patients to better define the natural history of BCR in the PSMA era. This preliminary data from the ongoing study thus far suggests that with appropriate counseling and a follow-up plan, the majority of patients are willing to monitor ppBCR. Given that no data has demonstrated a survival advantage for BCR or ppBCR, it is important for providers to have balanced conversations with patients about the implications of ppBCR, which often results in an indolent disease course. Clinical trial information: NCT05588128. Research Sponsor: None.

Informed decision-making about germline testing among Veterans with advanced prostate cancer (APC): A mixed-methods study.

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Background: To tailor care to cancer biology, oncologists offer germline testing to patients with APC. Little is known about whether pre-test counseling conducted by oncologists leads to well-informed, preference-concordant decisions in Veterans with APC. **Methods:** We conducted a prospective mixed-methods study of consecutive patients with APC who were offered germline testing at an oncology visit at the San Francisco VA. Seven days after the visit, patients were administered the Decisional Conflict Scale (DCS; 16 items scored 0-100, higher = more decisional conflict) and a True/False knowledge test (20 items, scored 0-100% correct). We conducted semi-structured interviews using a theory-informed guide to explore patients' knowledge, decision-making process, and decisional needs for germline testing. Two coders analyzed the interviews using thematic analysis. **Results:** Of 68 patients approached, 31 (46%) consented. Mean age was 76y, 21 (68%) were White, and 14 (45%) completed at least college. Mean DCS score was 24 (SD 22); six (19%) patients scored >37.5, which is associated with decision delay. Mean knowledge score was 69% (SD 16); four patients scored < 50%. Patients were least knowledgeable about the results disclosure process (37% correct), presence of privacy laws protecting genetics data (50%), types of test results (50%), and implications of a variant of uncertain significance (50%). Twenty-seven patients (87%) desired germline testing. The most common reasons were to help family and advance research; personal treatment benefits were rarely mentioned. Patients felt the decision was easy, but four experienced uncertainty and decided against testing due to fear of losing service-connected disability benefits. Themes included knowledge deficits about testing benefits/risks, results disclosure process, and impact on disability insurance; presence or absence of autonomy; misconceptions (commercialization or weaponization of genetics data, conflating germline testing and research); disparities due to racial discrimination or homelessness; barriers (poor memory, distress from APC, insufficient details about testing from oncologist, and no access to informational resources); and facilitators (trust in oncologist and the VA, family support, and extra time to make a decision). Patients requested a variable degree of decision support prior to germline testing, ranging from none to a combination of informational materials and coaching. **Conclusions:** Decisional conflict was low in most but not all patients. Patients' knowledge deficits, misconceptions, and unawareness of choice due to personal, oncologist, and systemic barriers suggest some did not make informed decisions. To deliver patient-centered oncologist-directed germline testing, future research should focus on developing and implementing decision support personalized to patients' needs. Research Sponsor: U.S. Department of Defense; W81XWH-21-PCRP-PRA.

Mutational burden among patients with metastatic prostate cancer differs by race in 3 key genes: An analysis of genomic and clinical data from the AACR Project GENIE biopharma collaborative in cBioPortal.

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Background: Prostate cancer exhibits a range of aggressive oncological traits due to its genomic heterogeneity. The extent to which clinical and demographic variables affect cancer behaviors and increase disparities is a complex and open question. Objective: We aim to comprehensively explore the genomic and epigenetic characteristics of metastatic prostate cancer (PCa) across different racial groups to elucidate potential molecular and immune mechanisms underlying disparities in disease progression and treatment response. **Methods:** Data from the Association for Cancer Research Project Genomics Evidence Neoplasia Information Exchange (AACR-GENIE) registry to study men diagnosed with PCa was queried. Patients with metastatic disease (n = 1,684) were stratified into three racial groups: White (80.5%), Black (8.1%), and Asian (3.1%). cBioPortal was used to analyze the differences in genetic mutation frequencies by race and to determine the importance of these mutations. The relationships between mutation frequencies and race were examined using chi-squared test. **Results:** In our study, among patients with metastatic prostate cancer, the following three genes demonstrated the highest differences in frequencies of mutation: TP53, ATR, and PTEN. The most significant differences in mutation frequencies by race in metastatic PCa patients were found in TP53 (White: 3.1%; Black: 16.7%; Asian: 11.8%; $P < 0.005$) and ATR (White: 2.39%; Black: 3.58%; Asian: 4.87%; $P = 0.035$). PTEN has a metastatic tumor frequency of 6.5% in Asians, 4.2% in Black men, and 7.1% in White men ($P = 0.0434$). **Conclusions:** Consistent with previous literature, our study provides new insight into the complex interplay between PCa pathogenesis and progression, paving the way for precision. In the TP53 gene, Black men were more likely than their counterparts to have a higher mutational burden. This research has significant implications for improving health equity in PCa. Research Sponsor: None.

TPS5107 **Poster Session**

SAVE: A prospective, single-arm, single-center clinical study of disitamab vedotin in combination with toripalimab in patients with advanced penile cancer that has progressed or is intolerant to cisplatin chemotherapy.

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Background: At present, penile cancer patients receiving chemotherapy with paclitaxel, ifosfamide and cisplatin or docetaxel, cisplatin and 5-fluorouracil have a lack of post-progression treatment, and some patients lose the opportunity for effective treatment due to inability to tolerate chemotherapy. Even though the epidermal growth factor receptor (EGFR) is ubiquitously expressed in penile squamous cell carcinoma, anti-EGFR-targeted drugs have not achieved significant survival benefit. Immune checkpoint inhibitors (ICIs) have achieved "de-tumor immune escape", and a small number of penile cancer cases have shown reactivity. However, only patients with high TMB, high PD-L1 expression, or MSI-H have benefited from ICIs. Antibody-drug conjugates (ADCs) have advanced rapidly in recent years, and HER2-targeted ADCs have shown significant efficacy in HER2-overexpressing urothelial carcinoma. HER2 ADC and ICI can simultaneously block HER2 and PD-1/PD-L1 signaling pathways, bridge PD-1-expressing T lymphocytes and HER2-expressing tumor cells, assist T cells to recognize and kill tumor cells, improve immunosuppression in the tumor microenvironment, and enhance the infiltration of immune cells into tumors. Recent cytology and animal studies have also shown that HER2-targeted ADCs exhibit significant anti-tumor activity in both HER2-positive and cisplatin-resistant penile cancers. Therefore, in order to explore the feasible and effective options for patients with advanced penile cancer who have progressed or are intolerant to cisplatin-based chemotherapy, a single-arm, single-center clinical study using Disitamab Vedotin combined with Toripalimab is proposed. **Methods:** About 20 patients with advanced penile cancer who have progressed or are intolerant to chemotherapy are planned to be enrolled with antibody-drug conjugates (Disitamab Vedotin for injection, 1 time/2 weeks, 2.0 mg/kg) and PD-1 (Toripalimab, 1 time/2 weeks, 3.0 mg/kg; or1 time/3 weeks, 240 mg/kg), regimen until the disease progresses or is intolerant. This study is expected to provide a basis for the treatment of advanced penile cancer using this regimen. Research Sponsor: None.

TPS5108 Poster Session

A phase II trial of enfortumab vedotin for locally advanced and metastatic squamous cell carcinoma of the penis.

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Background: Penile cancer is a devastating malignancy that affects just over 2000 patients per year in the United States and approximately 40,000 worldwide. Metastatic or unresectable penile cancer is rapidly fatal in most cases and there are few effective systemic therapy options.[1] There is an urgent need for alternatives to chemotherapy such as immunotherapy or targeted therapy. Enfortumab vedotin (EV) is an antibody-drug conjugate targeting nectin-4 protein on the tumor cell surface and having efficacy in treatment of metastatic urothelial carcinoma.[2] Recent studies have demonstrated frequent and strong expression of nectin-4 in penile squamous cell carcinoma (PSCC).[3,4] In this setting, Mayo Clinic is leading a phase II trial of EV for advanced PSCC, currently in progress. **Methods:** This single arm, open-label, two-stage, phase II trial evaluates best overall response rate (BRR) to EV in patients with PSCC regional lymph node involvement or distant metastatic (M1) disease. Participants may have had any prior systemic therapy or be treatment naïve. Previously untreated patients must be ineligible for or have refused surgery or radiotherapy, have N2-N3 disease and are ineligible for or have refused neoadjuvant chemotherapy, or have clinical evidence of M1 disease. Participants will receive treatment with EV until disease progression, withdrawal, death, or limiting toxicity. Participants will receive EV 1.25 mg/kg intravenous on days 1, 8, and 15 of a 28-day cycle, with tumor assessment performed at 8-week intervals. The primary endpoint is the combined BRR of partial and complete responses (whether confirmed or unconfirmed) according to RECIST 1.1. Secondary endpoints are confirmed response rate, duration of response, progression-free survival, overall survival, adverse events, and BRR in HPV related and unrelated subgroups. Stage 1 will consist of 15 participants, and if there are 2 or more responses will proceed to Stage 2 with an additional 10 participants. The trial opened to enrollment in December 2023, and is active at Mayo Clinic sites in Minnesota, Arizona, and Florida. Clinical trial information: Funding and drug supplied by Astellas Pharma Global Development, Inc./Seagen Inc. NCT06104618. 1. Chahoud J, et al., Curr Opin Urol. 2022 Jan 1;32(1):8-16. 2. Powles T, et al. N Engl J Med. 2021 Mar 25;384(12):1125-1135. 3. Tekin B, et al. Hum Pathol. 2023 Dec;142:42-50. 4. Grass GD, et al. Eur Urol Open Sci. 2023 Jan 10;49:1-5. Clinical trial information: NCT06104618. Research Sponsor: Astellas Pharma Global Development, Inc./Seagen Inc.

TPS5109 **Poster Session**

A phase 1/2, open-label, randomized, dose-finding and dose expansion study of gedatolisib in combination with darolutamide in metastatic castration-resistant prostate cancer (mCRPC).

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Background: Progression to metastatic castration-resistant prostate cancer (mCRPC) occurs in most patients treated with androgen receptor signaling inhibitors (ARSi) for advanced disease. Preclinical studies demonstrate that AR and PI3K - AKT - mTOR (PAM) pathways interact through reciprocal negative feedback, whereby inhibition of one pathway activates the other. Thus, combining a PAM inhibitor with an ARSi may deliver improved anti-cancer activity in patients with mCRPC. A Phase 2 trial in 129 patients with mCRPC who progressed on abiraterone demonstrated improved median radiographic progression-free survival (rPFS) when samotolisib, a dual PI3K-mTOR inhibitor, was added to enzalutamide. These results form the basis for this clinical trial of gedatolisib, a potent PAM inhibitor, in combination with darolutamide in men with mCRPC who have previously progressed on ARSi. **Methods:** This open-label, multicenter, Phase 1/2 study will evaluate the safety and efficacy of gedatolisib in combination with darolutamide in men with mCRPC who have progressed on ARSi. In Phase 1, 36 patients will be randomized to one of two dose arms to evaluate dose limiting toxicities (DLTs) and determine the recommended Phase 2 dose (RP2D). Gedatolisib will be administered once weekly for 3-weeks-on/1-week-off: Arm 1 – 120 mg and Arm 2 – 180 mg, with darolutamide 600 mg orally administered twice daily. Arm 2 may be dose de-escalated depending on the number of DLTs observed. In Phase 2, 12 additional patients will be enrolled at the RP2D (n= 30). Key inclusion criteria include adult males (≥ 18 years) with mCRPC who have progressed on or after treatment with one next-generation ARSi. Key exclusion criteria include males with adenocarcinoma with a small cell component and with ≥10% neuroendocrine type cells; prior treatment with PI3K, AKT, or mTOR inhibitor; prior chemotherapy or radiopharmaceutical therapy for mCRPC; uncontrolled type 1/2 diabetes; or active brain or leptomeningeal metastases. Primary endpoints for Phase 1 are safety and tolerability (incidence of DLTs, adverse events, and determination of maximum tolerated dose) determination of the recommended Phase 2 dose (RP2D), PK, and Bayesian Optimal Interval utility score. Primary endpoints for Phase 2 are rPFS rate at 6 months based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 with modifications as specified in Prostate Cancer Working Group 3 criteria. Secondary endpoints include rPFS rates at 9 and 12 months, overall rPFS, prostate-specific antigen response of ≥50% decrease from baseline at 4, 8, 12, and 16 weeks, overall response rate, duration of response, clinical benefit rate, overall survival rate at 18 and 24 months, and safety. The trial is currently open for enrollment (NCT06190899). Clinical trial information: NCT06190899. Research Sponsor: Celcuity.

TPS5110 Poster Session

A randomized phase 2 trial in progress of flexible and extended dosing of ^{177}Lu-PSMA-617 molecular radioligand therapy in mCRPC (FLEX-MRT).

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Background: The U.S. Food and Drug Administration (FDA) approved ^{177}Lu-PSMA-617 radioligand therapy (RLT) for patients with metastatic castration-resistant prostate cancer (mCRPC) with a fixed dosing schedule: Six cycles of 7.4 GBq administered in six-week intervals. However, a patient-tailored more flexible and extended dosing schedule of ^{177}Lu-PSMA RLT may increase treatment efficacy. No prospective data on such extended or abbreviated treatment schedule are available yet. In this randomized trial in men with mCRPC, we aim to determine the efficacy of a response-based flexible dosing schedule of ^{177}Lu-PSMA-617 RLT administered up to 12 treatment cycles compared to the current standard of care. **Methods:** This is an investigator-initiated prospective phase 2, open-label, randomized, controlled, parallel group, single-center trial. The aim is to assess the 2-year survival rate in mCRPC patients treated with a flexible dosing schedule of ^{177}Lu-PSMA RLT up to 12 cycles in comparison to the fixed dosing schedule of 6 cycles. Patients with progressive mCRPC post-ARSI, post taxane-based chemotherapy are eligible by PSMA positron emission tomography (PET) VISION trial criteria. Exclusion criteria include prior RLT and less than 6 weeks since the last myelosuppressive therapy. We hypothesized 2-year survival rates of 55% in the investigational group and 30% in the control group. A two-sided log rank test with an overall sample size of 90 subjects (45 treatment group, 45 control group) achieves 80.3% power at a 0.050 significance level to detect a hazard ratio of 0.4966. Patients will be randomized in a 1:1 ratio: The investigational arm is treated with up to 12 cycles including potential "treatment holidays" depending on the treatment response (n=45); the control arm receives 6 cycles administered in six-week intervals (n=45). Imaging response to RLT is assessed using ^{177}Lu-PSMA-617 SPECT/CT 24 h after each cycle and PSMA PET/CT during treatment holidays (every 12 weeks), respectively. In the investigational arm, RLT will be re-started after a treatment holiday if the patient experiences a ≥25% PSA progression and an imaging progression according to the Response Evaluation Criteria in PSMA PET/CT (RECIP). Primary endpoint is the 2-year survival rate calculated from the date of the first cycle of RLT. Secondary endpoints include safety by Common Terminology Criteria for Adverse Events (CTCAE) and dosimetry, and determination of overall and progression-free survival (evidence of progression as defined by either radiographic, PSA, or clinical progression, or death from any cause). The FLEX-MRT trial has been approved by the FDA (IND #168362), and the UCLA IRB (#23-000931). The trial is registered on ClinicalTrials.gov (NCT06216249). Start of enrollment is in February 2024. The study will last for 48 months of which subject accrual (entry) occurs in the first 12 months. Clinical trial information: NCT06216249. Research Sponsor: supported by Novartis (as an IIT); Prostate Cancer Foundation; Bavarian Cancer Research Center (BZKF); Munich Clinician Scientist Program (MCSP).

TPS5111 **Poster Session**

A phase 1/2 study of ONCT-534, a dual-action androgen receptor inhibitor (DAARI), in patients with metastatic castration-resistant prostate cancer.

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Background: Current therapeutic strategies for metastatic castration-resistant prostate cancer (mCRPC) include treatment with next-generation androgen receptor pathway inhibitors (ARPIs), which target the ligand-binding domain (LBD) of the AR. Approximately 5% to 10% of patients will have primary resistance to ARPIs and most initial responders will develop resistance within 1 to 3 years. Eventually, nearly all men with prostate cancer treated with ARPIs develop resistance via several mechanisms including AR genomic alterations, epigenetic alterations, and expression of truncated constitutively active AR splice variants. Hence, there is substantial unmet need for treatment of men with mCRPC resistant to at least one next-generation ARPI. ONCT-534 is a DAARI with a novel mechanism of action that combines inhibition of AR function with degradation of the AR protein. Importantly, this activity includes interaction with both LBD and the N-terminal domain (NTD) of the AR, rendering it effective against splice variants and LBD mutants, unlike existing ARPIs. ONCT-534 has demonstrated preclinical activity in prostate cancer models against unmutated AR and multiple forms of AR alteration, including amplification, mutations in the LBD, and splice variants with loss of LBD.
Methods: ONCT-534-101 is a phase 1/2, multi-center study to evaluate the safety, tolerability, antitumor activity, and pharmacokinetics of ONCT-534 in subjects with histologically confirmed mCRPC without neuroendocrine differentiation or small cell features who have relapsed or are refractory (R/R) to at least one next-generation ARPI. The study is separated into Phase 1 Dose Escalation and a Phase 2 Dose Expansion portions. The Phase 1 portion will evaluate approximately 27 subjects in 5 dose levels using an adaptive Bayesian Optimal Interval (BOIN) design to assess safety, tolerability and dose limiting toxicities (DLTs) at escalating doses and to determine the maximum tolerated dose and inform the 2 dose levels or schedules to be tested in Phase 2. DLTs will be assessed during the first 28 days of treatment. AR phenotype and AR levels will be evaluated for each subject pre- and post-treatment. The Phase 2 portion will evaluate approximately 32 subjects in 2 randomized cohorts to assess safety and tolerability of ONCT-534, compare the 2 different dose levels or schedules to select the optimal dose for further study, and assess the preliminary antitumor activity of ONCT-534. In both phases, after a screening period, eligible subjects with mCRPC will receive their assigned dose regimen of ONCT-534, which will be administered orally daily for 2 years or until disease progression and no longer clinically benefiting from treatment or development of unacceptable toxicity. Cohorts 1 and 2 have been completed without DLT. Enrollment into Cohort 3 began in January 2024 (NCT 05917470). Clinical trial information: NCT05917470. Research Sponsor: Oncternal Therapeutics Inc.

TPS5112 **Poster Session**

A phase 1b study of PSCA CAR T cells plus or minus radiation for the treatment of patients with PSCA+ metastatic castration-resistant prostate cancer.

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Background: Chimeric Antigen Receptor (CAR) T cell therapy has revolutionized the treatment of hematologic malignancies but application of CAR T cell therapy in solid malignancies remains a high priority. We previously demonstrated initial safety of a PSCA CAR T cells in patients with mCRPC following a reduced lymphodepletion regimen (LD) in a phase 1 trial (NCT03873805). There was preliminary evidence of anti-tumor activity (Dorff 2023) but escalation was not pursued due to concerns of toxicity. Additional dose exploration is needed. Preclinical work suggests that radiation therapy directed to tumor sites modifies the tumor microenvironment providing rationale for combining metastasis directed radiation therapy (MDRT) with CAR T cell therapy. The phase 1b dose exploration study aims to test a multi-dose strategy and whether the addition of MDRT could further enhance response. **Methods:** This is a single-center, open-label, phase Ib trial for patients with PSCA+ mCRPC. Key inclusion criteria are a diagnosis of mCRPC with evaluable disease, at least one area of metastasis amenable for radiation (for the MDRT cohort), PSCA expression by immunohistochemistry on archival tissue, and prior progression on abiraterone or enzalutamide or both; prior taxane chemotherapy is allowed. The primary objective will be to assess the feasibility, safety, and activity of PSCA CAR T cell therapy. Primary endpoints will include evaluation of toxicity through DLT's and activity through rate of PSA50 and objective responses. Secondary endpoints will include overall survival, progression-free survival (PCWG3 criteria), measurement of CAR T cell and cytokine kinetics, and T cell infiltration in pre- and post-treatment tumor biopsies. Exploratory endpoints will include phenotypes and frequencies of immune cell subsets in peripheral blood pre- and post-therapy, gene expression of CTCs, CAR immunogenicity by the presence of anti CAR antibodies or T cell mediated immune responses, urine analysis, cfDNA whole exome sequencing, and phenotype tumor infiltrating lymphocytes. This study includes 2 treatment plans (TP). The participants on TP 1 will receive 50 million PSCA CAR T cells every 2 weeks for up to 6 doses after LD chemotherapy. Based on these results, the number of cycles of CAR T will be determined for TP2. Participants on TP 2 will receive PSCA CAR T therapy after MDRT and LD. The first 3 participants on each TP will be staggered, all further participants will be treated in cohorts of 3. Toxicities will be monitored based on a Wald sequential probability ratio test. Rates and associated 90% Clopper and Pearson binomial confidence limits will be estimated for DLTs within the DLT period, disease response based on PSA50/RECIST/PCWG3 criteria, PFS at 6 months, and OS at 1 year. The results will be used to identify the optimal strategy to move to phase 2. The study is currently open to enrollment. Clinical trial information: NCT05805371. Research Sponsor: Prostate Cancer Foundation; Philanthropic Funds.

TPS5113 **Poster Session**

CYP11A1 inhibitor MK-5684 versus next-generation hormonal agent (NHA) switch in patients with metastatic castration-resistant prostate cancer (mCRPC) after NHA and taxane-based chemotherapy: Phase 3 MK-5684-003 trial.

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Background: Androgen receptor (AR) signaling remains a key driver of prostate cancer even after progression on androgen-directed therapies. Activating AR ligand binding domain (AR-LBD) somatic point mutations are a common mechanism of resistance to androgen-directed therapies in patients with mCRPC. MK-5684 (ODM-208) is an oral, nonsteroidal inhibitor of cytochrome P450 11A1 (CYP11A1), which catalyzes the first and rate-limiting step of steroid biosynthesis. Inhibition of CYP11A1 by MK-5684 suppresses the production of all steroid hormones and their precursors that may promiscuously activate the AR signaling pathway. In the phase 1/2 CYPIDES trial, MK-5684 showed antitumor activity in patients with heavily pretreated mCRPC, especially in those with AR-LBD mutations. The randomized, open-label, phase 3 MK-5684-003 trial (NCT06136624) is evaluating the efficacy and safety of MK-5684 versus NHA switch in patients with mCRPC previously treated with NHA and taxane-based chemotherapy. **Methods:** Eligible patients havemCRPC (unselected for AR-LBD mutations) that progressed on androgen deprivation therapy ≤6 months before screening and during or after treatment with 1 NHA for nonmetastatic (nm) hormone-sensitive prostate cancer (HSPC), nmCRPC, mHSPC, or mCRPC for ≥8 weeks (≥14 weeks with bone progression), and also progressed during or after 1 or 2 taxane-based chemotherapies for mCRPC. Approximately 1200 patients (300 with and 900 without AR-LBD mutations) will be randomly assigned 1:1 to receive MK-5684 5 mg PO BID (+ dexamethasone 1.5 mg and fludrocortisone 0.1 mg QD) or enzalutamide 160 mg PO QD (if prior abiraterone) or abiraterone acetate 1000 mg PO QD (+ prednisone 5 mg BID; if prior enzalutamide/darolutamide/apalutamide). Randomization to treatment will be stratified by measurable disease (yes/no), disease AR-LBD mutation status (positive/negative), and prior cabazitaxel use (yes/no). Treatment will continue until radiographic disease progression (verified per Prostate Cancer Working Group 3 [PCWG3]–modified RECIST v1.1 by blinded independent central review [BICR]), unacceptable toxicity, or other discontinuation criteria are met. Tumor assessments will be performed every 8 weeks up to week 24, then every 12 weeks thereafter. Dual primary end points are radiographic PFS (per PCWG3-modified RECIST v1.1 by BICR) and OS in patients with AR-LBD mutation-positive and -negative disease, separately. Secondary end points include time to initiation of first subsequent anticancer therapy or death; ORR and DOR per PCWG3-modified RECIST v1.1 by BICR; time to pain progression; time to prostate-specific antigen progression; time to first symptomatic skeletal-related event; and safety and tolerability. Enrollment is ongoing. Clinical trial information: NCT06136624. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and Orion Corporation, who are codeveloping MK-5684 (ODM-208).

TPS5114 Poster Session

CYP11A1 inhibitor MK-5684 versus next-generation hormonal agent (NHA) switch in patients with metastatic castration-resistant prostate cancer (mCRPC) after 1 prior NHA: Phase 3 MK-5684-004 study.

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Background: Activating androgen receptor (AR) somatic mutation is a known mechanism of resistance to AR-directed therapies in mCRPC, and it may permit continued hormone dependence. Upstream targeting of androgen biosynthesis may provide a therapeutic advantage over available AR-directed therapies in patients with mCRPC. MK-5684 (ODM-208) is an oral, nonsteroidal inhibitor of cytochrome P450 11A1 (CYP11A1), a catalyst of the first and rate-limiting step of steroid biosynthesis. Thus, MK-5684 has the potential to suppress the production of all steroid hormones and precursors that may activate the AR signaling pathway. MK-5684 demonstrated antitumor activity in patients with heavily pretreated mCRPC, especially in those with AR ligand binding domain (AR-LBD) mutations, in the phase 1/2 CYPIDES study. The efficacy and safety of MK-5684 in patients with molecularly unselected mCRPC after 1 prior NHA will be evaluated in the randomized, open-label, phase 3 MK-5684-004 study (NCT06136650). **Methods:** Eligible patients have mCRPC unselected for AR-LBD mutations that progressed during androgen deprivation therapy ≤6 months before screening and during or after 1 NHA for hormone-sensitive prostate cancer (HSPC) or nonmetastatic CRPC for ≥8 weeks (≥14 weeks with bone progression). Prior NHA + docetaxel for HSPC is permitted if patients received ≤6 cycles of docetaxel without radiographic disease progression. Approximately 1500 patients (AR-LBD mutation–positive, 375 patients; AR-LBD mutation–negative, 1125 patients) will be randomly assigned 1:1 to receive MK-5684 5 mg PO BID + dexamethasone 1.5 mg and fludrocortisone 0.1 mg PO QD or abiraterone acetate 1000 mg PO QD + prednisone 5 mg PO BID (if prior enzalutamide/darolutamide/apalutamide) or enzalutamide 160 mg PO QD (if prior abiraterone). Randomization will be stratified by metastasis (bone only/liver/other), AR-LBD mutation status (positive/negative), and prior docetaxel for HSPC (yes/no). Treatment will continue until unacceptable toxicity, radiographic disease progression (verified per Prostate Cancer Working Group 3 [PCWG3]–modified RECIST v1.1 by BICR), or other discontinuation criteria are met. Tumor assessments will be performed every 8 weeks through week 24, then every 12 weeks thereafter. Dual primary end points are radiographic PFS per PCWG3-modified RECIST v1.1 by BICR and OS in patients with AR-LBD mutation–positive and –negative disease, separately. Secondary end points include time to initiation of first subsequent anticancer therapy or death; ORR and DOR per PCWG3-modified RECIST v1.1 by BICR; time to pain progression; time to prostate-specific antigen (PSA) progression; PSA response rate; time to first symptomatic skeletal-related event; and safety and tolerability. Recruitment is ongoing. Clinical trial information: NCT06136650. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and Orion Corporation, who are codeveloping MK-5684 (ODM-208).

TPS5115 Poster Session

ProstACT GLOBAL: A phase 3 study of best standard of care with and without 177Lu-DOTA-rosopatamab (TLX591) for patients with PSMA expressing metastatic castration-resistant prostate cancer progressing despite prior treatment with a novel androgen axis drug.

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Background: The treatment of advanced prostate cancer (PC) is challenging, with no curative therapy to date and undesirable side effects that may impact patient quality of life. Monoclonal antibodies enable high specificity with low rates of off-target organ exposure, prolonged retention in PSMA+ tumors, and a predictable safety profile. There is a strong rationale for further investigation of the ^{177}Lu-labeled, chelator-conjugated antibody, ^{177}Lu-DOTA-rosopatamab (hereafter, TLX591), with prior studies demonstrating a favorable safety profile and efficacy, particularly with a fractionated (dose-dense) regimen Phase 1 ProstACT SELECT preliminary results demonstrate consistent uptake between TLX591 and ^{68}Ga-PSMA-11 imaging and reinforces advantages of this first-in-class radio-antibody drug conjugate investigational therapy. **Methods:** In this multinational, multicenter, prospective, randomized, open label phase 3 study, patients (N=400) with PSMA-expressing metastatic castration-resistant PC (mCRPC) that have progressed despite prior treatment with an androgen-receptor pathway inhibitor (ARPI) will be enrolled in a 2:1 ratio to receive best protocol-defined standard of care (SoC) with or without 2 intravenous injections of 2.8 GBq of TLX591, given 14 days apart. SoC may be alternative ARPI or docetaxel. Eligible patients must have received 1 prior ARPI in the mCSPC, nmCRPC, or 1L mCRPC setting. Patients must have $150x10^9$ /L platelets, and have PSMA-positive disease on ^{68}Ga-PSMA-11 PET/CT imaging. The primary endpoint is radiographic progression-free survival. Secondary endpoints include 5-year overall survival, tumor objective response rate, time to symptomatic skeletal event, health-related quality of life, and treatment-related adverse events count. An alpha control and 95% confidence intervals will be used; patients will be substratified between TLX591 + 2nd ARPI or TLX591 + docetaxel. This study is currently enrolling. This study is funded by Telix Pharmaceuticals. Clinical trial information: NCT04876651. Research Sponsor: None.

TPS5116 Poster Session

SECuRE: A dose escalation/expansion study to assess the anti-tumor efficacy of ^{67}Cu-SAR-bisPSMA in patients with metastatic castrate resistant prostate cancer.

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Background: Prostate cancer (PC) is common and despite recent advances in treatment options, patients with metastatic disease still have poor outcomes, warranting the development of new effective therapies in this setting. Prostate-specific membrane antigen (PSMA) is expressed in benign and malignant prostate tissues and luminal surface of salivary/lacrimal glands, small intestine and renal tubules. The double PSMA binding moiety of SAR-bisPSMA in ^{64}Cu-SAR-bisPSMA (imaging) and ^{67}Cu-SAR-bisPSMA (therapy) may offer advantages compared to currently used single-target PSMA agents. Clinical evidence demonstrated 2-3 times higher uptake of ^{64}Cu-SAR-bisPSMA compared to the single-target PSMA agent, ^{68}Ga-PSMA-11. Pre-clinical efficacy data of ^{67}Cu-SAR-bisPSMA in mice showed statistically significant tumor growth inhibition compared to the control group as well as a dose-dependent delay in eventual tumor regression in a PC xenograft study. These results led to the development of this clinical study, which aims to assess safety and anti-tumor efficacy of ^{67}Cu-SAR-bisPSMA in patients with metastatic castrate resistant PC (mCRPC). **Methods:** SECuRE is a phase I/IIa multi-center, open-label, non-randomized, dose-escalation and cohort expansion study of ^{64}Cu-SAR-bisPSMA and ^{67}Cu-SAR-bisPSMA (NCT04868604). mCRPC patients with progression, prior exposure to at least one androgen receptor pathway inhibitor, and positive ^{64}Cu-SAR-bisPSMA PET may be treated with ^{67}Cu-SAR-bisPSMA. This study is being conducted in 3 phases: a ^{64}Cu-SAR-bisPSMA Dosimetry Phase (n=6), a ^{67}Cu-SAR-bisPSMA Dose Escalation Phase (n=up to 24), and a ^{67}Cu-SAR-bisPSMA Cohort Expansion Phase (n=14). The primary and key secondary objectives include assessment of ^{64}Cu- and ^{67}Cu-SAR-bisPSMA safety and dosimetry, determining the maximum tolerated dose (MTD) or maximum feasible dose (MFD) and anti-tumor efficacy of ^{67}Cu-SAR-bisPSMA. The ^{67}Cu-SAR-bisPSMA dose levels investigated in the escalation phase include: 4 GBq (cohort 1, single dose), 8 GBq (cohort 2, single dose), 12 GBq (cohort 3, single dose) and up to 24 GBq across two doses (cohort 4, two doses at MTD or MFD). The Dose Expansion Phase of the study will allow the administration of up to 4 doses of ^{67}Cu-SAR-bisPSMA at the MTD/MFD. Response measurements include reduction in PSA levels, radiological progression-free survival, duration of response and overall survival. Radiological response will be assessed by RECIST V1.1 and PCWG3. At the time of submission of this abstract, no dose limiting toxicities have been observed to date in the first 3 cohorts. In the United States, 4 sites are active with additional sites in planning. Additional sites in the US and Australia are currently in start-up. Clinical trial information: NCT04868604. Research Sponsor: Clarity Pharmaceuticals Ltd.

TPS5117 Poster Session

TRAMP study: A phase 2 trial of tumor necrosis factor-α blockade and AR inhibition in men with CRPC.

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Background: Combining androgen receptor signaling inhibitors (ARSI) with androgen deprivation therapy (ADT) leads to improved clinical outcomes compared to ADT alone in patients with advanced prostate cancer (PC). However, treatment resistance and cancer progression invariably occur. Novel strategies to overcome resistance to AR pathway inhibition are needed. TNF-α is a "master regulator" of a pro-inflammatory cytokine cascade mediated through activation of the transcription factor nuclear factor kappa-B. TNF-α also mediates pro-survival signaling in tumor cells, elicits pro-tumor immune changes in the tumor microenvironment, and promotes tumor cell migration and metastases in PC models. Our group recently showed that TNF-α induces AR signaling and increases PC cell clonogenic growth, even in the presence of ARSIs. Pharmacologic inhibition and genetic ablation of TNF-α signaling subsequently rescued and thereby enhanced the activity of AR antagonists. Taken together, we hypothesize that the addition of TNF-α blockade to AR antagonist may overcome resistance and thus extend the duration of response to ARSI treatment. **Methods:** This Phase 2, single-center, single-arm trial aims to enroll 34 patients with castration-resistant prostate cancer (CRPC) and will employ a Bayesian continual reassessment method study design with early stopping rules for both toxicity and futility. Eligible patients must have progressing CRPC (defined as either a confirmed rising PSA ≥ 2 ng/ml or radiographic progression) and previously received at least 6 months of ARSI therapy in the hormone-sensitive setting. Prior taxane chemotherapy is allowed in the hormone-sensitive setting, but must be completed ≥ 6 months prior to enrollment. All patients will receive the TNF-α inhibitor golimumab (50mg SC monthly) for up to six months plus AR antagonist apalutamide (240mg PO daily). The primary endpoint is the rate of PSA50 (defined as ≥50% decline from baseline PSA) at 12 weeks. The null hypothesis is that the true response rate is 0.22 (ARN-509-001, NCT01171898), and the alternative hypothesis is that the true response rate is 0.44. Secondary endpoints include objective response rate, PSA progression-free survival (PFS), radiographic PFS, time to subsequent antineoplastic therapy, and overall survival. Correlative studies will quantify pre-treatment proinflammatory cytokines and classify ctDNA and metastatic tumor biopsies into 3 phenotypic categories based on AR activity levels ("high," "weak/heterogeneous," or "absent") using quantitative gene expression and digital spatial profiling. We plan to evaluate treatment-induced changes and assess if AR activity is modulated by TNF- inhibition and determine whether the modulation is associated with improved clinical outcomes. The trial is open to enrollment. Clinical trial information: NCT05960578. Research Sponsor: J&J; U.S. Department of Defense.

TPS5118 Poster Session

A phase 2 trial of ADT interruption in patients responding exceptionally to AR-pathway inhibitor in metastatic hormone-sensitive prostate cancer (A-DREAM/ Alliance A032101).

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Background: Novel androgen receptor pathway inhibitors (ARPIs) improve overall survival (OS) in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC) in conjunction with testosterone suppression (TS) relative to TS alone. However, the duration of treatment required to derive clinical benefit is unclear, as is whether continuous treatment is requisite for optimal cancer outcomes. Favorable PSA declines have been associated with prolonged OS in clinical trials testing TS + ARPIs. We thus designed this single-arm Phase 2 trial to test the hypothesis that pts who achieve exceptional response to upfront TS + ARPI can suspend treatment, allowing for T recovery and improvement in quality of life while maintaining favorable clinical outcomes. **Methods:** Eligible pts had mHSPC by conventional imaging with PSA $\geq$ 5 ng/ml and T $\geq$ 150 ng/dl (or not known to have been hypogonadal) prior to starting treatment, have been receiving TS for 540-750 days and ARPI for $\geq$ 360 days, and have achieved PSA $<$ 0.2 ng/ml (stable or falling for 3 consecutive measurements) with castrate T $<$50 ng/dl at the time of enrollment. Intermittent ADT for biochemical recurrence prior to mHSPC diagnosis, prior local therapy, prior radiation to metastatic sites, and up to 6 cycles of docetaxel in mHSPC are permitted. Pts who underwent surgical castration, received ARPI prior to mHSPC diagnosis, or are receiving experimental treatment for mHSPC or participating in a clinical trial that does not allow for TS or ARPI interruption are excluded. After enrollment, pts discontinue both TS and ARPI and are followed with PSA and T levels every 3 months, conventional CT/MRI and bone scan at least every 6 months, and FACT-P questionnaire for patient-reported outcomes every 6 months. Treatment re-initiation triggers are PSA increase to $\geq$ 5 ng/ml, radiographic change (progressive disease per modified RECIST 1.1 on CT/MRI or unconfirmed progressive disease per PCWG3 on bone scan), or symptoms attributable to prostate cancer. Subsequent management is per physician discretion. The primary endpoint is remaining treatment-free with eugonadal T ($>$ 150 mg/dl) 18 months after the start of treatment interruption, with 75 pts to be enrolled to differentiate 18-month treatment free rates of 0.30 (null hypothesis) and 0.45 (alternative hypothesis). Secondary endpoints include time to eugonadal T, duration off treatment, and changes in patient-reported outcomes. Exploratory endpoints include radiographic progression-free survival, time to next treatment, OS, and correlation of tissue- and blood-based biomarkers with clinical endpoints. The study was activated in July 2022 and accrual is ongoing throughout the NCTN. Support: U10CA180821, U10CA180882, UG1CA189823, https://acknowledgments.alliancefound.org, Veracyte Inc. Clinical trial information: NCT05241860. Research Sponsor: National Cancer Institute.

TPS5119 Poster Session

LIBERTAS: A degendered and transgender-inclusive phase 3 study of apalutamide (APA) plus intermittent vs continuous androgen deprivation therapy (ADT) in participants (pts) with metastatic hormone-sensitive prostate cancer (mHSPC).

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Background: Individuals with mHSPC may experience adverse events and decreased quality of life associated with ADT. LIBERTAS, the first degendered and transgender-inclusive PC study, explores the use of APA + intermittent ADT as an ADT-minimizing approach in pts who achieve prostate-specific antigen (PSA) <0.2 ng/mL after 6 mo of APA + ADT. mHSPC has been studied almost exclusively in cisgender men. With inclusion of transgender pts who may be receiving feminizing gender-affirming care (GAC), reducing ADT must be approached with deliberate care. LIBERTAS uses broad eligibility criteria to allow inclusion of pts under-represented in clinical trials, including Black and African American pts, transgender, nonbinary, and gender-diverse pts and pts with disabilities. **Methods:** A patient voice exercise was conducted to gather feedback from pts and caregivers on their experiences with mHSPC and on the proposed study design. All gender-specific language was removed. SOGI (sexual orientation and gender identity) data are collected and reported in the United States. Study site staff are offered healthcare-specific sexual and gender minority cultural sensitivity training. This prospective, international, open-label, randomized study is enrolling pts with metastatic PC documented by conventional imaging, ≤3 mo ADT before enrollment (except as part of GAC), and ECOG PS 0/1; pts with ECOG PS 2/3 are eligible if their score is related to stable disabilities (eg, spinal cord injury, blindness) and not to PC/PC therapy. Pts with bilateral orchiectomy are excluded (except as part of GAC). Stratification factors: tumor volume and prior treatment for localized PC. Pts with confirmed PSA <0.2 ng/mL after initial 6-mo treatment with APA 240 mg/d + ADT are randomized 1:1 to APA 240 mg/d + intermittent ADT or APA + continuous ADT. ADT can be restarted until radiographic progression (assessed by conventional imaging) for pts in the intermittent ADT group with new/worsening cancer symptoms, PSA increase to >10 ng/mL (or return to baseline when PSA <10 ng/mL before ADT), or PSA doubling time <6 mo. Outcomes of pts undergoing medical or surgical GAC are evaluated descriptively as a separate cohort. Primary end points: radiographic progression-free survival and hot flash frequency and severity score at 18 mo from randomization. Secondary end points include findings from electronic patient-reported outcomes completed on a mobile device, digital health assessments measuring physical activity and sleep (measured from a wrist-worn device), and neurocognitive function measured using touchscreen-based interactive assays. An independent data monitoring committee will review safety data. ~333 pts will be enrolled over 2 yrs at 86 sites in 9 countries. Clinical trial information: NCT05884398. Research Sponsor: Janssen Research & Development.

TPS5120 **Poster Session**

Veterans Affairs seamless phase II/III randomized trial of standard systemic therapy with or without PET-directed local therapy for oligometastatic prostate cancer (VA STARPORT).

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Background: The concept of metastasis-directed therapy (MDT) using radiation or surgery for oligometastatic (OM) prostate cancer (pCa) has evolved from an anecdotal hypothesis to a promising approach that may optimally balance toxicity and oncologic efficacy. Recently, there have been multiple smaller phase II randomized trials that have shown a signal of efficacy for MDT in OM pCa. Most studies have compared MDT to observation alone as the control arm, included only recurrent OM patients, and included up to 3-5 sites of metastasis. It is in this context, that the VA STARPORT trial was initiated in 2021 to definitively determine the role of MDT in Veterans with oligorecurrent pCa in 1-5 sites. Yet, the diagnosis and management of metastatic pCa have since evolved. The SABR-COMET-10 trial recently completed enrollment and compares systemic therapy alone or with MDT in patients with 1-10 metastases from various histologies. While pCa PET/CT imaging was only available for Veterans with biochemical recurrence in 2021, PSMA PET/CT now allows for the improved diagnosis of OM in Veterans with *de novo* pCa—a growing cohort of patients without a clear standard of care. Therefore, to maximize the impact and generalizability of the trial, VA STARPORT has been amended to allow for *de novo*OM and 1-10 metastases. The primary goal of VA STARPORT is to determine if adding PET-directed local therapy (PDLT) to standard systemic therapy (SST) improves disease control compared to SST alone in Veterans with recurrent and *de novo*oligometastatic pCa. **Methods:** VA STARPORT is a phase II/III randomized trial open at 18 VA medical centers comparing SST alone (Arm 1) or with PDLT (Arm 2) in Veterans with OM pCa. Key eligibility criteria include recurrent or *de novo*hormone-sensitive metastatic pCa and 1-10 metastatic lesions on any FDA-approved pCa PET/CT. The primary endpoint is castration-resistant prostate cancer-free survival (CRPC-free survival). Secondary endpoints include radiographic PFS, clinical PFS, freedom from index lesion progression, toxicity, quality of life, and prostate cancer-specific and overall survival. SST is delivered using any NCCN guideline-concordant regimen in both arms. PDLT can be either radiation or surgery to all sites of cancer. Regarding local therapy, *de novo* patients in Arm 1 receive prostate-directed RT, and in Arm 2 receive PDLT to all metastases and the prostate. For recurrent patients in Arm 1 there is no local therapy, while in Arm 2 patients receive PDLT. All participants undergo somatic tumor sequencing using the VA National Precision Oncology Program. Assuming a hazard ratio of 0.60 for SST + PDLT vs SST, two-sided alpha = 0.05 and 90% power, a total of 464 participants will be randomized to generate 166 CRPC-free survival events by the end of the active study phase. Recruitment is ongoing and 150 patients have been enrolled. Clinical trial information: NCT04787744. Research Sponsor: Veterans Affairs Office of Research and Development; 1I01CX002277-01.

TPS5121 Poster Session

A randomized phase II study of ADT + abiraterone versus ADT + abiraterone + docetaxel in patients with low-volume metastatic hormone-sensitive prostate cancer.

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Background: The PEACE-1 and ARASENS phase III trials showed benefit of "triplet" therapy in patients with metastatic hormone sensitive prostate cancer (mHSPC). Triplet therapy is defined as androgen deprivation therapy (ADT), docetaxel and an androgen receptor signaling inhibitor. Both trials showed improved outcomes in patients with a high volume of disease per CHAARTED criteria ($\geq$ 4 bone lesions with $\geq$1 beyond the axial skeleton or visceral metastasis). The benefit was less clear in patients with low volumes of disease, this may be due to the use of docetaxel as the control arm in this patient population. In the CHAARTED study the benefit of docetaxel in addition to ADT was most pronounced in patients with high volume mHSPC, and the benefit was less certain in low volume disease. To address this uncertainty, we are conducting this phase II trial evaluating ADT/abiraterone versus ADT/abiraterone plus docetaxel in patients with low volume mHSPC. **Methods:** This is a multisite, randomized trial of ADT (physician's choice) and abiraterone (1000mg daily + 5 mg prednisone) versus ADT, abiraterone and docetaxel (75 mg/m^2 q3 weeks for 6 cycles). Patients may have started ADT up to 12 weeks prior to randomization. Key eligibility criteria include a tissue-confirmed diagnosis of prostate cancer (PCa) and evidence of metastatic disease on CT, MRI and/or bone scan that meets CHAARTED criteria for low volume disease. Recurrent PCa and exposure to ADT prior to the diagnosis of metastatic disease are allowed, as is concurrent treatment with radiation therapy. The primary objective is to assess and compare radiographic progression free survival (rPFS) between treatment arms. Power calculations assume the median rPFS of the control arm is 33 months (based on the LATITUDE trial) versus 55 months in the docetaxel arm (based on the PEACE-1 trial). A sample size of 120 patients will provide 80% power with a one-sided α = 0.10 Type I error rate based on the log rank test to detect a hazard ratio = 0.60. Assuming a 36-month accrual duration and an additional 3 years of follow up, a total of 70 events are expected to occur on this study. The study will enroll 150 patients (75 per arm) to obtain 120 evaluable patients (assuming a 20% attrition rate). Secondary endpoints include overall survival, PSA response rate, overall response rate, time to castration resistant PCa and time to initiation of subsequent anti-neoplastic therapy. Exploratory endpoints include quality of life assessments and rates of adverse events. Enrollment in this trial began in Dec 2023. It is open at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University and other satellite sites affiliated with Northwestern University. Clinical trial information: NCT06060587. Research Sponsor: Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

TPS5122 Poster Session

Darolutamide plus androgen-deprivation therapy in patients with high-risk biochemical recurrence of prostate cancer: A phase 3, randomized, double-blind, placebo-controlled study (ARASTEP).

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Background: Up to half of patients (pts) whose prostate cancer (PC) has been treated with radiotherapy (RT) or radical prostatectomy (RP) as primary therapy will develop biochemical recurrence (BCR), defined as a prostate-specific antigen (PSA) increase without evidence of metastases on conventional imaging (e.g., CT/MRI). Compared with conventional imaging, prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) is a more precise imaging method that may detect small PC lesions in pts with BCR. Effective treatment is needed for pts with BCR at high risk of metastatic progression, and who have lesions identified by PSMA PET/CT, to delay progression. Darolutamide (DARO) is a structurally distinct and highly potent androgen receptor inhibitor with low blood–brain barrier penetration and limited potential for drug–drug interactions. In ARAMIS (phase 3; NCT02200614), DARO significantly improved metastasis-free survival (MFS) and reduced risk of death in pts with nonmetastatic castration-resistant prostate cancer (nmCRPC). ARASTEP (NCT05794906) is evaluating whether DARO plus androgen-deprivation therapy (ADT) improves radiological progression-free survival (rPFS) by PSMA PET/CT vs placebo (PBO) plus ADT in pts with BCR following primary therapy and PSMA PET/CT-positive lesions. **Methods:** ARASTEP is a global, phase 3, double-blind, placebo-controlled study in which ~750 pts from 192 sites will be randomized to receive oral DARO 600 mg twice daily or PBO, both with ADT, for 24 months. Eligible pts have PC previously treated with primary RT or RP followed by adjuvant RT (ART) or salvage RT (SRT) or RP alone if unfit for ART/SRT, ECOG PS 0/1, serum testosterone >150 ng/dL, and high-risk BCR. High-risk BCR is defined as PSA doubling time (PSADT) <12 months, PSA ≥0.2 ng/mL above the nadir after primary RP followed by ART or SRT or ≥2 ng/mL after primary RT only, and ≥1 PSMA PET/CT-positive lesion with no evidence of metastasis on conventional imaging. Image-guided RT (IGRT) or surgery of baseline (BL) PSMA PET lesions assessed by blinded independent central review (BICR) is allowed ≤12 weeks from randomization. Stratification factors are PSADT (<6 vs ≥6–<12 months), intent to treat BL PSMA PET/CT lesions by BICR with IGRT/surgery (Yes vs No), and distant ± locoregional vs locoregional-only metastases. The primary endpoint is rPFS by PSMA PET/CT assessed by BICR. Secondary endpoints are MFS by BICR, time to CRPC, time to first subsequent systemic antineoplastic therapy, time to locoregional progression by PSMA PET/CT, time to first symptomatic skeletal event, overall survival, PSA <0.2 ng/mL at 12 months, time to deterioration in FACT-P score, safety, and time to symptomatic progression. Enrollment for ARASTEP began in April 2023. Currently 18 patients have been enrolled. Clinical trial information: NCT05794906. Research Sponsor: Bayer.

TPS5123 Poster Session

Phase III, double-blind, placebo-controlled, 2-cohort, randomized study of saruparib (AZD5305) in combination with new hormonal agents in patients with metastatic castration-sensitive prostate cancer with and without homologous recombination repair mutation (EvoPAR-Prostate01).

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Background: PARP inhibitors (PARPi) in combination with new hormonal agents (NHAs) are approved for treatment of metastatic castration-resistant prostate cancer (mCRPC). PARPi utilization in earlier lines of treatment may result in greater magnitude of benefit. Saruparib is a potential best-in-class PARPi, which selectively inhibits and traps PARP1, has minimal effect on PARP2, and hence may offer an improved therapeutic window compared with currently approved nonselective PARPi. The efficacy and safety of saruparib plus NHAs for the treatment of metastatic castration-sensitive prostate cancer (mCSPC) and mCRPC are being assessed in the phase I/IIa PETRANHA study (NCT05367440). The phase III EvoPAR-Prostate01 study (NCT06120491) is evaluating the efficacy and safety of saruparib plus physician's choice of NHA (abiraterone, darolutamide, or enzalutamide) compared with placebo plus physician's choice of NHA in participants with mCSPC. **Methods:** This is a 2-cohort, 2-arm, randomized, double-blind, placebo-controlled, multicenter global study. Key eligibility criteria include age ≥18 years, histologically confirmed mCSPC (*de novo* or recurrent low- or high-volume disease), ECOG PS 0-1, and confirmed, prospectively defined homologous recombination repair gene mutation (HRRm) status (defined by the presence/absence of pathogenic/likely pathogenic mutations in ≥1 of the genes *BRCA1, BRCA2, ATM, CDK12, PALB2, RAD51B, RAD51C, RAD51D,*and *BARD1*). Participants must be receiving androgen deprivation therapy throughout the study or have undergone bilateral orchiectomy, and must be suitable for treatment with NHAs. Key exclusion criteria include prior therapy with PARPi, prior chemotherapy or NHAs in the mCSPC setting (prior NHAs for localized disease permitted), and history of, or suspected, myelodysplastic syndrome/acute myeloid leukemia. Participants are allocated to either the HRRm or non-HRRm cohort based on prospective testing of both tumor tissue and circulating tumor DNA. Participants are randomized 1:1 to receive saruparib plus physician's choice of NHA or placebo plus physician's choice of NHA. Treatment continues until disease progression, unacceptable toxicity, or participant-initiated withdrawal. The primary endpoint is radiographic progression-free survival (rPFS), with overall survival (OS) a key secondary endpoint. Planned statistical analyses of rPFS and OS will be conducted within each cohort using a stratified log-rank test. Approximately 1,800 participants (550 HRRm; 1,250 non-HRRm) will be randomized. Enrollment began in November 2023 and is ongoing. Clinical trial information: NCT06120491. Research Sponsor: AstraZeneca.

TPS5124 **Poster Session**

Debunking the frailty-sarcopenia-ADT axis in metastatic prostate cancer with multicomponent exercise: The FIERCE trial.

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Background: Metastatic prostate cancer (mPCa) incidence is growing despite a decrease in the prevalence of prostate cancer (PCa). Androgen deprivation therapy (ADT), the mainstay treatment for mPCa, is accompanied by a number of side effects, such as decline in muscle mass and physical function, leading to the exacerbation of age-related conditions including frailty and sarcopenia. Frailty is characterized by a loss of functional reserve, where frail men with mPCa have a worse prognosis. Sarcopenia refers to a decrease in muscle mass, strength, and function, and is associated with increased mortality in men with mPCa. Notably, PCa patients who received ADT are 3 times more likely to develop frailty compared to patients who never received ADT and 2 times more likely to develop sarcopenia compared to men without cancer. Exercise plays a key role in ameliorating or preventing further deterioration of ADT-related side effects and improving muscle mass, fitness, and strength. However, while there is a number of exercise studies in men with PCa, those with mPCa have been vastly understudied, with a lack of studies focusing on frailty and sarcopenia and the mechanisms of how exercise could address such outcomes. Thus, we have designed the FIERCE Trial to assess the effects of a 16-week multicomponent exercise intervention, encompassing resistance, aerobic, and functional training on frailty and sarcopenic status and their potential mechanistic biomarkers, and disease progression. **Methods:** The FIERCE trial is a prospective study aiming to recruit eighty pre-frail/frail men with mPCa receiving ADT who will be randomized to an exercise or attention control group. The 16-week exercise intervention will include thrice weekly clinic supervised, resistance and functional exercise circuit training, and self-directed home-based aerobic exercise. The attention control group will receive a stretching program and will be offered the exercise program following the study period. The primary outcome will be frailty, measured by the Fried Frailty phenotype (i.e., muscle loss, exhaustion, physical activity, gait speed, and strength) and frailty associated biomarkers (IL-6, TNF-α, CRP). Secondary outcomes include sarcopenia, measured using computerized tomography scans and sarcopenia associated muscle biopsy-driven biomarkers (myokines and insulin pathway markers). An exploratory outcome will assess the effect of exercise on cancer cell line growth (LNCaP cell line). To date, eight out of planned 80 patients have been enrolled. This trial is registered in clinicaltrials.gov (NCT06040125). Clinical trial information: NCT06040125. Research Sponsor: Prostate Cancer Foundation.

TPS5125 Poster Session

A phase 2 randomized trial of neoadjuvant enoblituzumab versus standard of care in men with high-risk localized prostate cancer: The help elucidate and attack longitudinally (HEAT) prostate cancer randomized study.

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Background: B7-H3 is a member of the B7 superfamily, which includes PD-L1 (B7-H1) and PD-L2 (B7-DC). Enoblituzumab is a humanized Fc-optimized B7-H3–targeting antibody that induces antibody-dependent cellular cytotoxicity (ADCC). A recent investigator-initiated trial demonstrated that enoblituzumab therapy, used in the neoadjuvant prostate cancer setting, is feasible, safe, may enhance short-term clinical outcomes, and appears to stimulate intratumoral immune activation including CD8+ T cell infiltration and peripheral expansion of tumor-infiltrating T-cell clones that correlated with undetectable PSA at 1-year post-prostatectomy. To assess the impact of enoblituzumab on recurrence-free survival following prostatectomy, a phase 2, randomized, neoadjuvant clinical trial in high-risk localized prostate cancer patients has been started. *We hypothesizethat targeting B7-H3with enoblituzumabwilldelay or prevent recurrence following prostatectomy compared to standard of care (SOC).* **Methods:** The HEAT trial is an investigator-initiated, multi-center, randomized, phase 2 study that is presently enrolling (NCT06014255). Eligible patients will undergo a pre-treatment prostate biopsy and conventional imaging (CT and bone scan) as well as PSMA-PET. Patients who have clinical stage cT1c-T3b, cN0 cM0 disease by conventional imaging (N1 by PSMA allowed with up to 3 LNs each ≤1 cm) will be eligible as long as concurrent hormonal or radiation therapy is not given. Prostate biopsy, within 3 months of enrollment, needs to show at least 3 positive cores containing at least 1 core with at least 50% disease involvement with Gleason ≥4+3=7 disease (with at least 1 additional high-risk feature such as PSA>20 ng/ml or cT3) or a Gleason sum ≥8. Patients will receive enoblituzumab at a dose of 15mg/kg IV biweekly for 6 doses (12 weeks) on the treatment arm, followed by prostatectomy, or will be scheduled for prostatectomy directly within 4-8 weeks on the SOC arm. 219 patients will be randomized (2:1) to treatment versus SOC. Pre-treatment, on-treatment, and post-treatment biomarkers of response and resistance will be collected. Patients will be followed according to standard institutional practices, but will require PSA evaluations every 3 (±1) months during year 1 and every 6 (±2) months during years 2-5. In both arms, salvage or adjuvant therapy will occur after biochemical or radiographic progression. The primary endpoint is recurrence-free survival (RFS) defined as any metastasis events, local pelvic visceral or lymph node recurrence, detectable prostate-specific antigen (PSA), or start of subsequent local or systemic therapy (including salvage or adjuvant therapy), or death for any cause, whichever occurs first. Secondary endpoints include additional clinical and immunologic correlates. Clinical trial information: NCT06014255. Research Sponsor: Macrogenics, Inc; U.S. Department of Defense; HT94252310390.

TPS5126 **Poster Session**

A phase 1 safety and feasibility study of intratumoral placement of bicalutamide implants combined with radiotherapy for localized prostate cancer.

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Background: Systemic androgen deprivation therapy (ADT) is an integral part of therapy for unfavorable intermediate or high-risk prostate cancer treated with radiation therapy (RT). However, systemic anti-androgens are associated with considerable cardiovascular, metabolic, and sexual side effects leading to omission and contraindication in many men. We tested the feasibility of replacing systemic ADT with targeted local delivery of an anti-androgen agent (bicalutamide, Biolen Implant). The Biolen implant consists of a medical grade silicone polymer mixed with 6.3mg bicalutamide into a solid rod-shaped scaffold approximately 0.95 x 15 mm in size. Pre-clinical studies have demonstrated that a silicone/bicalutamide implant is a feasible method for durable localized delivery of an anti-androgen into the prostate. Results for the preclinical studies were presented at the AACR Symposium in April 2023 (Poster # 5261). **Methods:** Trial Design: This study (CP-002, NCT04943536) is a prospective, single-center, single-arm feasibility study to assess the safety, feasibility and PK profile for Biolen for the localized delivery of bicalutamide into the prostate when delivered with radiotherapy. Up to 20 participants with intermediate to high risk localized prostate cancer who are planned to receive RT and are candidates for systemic ADT will be enrolled. Study participants will have placement of the drug eluting Biolen (bicalutamide) implants. Participants will receive standard of care radiation 9 weeks after implant and will be followed through 2 years post radiation. Patients will undergo plasma collection after Biolen implant at Day 1, 3, Week 1, 2, 4 and seminal fluid collection at 4-7 and 8 weeks for assessment of bicalutamide levels. An MRI will be performed at 6 and 24 months after completion of radiation. Key Eligibility: Patients must have at least 1 MRI detected, biopsy proven localized prostate cancer lesion in whom prostate radiation and ADT is appropriate therapy (such as Intermediate Risk localized prostate cancer). Patients diagnosed as one of the following: a) NCCN intermediate risk prostate cancer, b) NCCN high risk prostate cancer due to Gleason Grade 4 or 5 AND refuses to receive systemic ADT, c) NCCN high risk prostate cancer due to PSA $>$ 20 AND refuses to receive systemic ADT. Trial Status: The study is ongoing at the NCI and 9 patients have been enrolled to date. Clinical trial information: NCT04943536. Research Sponsor: National Cancer Institute.

TPS5127 **Poster Session**

ALADDIN: Evaluation of darolutamide addition to androgen deprivation therapy and radiation therapy in newly diagnosed prostate cancer with pelvic lymph nodes metastases.

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Background: Standard of care for patients with prostate cancer (PC) with pelvic lymph node metastases is radiotherapy (RT) with long-term androgen deprivation therapy (ADT). In the STAMPEDE trial, James et al. assessed the role of abiraterone acetate with prednisolone (AAP) earlier in the disease for N+M0 PC patients. They showed that the addition of AAP to ADT and RT significantly improved failure-free survival (FFS) from 61% to 92.5% (ESMO 2017). Darolutamide improves survival in men with castration-refractory non-metastatic prostate cancer and in mHSPC patients with the addition of ADT plus docetaxel. We hypothesize that adding Darolutamide to ADT and RT could improve FFS for these high-risk patients. **Methods:** The ALADDIN study (NCT05116475) is a French, prospective, phase 3 trial that will enroll an estimated 152 patients with hormone-naive prostate cancer and pelvic lymph node metastases. Eligible patients are treatment-naive for hormonal therapy, with positive lymph node disease (upper limit defined as L4/L5 interspace) determined by conventional imaging or TEP choline or PSMA, ECOG performance status of 0 to 2, and adequate major organ function. Patients will be randomized by minimization 1:1 to receive ADT + Intensity-Modulated Image-Guided Radiation Therapy (IMRT) with darolutamide or placebo (of darolutamide). IMRT will deliver 78 Gy to the prostate, 70 Gy to the metastatic lymph nodes, and 46 Gy to the pelvic lymph node areas (2 Gy per fraction, 5 days a week) with daily CBCT imaging. ADT will be achieved with LHRH agonists or antagonists for 24 months. The darolutamide regimen will be two tablets of 300 mg orally twice daily for 24 months. The primary endpoint is failure-free survival. Secondary endpoints will be: MFS, progression-free survival, safety, overall survival, and health-related quality of life. Stratification factors are D'Amico risk group and sites. The planned sample size provides 80% power to detect a difference of 20% in FFS (60 vs 80%) at a two-sided 0.05 significance level. The study is expected to last for 7 years, of which accrual will last for 2 years. The first participant was enrolled in the study in August 2022. In total, 23 centers are participating in the ALADDIN study. The DSMB occurred on November 13th 2023 and allowed the study to continue as planned. Clinical trial information: NCT05116475. Research Sponsor: BAYER.

TPS5128 **Poster Session**

A phase 2 study of neoadjuvant PARP inhibition followed by radical prostatectomy (RP) in patients with unfavorable intermediate-risk or high-risk prostate cancer with *BRCA1/2* gene alterations (NePtune).

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Background: Patients with localized high-risk prostate cancer have an increased risk of relapse following RP. Approximately 6% of patients with high-risk disease harbor germline alterations in the DNA repair pathway, of which *BRCA1/2* alterations are the most common. Patients with germline *BRCA1/2* mutations have higher rates of aggressive disease, distant metastases, and worse survival compared to non-carriers. Olaparib is a PARP inhibitor which demonstrates improved overall survival in patients with metastatic castration resistant prostate cancer with *BRCA1/2* germline and somatic alterations. Additionally, olaparib has demonstrated improved invasive disease-free survival as adjuvant therapy in patients with germline *BRCA1/2* HER-2 negative breast cancer. Novel, multimodal treatment strategies for patients with high-risk localized prostate cancer with germline or somatic *BRCA1/2* may improve outcomes for these patients. **Methods:** We designed a multicenter phase 2 single arm study evaluating neoadjuvant olaparib in combination with a LHRH agonist for 6 months followed by RP. Eligible patients include those with a Gleason score ≥4+3=7, PSA >20 ng/mL or T3 disease (by DRE or prostate MRI) and lymph node <20 mm. Patients with intraductal carcinoma are eligible independent of Gleason score, PSA, or T stage. Patients must have a germline or somatic *BRCA1/2*pathogenic or likely pathogenic alterations identified on standard of care molecular profiling. Eligible patients receive olaparib 300 mg by mouth twice daily and a LHRH agonist for 6 months followed by RP. The primary endpoint is the rate of a pathologic complete response (pCR) or minimum residual disease (MRD, tumor ≤5 mm) as determined by central pathology review. Secondary endpoints include PSA response, surgical staging at RP, positive margin rate, time to testosterone recovery, and safety. Exploratory endpoints include quality of life assessment, proportion of downstaging on multi-parametric MRI (mpMRI), correlation of mpMRI with pathologic response, and tissue based molecular predictors of response and resistance. The sample size was estimated based a Binomial Exact test to assess the null hypothesis of the pCR/MRD rate ≤10% with one-sided 5% significance level. If the observed rate from this study is ≥32.5%, to have 90% power to conclude that the pCR/MRD rate is above 10%, a total of 30 patients will be enrolled. We can reject the null hypothesis if there are at least 7 responses. This trial is enrolling patients through the Hoosier Cancer Research Network. The study is activated at the University of California San Diego, University of Pennsylvania, and Johns Hopkins Hospital. Sites pending activation include: Memorial Sloan Kettering Cancer Center, Columbia University, and University of Buffalo. Clinical trial information: NCT05498272. Research Sponsor: AstraZeneca.

TPS5129 Poster Session

CLARIFY: Positron emission tomography using ^{64}Cu-SAR-bisPSMA in patients with high-risk prostate cancer prior to radical prostatectomy (a phase 3 diagnostic study).

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Background: Prostate cancer (PC) is the second most prevalent cancer in men globally. Metastasis typically involves pelvic lymph nodes (LNs), progressing to extra-pelvic LNs as well as bone, liver and lungs. Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that is expressed in normal, benign and malignant prostate tissue. PSMA is strongly overexpressed in PC, making it an ideal target for imaging and therapy. ^{64}Cu-SAR-bisPSMA offers several potential advantages over approved positron emission tomography (PET) imaging agents targeting prostate-specific membrane antigen (PSMA), including its bivalent structure (bisPSMA) and longer half-life of ^{64}Cu (12.7h vs. $<$ 2h for ^{18}F and ^{68}Ga). This has been shown to lead to prolonged tumor retention, 2-3 times higher tumor uptake and detection of additional PC lesions using ^{64}Cu-SAR-bisPSMA compared to approved PSMA PET agents. In this phase 3 diagnostic trial, we aim to establish the diagnostic performance of this radiotracer in men with high-risk prostate cancer. **Methods:** CLARIFY (NCT06056830) is a multi-center, single-arm, non-randomized, open-label Phase 3 diagnostic study of ^{64}Cu-SAR-bisPSMA. The target population is patients with untreated, histopathology-confirmed PC with high-risk features, who are proceeding to radical prostatectomy (RP) with pelvic lymph node dissection (PLND). The primary objective is to assess the sensitivity and specificity of ^{64}Cu-SAR-bisPSMA PET to detect regional (pelvic) nodal metastases. Secondary objectives include assessment of safety and determining the positive and negative predictive value of ^{64}Cu-SAR-bisPSMA PET for the detection of PC within the pelvic LN field. A total of 383 patients will be enrolled. Standard of care (SOC) imaging will be captured at screening (e.g. computed tomography [CT], approved PSMA PET/CT). Eligible patients will receive a single administration of ^{64}Cu-SAR-bisPSMA (200 MBq) followed by a PET/CT scan on Day 1 (1-4 hours post-dose) and on Day 2 (24$\pm$6 hours post-dose). Patients will proceed to RP with PLND. The specimens from surgery will be processed and analyzed locally to derive the Standard of Truth (SOT). The ^{64}Cu-SAR-bisPSMA PET/CT scans will be interpreted locally and by 3 independent, blinded, central readers. Each reader will assess the scans for ^{64}Cu-SAR-bisPSMA uptake in the pelvic LNs, prostate gland, extra-pelvic LNs, visceral/soft tissue and bone. The diagnostic performance of ^{64}Cu-SAR-bisPSMA will be based on the scan result for the respective day independently (Day 1 and 2) matched against the SOT. The diagnostic performance of ^{64}Cu-SAR-bisPSMA PET to detect PC within the pelvic LNs will be compared to that of the baseline SOC imaging using histopathology results. The study is open for recruitment in sites in the United States, with additional sites in start-up in Australia. Clinical trial information: NCT06056830. Research Sponsor: Clarity Pharmaceuticals Ltd.

TPS5130 Poster Session

Randomized PROSTATE-IQ trial to reduce ADT treatment burden for patients with biochemical recurrence after prostatectomy.

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Background: Men with PSA recurrence of prostate cancer after prostatectomy often receive Androgen Deprviation Therapy (ADT) with salvage radiation therapy to the prostate resection bed. Traditional ADT improves cancer control; however, it also causes fatigue, sexual dysfunction, hot flashes, cognitive changes, metabolic dysregulation, body composition changes, and negatively impacts men's quality of life. **Methods:** The PROSTATE-IQ trial is a randomized multi-center clinical trial that is investigating ways to reduce the adverse effects of ADT treatment. First, the trial uses intrinsic cancer properties assessed by ArteraAI and clinical-pathologic variables to personalize the intensity of Androgen Axis Therapy (AAT). Those with low ArteraAI score are assigned to the Artera Low Cohort and those with either high ArteraAI score, PSA >0.5 ng/ml or nodal involvement are assigned to the Higher-risk Cohort. Second, the trial randomizes men between traditional ADT and apalutamide-based therapy. We hypothesize that the apalutamide-based therapy will reduce the adverse effects of treatment and thereby improve quality of life. 220 men in the Artera Low Cohort are being randomized between 6 months of ADT vs. 6 months of apalutamide monotherapy. 220 men in the Higher-risk Cohort are being randomized between 24 months of ADT (winning arm of RADICALS-HD trial) vs. 6 months of apalutamide and ADT (winning arm of FORMULA 509 trial). We hypothesize that the apalutamide-based treatments will reduce fatigue and boost activity, sleep, and cognitive function. Patients wear an activity and sleep tracker, undergo cognitive assessments, and complete validated fatigue, leisure activity, and mental health questionnaires. We will compare fatigue, activity, sleep, mental health, body composition, metabolic dysregulation, quality of life, and cancer control between treatment arms. This trial will be impactful because it is the first to use the validated ArteraAI test to personalize intensity of androgen axis therapy and because it will reduce the adverse effects of treatment and improve quality of life for prostate cancer survivors treated with salvage radiation and androgen axis therapy. Research Sponsor: Janssen Oncology.