

Clinico-transcriptomic risk stratification to guide abiraterone treatment intensification in high-risk prostate cancer: A combined analysis of NRG/RTOG 9202, 9413, 9902, and 0521.

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Background: Outcomes for some patients with $\geq$ high-risk localized prostate cancer (HR-PCa) who receive radiation therapy (RT) remain poor. Current guidelines recommend intensification with abiraterone/prednisone (AAP) in select patients; however, the current guideline-defined candidate population may be suboptimal. **Methods:** This is a secondary analysis of available biopsy samples from NRG/RTOG 9202, 9413, 9902, and 0521. The primary objective was to determine if a specific subgroup of $\geq$ HR-PCa patients had sufficiently poor prognoses to derive a clinically meaningful benefit from AAP intensification. The prognostic impact of the Decipher 22-gene genomic classifier (GC; Veracyte, San Diego, CA) was first evaluated for metastasis-free survival (MFS, primary), overall survival (OS), and distant metastases (DM). GC scores were analyzed using both continuous (per 0.1 GC units) and pre-specified categorical cutpoints: $\leq$ intermediate transcriptomic risk (IR-PCa, GC $\leq$ 0.6), HR-PCa (GC: 0.6–0.85), and very high risk (VHR-PCa, GC > 0.85). A tree-based model was then used to combine clinical and transcriptomic risk category. **Results:** This study characterized outcomes of 427 patients (64% NCCN HR-PCa; 36% NCCN VHR-PCa) with a median follow-up of 10.4 years. Continuous GC score was observed to discriminate risk when adjusted for age, PSA, grade, T-stage, and treatment received for the endpoints of MFS (HR_{GC}: 1.19 [95% CI: 1.10–1.29], $p < 0.001$), DM (HR_{GC}: 1.31 [95% CI: 1.13–1.51], $p < 0.001$), and OS (HR_{GC}: 1.18 [95% CI: 1.09–1.28], $p < 0.001$). MFS and OS were estimated using the Kaplan-Meier method by pre-specified GC subgroup within each NCCN risk group (HR-PCa, VHR-PCa). Based on outcomes by subgroup, a novel clinico-transcriptomic risk stratification system was constructed, where patients receive 1 point for NCCN/GC HR categorization and 2 points for NCCN/GC VHR categorization. The combined risk score ≥ 3 subgroup had a prognosis similar to the STAMPEDE Mo control arm, whereas the combined score ≤ 2 subgroup had a substantially better prognosis. Utilizing this system could enhance the specificity of AAP recommendations, increasing the candidate pool eligible for AAP intensification by approximately 20% and identifying approximately 25% of NCCN VHR in whom the therapeutic ratio of AAP may be less favorable. **Conclusions:** This study defines a novel clinico-transcriptomic risk stratification system to augment current clinical eligibility for AAP intensification. This system may increase the population who benefit from AAP by approximately 20% and simultaneously identify approximately 25% of NCCN VHR patients who may avoid AAP intensification. **Acknowledgement:** We would like to acknowledge Dr. Felix Feng for his contributions in his capacity as the former GU Committee Chair. **Research Sponsor:** U.S. National Institutes of Health; U10CA180868; U.S. National Institutes of Health; U10CA180822; U.S. National Institutes of Health; UG1CA189867; U.S. National Institutes of Health; U24CA196067; U.S. National Institutes of Health; NCI CCR Intramural Research Program; Sanofi; Veracyte; Pfizer; Bristol Myers Squibb.

Assessment of the ability of Decipher Prostate Genomic Classifier (DGC) >0.85 to identify patients who benefit from adding docetaxel (DOC) to androgen deprivation therapy (ADT) plus enzalutamide (ENZ): Level 1B evidence from the ENZAMET study.

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Background: DGC predicts overall survival (OS) benefit from DOC when added to ADT while the benefit of adding DOC to ADT and ENZ is unknown. We hypothesized in a locked prespecified statistical analysis plan that higher GC score (> 0.85 , the locked threshold on clinical test report) will identify patients who benefit from addition of DOC to ADT plus ENZ independently of metastases volume and timing. **Methods:** DGC scores were generated from transcriptome profiling using a clinical test (Veracyte) on tumor index cores from participants (pts) randomised on ENZAMET study ($N = 1,125$) 1:1 ADT with NSAA or ENZ with clinical discretion to add DOC as part of standard of care. Primary tumor samples were available from 764 pts. Differential DOC OS benefit was assessed by testing the marker-by-treatment interaction term in propensity score-weighted Cox models, with weights based on factors associated with planned DOC use. Prognostic effects of DGC were estimated using Cox for age, WHO PS, Gleason, randomized arm +/- planned DOC, metastases volume and timing, with adjusted hazard ratios (aHR) and 95% CIs. Analyses were prespecified and conducted independently by two statisticians. **Results:** DGC scores were available for 634 (83%) unique pts (median follow-up 5.6 years) with clinical factors representative of the overall trial. Median age was 68 yrs with 50% HV, 62% synchronous presentation, and 44% with planned DOC. Planned DOC was associated with younger age, high volume and synchronous presentation (all $p \leq 0.002$). Median DGC score was 0.88 (IQR 0.75–0.96) and 55% had DGC > 0.85 (62% in pts with DOC planned, 49% in others). Overall, higher GC was significantly associated with poorer OS (aHR 1.37 [1.06–1.78], $p = 0.02$). DOC benefit differed by GC level [higher vs lower] in pts treated with ADT plus ENZ (p -interaction 0.043). Higher DGC was associated with worse OS in pts treated with ADT plus ENZ (aHR 2.31 [95% CI 1.26–4.21], $p = 0.007$) while pts treated with DOC added to ADT plus ENZ showed no significant difference by DGC (aHR 1.08 [0.63–1.86]). Effects were more pronounced in pts with high vs. low volume disease. **Conclusions:** DGC > 0.85 is predictive of benefit from adding DOC to ADT plus ENZ as it negated the poor prognostic outcome of DGC > 0.85 with ADT plus ENZ alone, whereas there was no evidence of benefit for adding DOC for pts with GC ≤ 0.85 . Research Sponsor: Nantional Cancer Institute; Movember Foundation; Australian Department of Health; Astellas and Pfizer; Veracyte.

5yr OS	N	Lower Decipher	Higher Decipher	Higher vs. loweradj. HR (95% CI)
Overall	634	71% (66-77%)	57% (51-62%)	1.37 (1.1, 1.8)
ADT+ENZ	178	86% (78-93%)	62% (52-72%)	2.29 (1.3, 4.2)
ADT+ENZ+DOC	142	66% (53-79%)	58% (48-68%)	1.08 (0.6, 1.9)
ADT+ENZ (LV)	123	88% (80-96%)	72% (61-84%)	1.96 (0.9, 4.3)
ADT+ENZ+DOC (LV)	44	86% (67-100%)	79% (64-94%)	1.70 (0.3, 9.0)
ADT+ENZ (HV)	55	81% (65-96%)	41% (23-60%)	2.83 (1.1, 7.5)
ADT+ENZ+DOC (HV)	98	58% (42-75%)	48% (36-61%)	1.07 (0.6, 1.9)

Spatial transcriptomics–guided computational pathology model to stratify docetaxel benefit in metastatic hormone-sensitive prostate cancer: CHAARTED trial (ECOG-ACRIN E3805).

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Background: The CHAARTED trial demonstrated improved overall survival (OS) with the addition of docetaxel (DTX) to androgen deprivation therapy (ADT) in metastatic hormone-sensitive prostate cancer (mHSPC), but many patients do not benefit and experience significant toxicity. Clinical factors (e.g., metastatic burden) are suboptimal for predicting DTX benefit, indicating a need for better biomarkers. We developed ST-DoxPCa (Spatial Transcriptomics–Guided Docetaxel Therapy Stratification in Prostate Cancer), an artificial intelligence (AI)–driven biomarker that infers intratumoral gene expression from routine H&E slides (via virtual spatial transcriptomics) to stratify patients by likelihood of benefiting from DTX. **Methods:** ST-DoxPCa was developed using paired H&E and spatial transcriptomics from the HEST1K prostate cohort to train a Vision Transformer–based regressor to predict a 208–gene panel at spot/patch level; predictions were distilled into a biologically informed 26–gene signature and summarized into patient–level features capturing expression level and heterogeneity. In CHAARTED, a Cox model for overall survival (OS) was trained and internally validated in the ADT–only arm ($n = 154$; 50/50 split: $n = 77$ train, $n = 77$ validation) to derive an ST-DoxPCa risk score and fixed median threshold. This locked model was then applied to the ADT validation cohort ($n = 77$) and the held–out ADT+DTX arm ($n = 129$), and OS was compared between treatment arms within biomarker–defined risk groups using Kaplan–Meier estimates and Cox hazard ratios. **Results:** ST-DoxPCa stratified patients into biomarker–defined risk groups using aggregated spatial–expression features from a biologically informed gene panel; key genes included AR, PTEN, FASN, FOXA1, and ACPP. In ST-DoxPCa–positive (high–risk) patients, adding DTX to ADT significantly improved OS versus ADT alone (HR = 0.53, 95% CI 0.31–0.90; $p = 0.018$), with no benefit in ST-DoxPCa–negative (low–risk) patients (HR = 1.32, 95% CI 0.74–2.34; $p = 0.34$). **Conclusions:** ST-DoxPCa is a novel spatial transcriptomics guided histology biomarker that predicts differential benefit from docetaxel in mHSPC. ST-DoxPCa identified a subset of patients who achieve substantial survival gains from upfront DTX and another subset with no benefit, enabling personalized treatment intensification. ST-DoxPCa has the potential to spare low–risk patients unnecessary chemotherapy while directing therapy to those most likely to benefit. Clinical trial information: NCT00309985. Research Sponsor: National Cancer Institute (NCI), National Institutes of Health (NIH); United States Department of Veterans Affairs; U.S. Department of Defense (DoD) – Prostate Cancer Research Program.

First interim analysis of SWOG S1823: Operating characteristics of circulating microRNA 371a-3p (miR371) in predicting active germ cell malignancy (aGCM) in patients (pts) with early-stage testicular cancer.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

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

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Background: Patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC) treated continuously with testosterone suppression (TS) plus an androgen receptor pathway inhibitor (ARPI) can experience cumulative toxicity. We conducted this single-arm phase 2 trial (NCT05241860) to test the hypothesis that pts who achieve favorable response to TS + ARPI can have prolonged treatment-free interval with testosterone recovery after treatment interruption (TI). Here we report on the primary endpoint. **Methods:** Eligible pts had mHSPC by conventional imaging with prostate-specific antigen (PSA) ≥ 5 ng/ml and testosterone ≥ 150 ng/dl prior to starting TS+ARPI, with PSA < 0.2 ng/ml and testosterone < 50 ng/dl at the time of enrollment after having received TS for 540–750 days and ARPI for ≥ 360 days. Prior local therapy, radiation to metastases and docetaxel were permitted. After enrollment, pts discontinued TS and ARPI and were followed with PSA and testosterone levels every 3 months (mo), CT/MRI and bone scan at least every 6 mo, and FACT-P questionnaire for patient-reported outcomes (PROs) every 6 mo. Treatment was resumed for PSA ≥ 5 ng/ml, radiographic change (progressive disease [PD] per RECIST 1.1 on CT/MRI or unconfirmed PD per PCWG3 on bone scan), or prostate cancer-related symptoms. The primary endpoint was proportion of men remaining treatment-free 18 mo after TI with eugonadal testosterone (> 150 ng/dl). Target enrollment was 75 pts to differentiate 18-mo treatment-free rates of 0.30 (H_0) and 0.45 (H_A). **Results:** Of 79 pts enrolled between 07/2022 and 03/2024, 78 were eligible and underwent TI. Among these 78, median PSA prior to starting TS+ARPI was 19 (range 5–6759), 27 (35%) had high volume disease, 31 (40%) never received local therapy, and 55 (71%) did not receive radiation to metastases. By 18 mo after TI, 67% (52/78) recovered testosterone and 58% (45/78) remained treatment-free; 41% (32/78) remained treatment-free with testosterone recovery (80% CI 33.5–48.9%, one-sided p 0.0249). At median follow-up of 21.2 mo, 35% (27/78) resumed initial TS+ARPI after meeting re-initiation criteria (of whom 1 required treatment switch for PD 9 mo later); 5% (4/78) resumed prior to meeting criteria; 9% (7/78) pursued alternative therapy instead of resuming TS+ARPI per protocol; 5% (4/78) withdrew; 1 died of myocardial infarction prior to resuming treatment. 4 pts died, 1 of prostate cancer. **Conclusions:** The primary objective was achieved with 41% of favorable responders to TS+ARPI remaining treatment-free with testosterone recovery at 18 mo after TI. Analyses of biomarkers and PROs are in progress, and pts will be followed for long-term outcomes. Support: U10CA180821, U10CA180882, UG1CA189823, <https://acknowledgments.alliancefound.org>, Veracyte Inc. Clinical trial information: NCT05241860. Research Sponsor: National Cancer Institute; Veracyte.

Cognitive effects of darolutamide vs enzalutamide: Results of ARACOG (AFT-47), a randomized clinical trial from the Alliance for Clinical Trials in Oncology.

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Background: Androgen receptor pathway inhibitors (ARPIs) may have distinct central nervous system (CNS) penetration and differential effects on cognition or quality of life (QOL). AFT-47, “ARACOG” is a prospective, randomized open-label phase 2 trial comparing objective and patient-reported cognitive and QOL outcomes between patients with metastatic hormone sensitive prostate cancer (mHSPC), metastatic castration-resistant prostate cancer (mCRPC) or non-metastatic castration-resistant prostate cancer (nmCRPC) treated with darolutamide (DAR) or enzalutamide (ENZ). **Methods:** Between 8/17/2021 and 3/11/2025, 111 pts were enrolled and randomized 1:1 to treatment with ENZ or DAR. CANTAB, a validated computer-based platform evaluating 5 cognitive domains (PALFAM-memory recall, SWM- spatial working memory, SSP-short-term visual memory, working memory, RVP-rapid visual processing, and OTSMCC- executive function), was performed at baseline, 12, 24, and 48 weeks. Crossover (Xover) was allowed at 12 or 24 weeks for significant pre-specified decline in cognitive testing or patient reported outcome measures (PROMs), or for CNS-associated adverse events, including falls. The primary endpoint was the percent change in the maximally changed cognitive domain (MCCD) from baseline to 24 weeks and was compared between groups with the Wilcoxon rank sum statistic. Patients crossing over prior to 24 weeks were evaluated at the time of Xover and analyzed with their randomized arm. Secondary endpoints included comparison of Xover rates. **Results:** Among 111 pts, 55 received DAR and 56 received ENZ; median age was 71, 83% White. 95 pts (48 DAR, 47 ENZ) were evaluable for the primary endpoint. Baseline CANTAB was similar between groups. Median cognitive change in MCCD between baseline and 24 weeks was -15.8% and -36.1% for the DAR and ENZ pts, respectively ($p = 0.009$) (Table). Individual cognitive domains suggest possible learning effect (increased scores) for DAR and are stable or show mild decline for ENZ treated patients at 24 weeks. 32 DAR (58%) and 33 ENZ (59%) participants were eligible for Xover by 24 weeks, and 23 pts crossed over by 24 weeks. All Xover was pts randomized to ENZ (crossed to DAR), with the most common causes being decline in objective ($N = 14$) or subjective ($N = 11$) cognitive testing. **Conclusions:** In this US randomized trial comparing DAR to ENZ, the primary endpoint of differential cognitive effects was met. ENZ showed significantly greater cognitive score decline than DAR at 24 weeks in the MCCD after treatment initiation. Learning effect was seen with DAR but not ENZ. Longer term follow-up of cognitive change and PROM analyses are ongoing. Clinical trial information: NCT04335682. Research Sponsor: Prostate Cancer Foundation; Alliance Scholar Award; Bayer; <https://acknowledgments.alliancefound.org>.

Percent change in maximally changed cognitive domain by treatment.

	DAR (N=48)	ENZ (N=47)	Wilcoxon Rank Sum Test Result
CANTAB domain	PALFAM	SWM	
Degree of change	-15.8 (-38.8, -2.6)	-36.1 (-59.3, -16.7)	$P=0.009$

Final results from ZZFIRST: A randomized phase 2 trial of enzalutamide (EZ) and talazoparib (TALA) in metastatic hormone-naïve prostate cancer (mHNPC).

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Background: ADT plus AR pathway inhibition (ARPI) improves outcomes in mHNPC, yet responses remain heterogeneous. AR–PARP cotargeting has shown enhanced clinical activity in prostate cancer, but the underlying mechanisms are incompletely defined. ZZFIRST evaluated enzalutamide (EZ) plus talazoparib (TALA) in mHNPC, including the study of tumor adaptation response to ADT+ARPI through biopsies obtained on therapy. **Methods:** ZZFIRST (NCT04332744) is an open label, randomized academic phase 2 trial that included patients (pts) with high-volume (HV)-mHNPC (CHAARTED), ECOG PS ≤ 1 , PSA ≥ 4 ng/mL. All pts received standard ADT and started EZ 160 mg/day. After two 28-day cycles, pts were randomized 2:1 to EZ+TALA 0.5 mg/day or continue EZ alone until progressive disease (PD), unacceptable toxicity, or withdrawal. Randomization was stratified by DDR mutation status. Primary endpoint was confirmed PSA < 0.2 response rate (PSA < 0.2 -RR) at 12 months (mo) for EZ+TALA. Key secondary endpoints included rPFS, time to PSA-PD, time to castration resistance, and safety. The study was powered (80%, one-sided $\alpha = 5\%$) to detect improved PSA < 0.2 -RR (H₀: 20%; H₁ $\geq 40\%$) for EZ+TALA. Between-arm comparisons were exploratory. Spatial transcriptomics (Visum HD) was performed on baseline (BL) and Cycle 2-Day 1 (C2D1) on-treatment tumor biopsies. **Results:** 54 pts were enrolled (37 EZ+TALA, 17 EZ). 7 pts harbored HRR alterations by tumor tissue NGS (13%; 5 EZ+TALA, 2 EZ). Visceral metastases were present in 17 pts (32%); 51 pts (94%) had *de novo* M1 disease. Median follow-up was 3.6 years. The primary endpoint was met, with a 73% 12-mo PSA < 0.2 -RR for EZ+TALA (95%CI, 55.9%-86.2%, $p < 0.001$); the rate was 64.7% for EZ. Median rPFS was 45.3 mo (29.4-NR) for EZ+TALA vs 31.1 mo (13.5-NR) for EZ (HR = 0.62; 95%CI, 0.28-1.37). Median time to PSA-PD was not reached (30.4-NR) for EZ+TALA vs 30.7 mo (6.6-NR) for EZ (HR = 0.47; 95%CI, 0.21-1.04). Median TTCR was 30.4 mo (23.0-NR) for EZ+TALA vs 22.8 mo (6.3-45.4) for EZ (HR = 0.62; 95%CI, 0.30-1.26). In TALA+EZ, common treatment-emergent AEs were fatigue (any grade: 83.8%; $G \geq 3$: 13.5%) and anemia (67.6%; $G \geq 3$: 40.5%). 14 (38%) pts required TALA dose reductions. Two pts on EZ+TALA developed acute myeloid leukemia (AML) 26.0 and 32.8 mo after study entry. Transcriptomics analysis on C2D1 vs BL biopsies showed induction of cell cycle arrest, with downregulation of AR and DDR signatures and upregulation of IFN-related and inflammatory response signatures upon ADT+EZ. **Conclusions:** EZ+TALA demonstrated promising antitumor activity in HV-mHNPC. The toxicity profile was consistent with prior AR+PARP trials, although two cases of AML were observed with prolonged TALA exposure. Paired tumor biopsies revealed mechanisms of tumor adaptation to ADT+EZ inhibition, supporting a biologically informed rationale for AR+PARP treatment intensification strategies in mHNPC. Clinical trial information: NCT04332744. Research Sponsor: Pfizer S.L. and Astellas Pharma Europe LTD.

TALAPRO-3: Talazoparib (TALA) + enzalutamide (ENZA) compared with placebo (PBO) + ENZA for the treatment of patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) harboring homologous recombination repair (HRR) gene alterations.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

Fuzuloparib combined with abiraterone acetate and prednisone (AA-P) as first-line (1L) treatment for metastatic castration-resistant prostate cancer (mCRPC): Interim results from the FUZUPRO trial.

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Background: The combination of PARP inhibitors with standard AA-P may offer enhanced antitumor activity over AA-P. We conducted FUZUPRO, an international, randomized, double-blind, placebo-controlled phase 3 trial, to compare the efficacy of fuzuloparib, a novel PARP inhibitor, plus AA-P vs AA-P as 1L treatment for mCRPC. **Methods:** 1L mCRPC patients were randomized (1:1) to orally receive fuzuloparib 150 mg BID plus AA-P (abiraterone acetate 1000 mg QD; prednisone 5 mg BID) or placebo plus AA-P. Randomization was stratified by DNA-repair gene defect (DRD) status (positive vs negative/unknown) and other factors. Primary endpoint was blinded independent central review (BICR)-assessed radiographic progression-free survival (rPFS) per RECIST v1.1 and PCWG3. As of March 23, 2025, 259 (85% of total expected) BICR-assessed rPFS events occurred, and a prespecified interim analysis was conducted. **Results:** 496 patients were randomized to fuzuloparib-AA-P (n = 249) or AA-P (n = 247). Median follow-up was 33.3 mo. Fuzuloparib-AA-P significantly prolonged rPFS compared with AA-P (median, 24.8 mo vs 19.9 mo; HR 0.71, 95% CI 0.55-0.91; 1-sided p = 0.0034). rPFS benefit with fuzuloparib-AA-P was generally consistent across clinically relevant subgroups. Among DRD-positive patients (n = 116), median rPFS was 27.7 mo and 13.9 mo in the fuzuloparib-AA-P and AA-P groups, respectively (HR 0.51, 95% CI 0.31-0.85; 1-sided p = 0.0039). Subgroup analysis suggested improved rPFS among DRD-positive patients regardless of their *BRCA1/2* mutation status. Among DRD-negative/unknown patients (n = 380), median rPFS was 22.8 and 21.2 mo, respectively. Overall survival showed a benefit trend in favor of fuzuloparib-AA-P (Table). Treatment-related adverse events (TRAEs) were reported by 81.9% and 76.0% of patients in the two groups, respectively. The most common grade ≥ 3 TRAEs were mainly hematological toxicities, including anemia (20.1%), decreased white blood cell count (5.6%), decreased platelet count, and decreased neutrophil count (5.2% for each). **Conclusions:** Fuzuloparib plus AA-P as 1L treatment significantly prolonged rPFS in patients with mCRPC. The combination showed acceptable safety and tolerability with no new safety signals identified. Clinical trial information: NCT04691804. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

	Overall Fuzuloparib- AA-P (N = 249)	AA-P (N = 247)	DRD-positive Fuzuloparib- AA-P (N = 60)	AA-P (N = 56)	DRD-negative/unknown Fuzuloparib- AA-P (N = 189)	AA-P (N = 191)
rPFS, mo, median (95% CI)	24.8 (20.4, 30.4)	19.9 (15.2, 22.2)	27.7 (17.7, NR)	13.9 (8.3, 24.9)	22.8 (19.9, 30.2)	21.2 (16.5, 24.6)
HR (95% CI), vs. AA-P	0.71 (0.55, 0.91)		0.51 (0.31, 0.85)		0.81 (0.61, 1.08)	
Overall survival, mo, median (95% CI)	41.9 (31.1, NR)	36.8 (28.7, NR)	NR (27.0, NR)	36.8 (24.7, 40.3)	37.3 (29.0, NR)	36.8 (28.7, NR)
HR (95% CI), vs. AA-P	0.96 (0.73, 1.24)		0.76 (0.44, 1.32)		1.00 (0.74, 1.35)	

NR, not reached.

Safety and dosimetry of ^{177}Lu -rosopitamab tetraxetan plus SoC in patients with metastatic castration-resistant prostate cancer: Preliminary results from part 1 of phase 3 ProstACT Global study.

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AcTION: Phase 1 study of [²²⁵Ac]Ac-PSMA-617 (²²⁵Ac-PSMA-617) in men with metastatic castration-resistant prostate cancer (mCRPC) with or without prior [¹⁷⁷Lu]Lu-PSMA (¹⁷⁷Lu-PSMA) radioligand therapy (RLT).

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Background: AcTION is the first prospective dosage escalation study of ²²⁵Ac-PSMA-617, an alpha-emitting, PSMA-targeted RLT in patients (pts) with mCRPC (NCT04597411). **Methods:** This study enrolled pts with progressive, PSMA-positive mCRPC in 3 groups (Gps). Gp A: prior chemotherapy (ChT) and an androgen receptor pathway inhibitor (ARPI) but no prior ¹⁷⁷Lu-PSMA RLT; Gp B: no prior ChT, ARPI, or ¹⁷⁷Lu-PSMA RLT (ChT/ARPI-naïve); Gp C: prior ¹⁷⁷Lu-PSMA RLT. Dosage escalation of ²²⁵Ac-PSMA-617 used a Bayesian logistic regression model with administered activities of 4, 6, 8 or 10 MBq given intravenously for ≤6 cycles every 8 weeks. Primary objective was to identify the recommended phase 2 dosage (RP2D), based on dosage-limiting toxicities (DLTs) within the first 6 weeks of ²²⁵Ac-PSMA-617 administration. This analysis includes all 101 treated pts per 13 Nov 2025. **Results:** Gp A pts had a median of 3 prior systemic therapies and median baseline [BL] PSA 73.4 (range 1–3320) ng/mL. At a median follow-up [FU] of 7.46 months (mos), PSA50 response rate (PSA50) was 20/34 (58.8%; 95% CI 40.7, 75.4) and PSA90 was 15/34 (44.1%; 95% CI 27.2, 62.1). Gp B pts had BL PSA 223.4 (5–12308) ng/mL. At a FU of 13.24 mos, PSA50 was 23/27 (85.2%; 95% CI 66.3, 95.8) and PSA90 was 22/27 (81.5%; 95% CI 61.9, 93.7). Gp C pts had 5 prior systemic therapies and BL PSA 85.5 (5–1760) ng/mL. At a FU of 8.57 mos, PSA50 was 21/40 (52.5%; 95% CI 36.1, 68.5) and PSA90 was 7/40 (17.5%; 95% CI 7.3, 32.8). Across all 3 Gps, there were no DLTs and a maximum tolerated dosage was not reached. No Grade [G] 4/5 TRAEs occurred. No dosage-dependent safety signals were observed. Dry mouth (G1/2 only) was the most common treatment-related (TR) adverse event (AE), observed in > 90% of pts across all Gps and mostly reported as not resolved at data cut off. Two TRAEs led to treatment discontinuation (G2 dry mouth at 8 MBq, and G3 anemia at 10 MBq; both occurring in Gp C). The RP2D for all 3 Gps was 10 MBq. Additional efficacy data will be presented. **Conclusions:** ²²⁵Ac-PSMA-617 demonstrated an acceptable safety profile and promising anti-tumor activity up to 10 MBq in pts with mCRPC regardless of prior ¹⁷⁷Lu-PSMA RLT. Two phase 3 trials, AcTFirst (NCT06855277) and PSMAcTION (NCT06780670), are currently recruiting. Clinical trial information: NCT04597411. Research Sponsor: Endocyte, Inc., A Novartis Company.

Overall pts	A: Prior ChT + ARPI; N=34	B: ChT/ARPI-naïve; N=27	C: Prior ¹⁷⁷ Lu-PSMA RLT; N=40
Selected AEs regardless of study dose, n (%): All Gs / G ≥3			
Dry mouth	33 (97.1) / 0	26 (96.3) / 0	36 (90.0) / 0
Fatigue	18 (52.9) / 0	4 (14.8) / 0	27 (67.5) / 0
Anemia	9 (26.5) / 6 (17.6)	4 (14.8) / 4 (14.8)	16 (40.0) / 6 (15.0)
Thrombocytopenia	2 (5.9) / 0	2 (7.4) / 1 (3.7)	5 (12.5) / 0
Renal impairment	1 (2.9) / 1 (2.9)	0 / 0	3 (7.5) / 1 (2.5)
Anti-tumor activity, n (%) [95% CI]			
PSA50	20 (58.8%) [40.7, 75.4]	23 (85.2%) [66.3, 95.8]	21 (52.5%) [36.1, 68.5]
PSA90	15 (44.1%) [27.2, 62.1]	22 (81.5%) [61.9, 93.7]	7 (17.5%) [7.3, 32.8]

CONVERGE-01 part 3: Ac-225 rosopatamab tetraxetan (CONV01-α) in Lu-PSMA-pretreated metastatic castration-resistant prostate cancer (mCRPC).

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Background: Ac-225 rosopatamab tetraxetan (CONV01-α, Convergent Therapeutics, Cambridge, MA), an alpha-emitting radionuclide conjugated to a PSMA-targeting monoclonal antibody, has demonstrated safety and encouraging activity in prior investigator-initiated trials (Tagawa et al. JCO 2024, Nauseef et al. AACR 2023). This phase 2 Convergent Therapeutics-sponsored multi-center CONVERGE-01 trial is evaluating the safety and efficacy of CONV01-α in pts with mCRPC, including those previously treated with Lu-PSMA-617 or -I&T (Lu-PSMA), in a dose-escalation (DE) and in an Initial Expansion (IE) cohort. **Methods:** Eligible pts had PSMA PET-positive (VISION criteria) mCRPC with previous exposure to ≥1 ARPI, 0-1 taxane regimens, and 1-6 cycles of Lu-PSMA. CONV01-α was administered in a single cycle of two doses (D1 & D15). Dose escalation used a BOIN design protocol (dose levels [DLs]: 45 and 55 kBq/kg, with optional IE). Primary endpoints: safety (CTCAE v5, all pts) and proportion of patients with decline in PSA of 50% or greater (PSA50) (at recommended phase 2 dose [RP2D]). Secondary endpoints: biodistribution and pharmacokinetic profile. Exploratory endpoints: bPFS, rPFS, genomic and imaging biomarkers. Enrollment into DE and IE cohorts of Part 3 was conducted between 8/2024 and 12/2025. Data within reflect current status and are subject to change with continued follow up and analysis. **Results:** DE was completed without DLTs in all evaluable pts (n=3 at DL45, n=6 at DL55). This was followed by an IE at both DLs (total n=22, incl pts in DE; DL45: n=12, DL55: n=10). ECOG: PS 0 - 12/22, PS 1 - 10/22. 21/22 pts were taxane exposed (19 for CRPC). Common grade (Gr) ≥3 treatment emergent adverse events (TEAEs) (occurring in >1 pt) are in shown Table. Among all TEAE at DL45: thrombocytopenia occurred in 5/12 patients (Gr 1 3/12, Gr 2 2/12), without clinical sequelae. Dry mouth was limited to Gr 1 (5/12) and Gr 2 (1/12). Among pts at who were evaluable for PSA change, 45.4% (5/11) achieved a PSA50 at DL45, with several pts experiencing ongoing PSA declines including pts who were primarily refractory to Lu-PSMA. Based on the combined safety and activity profile, DL45 was chosen as RP2D and Subsequent Expansion is underway. **Conclusions:** CONV01-α at the RP2D of DL45 is well-tolerated and shows promising activity in a heavily pretreated and Lu-PSMA-exposed population where there are limited therapeutic options available. Subsequent Expansion continues for pts exposed to Lu-PSMA (Part 3) at RP2D of DL45. A pivotal study is planned. Clinical trial information: NCT06549465. Research Sponsor: Convergent Therapeutics, Inc.

Grade ≥3 TEAE.					
	Overall n=22	DL45 Grade 3	DL45 Grade 4	DL55 Grade 3	DL55 Grade 4
	n (%)	n (%)	n (%)	n (%)	n (%)
Lymphopenia	8 (36)	3 (25)	0	3 (30)	2 (20)
Thrombocytopenia	5 (23)	0	0	5 (50)	0
Neutropenia	4 (18)	2 (16)	0	2 (20)	0
Anemia	3 (14)	1 (8)	0	2 (20)	0
Hypotension	2 (9)	1 (8)	0	1 (10)	0

Early results of COMPPARE, a prospective comparison of outcomes with proton and photon radiation in prostate cancer.

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Genomic classifier–driven NCCN risk reclassification to track distinct transcriptomic signatures in early prostate cancer.

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Background: NCCN clinicopathologic risk stratification in early prostate cancer (EPC) may under- or overestimate biologic risk and contribute to over- or undertreatment. The RNA-based Decipher genomic classifier (DGC), endorsed by NCCN, frequently drives NCCN risk reclassification, yet the transcriptomic biology that tracks with reclassification remains incompletely defined. We investigated whole-transcriptome signatures underlying DGC-based risk stratification and NCCN risk reclassification in a real-world EPC cohort. **Methods:** We performed a retrospective, real-world analysis, of prostate biopsy Decipher testing of 1,272 men with EPC, using the Decipher genomic classifier clinical database (Veracyte, San Diego, CA) and the GRID RWD registry (NCT02609269). Associations between NCCN risk reclassification and clinicopathologic variables (PSA, clinical T stage, and Gleason Grade Group) were evaluated, along with genomic risk scores, transcriptomic signatures, and a panel of gene expression signatures associated with adverse molecular features, including androgen receptor (AR) signaling, PAM50 subtype (Luminal B), inferred TP53/PTEN activity, and pathways related to proliferation, DNA repair, and immune response. **Results:** By DGC, 21% of tumors were classified as low risk, 34% as intermediate risk, and 45% as high risk. Decipher testing resulted in NCCN risk up-classification in 38% and down-classification in 19%, while 43% remained in the same NCCN risk category. Whole-transcriptome analysis revealed distinct molecular patterns across reclassification groups. Tumors that were up-classified exhibited a shift toward a more proliferative, less androgen-dependent phenotype, with significant increases ($p < 0.05$) in proliferation, DNA-repair, and immune-related pathways, increased Luminal B prevalence, reduced androgen receptor (AR) signaling, and decreased TP53 and PTEN activity. In contrast, down-classified tumors demonstrated significant downregulation of proliferation, DNA-repair, and immune-related pathways, with preservation of AR signaling and PTEN activity ($p < 0.05$). **Conclusions:** Genomic classifier–driven NCCN risk reclassification tracks coherent transcriptomic patterns that extend beyond clinicopathologic stratification. Higher genomic risk and up-classification align with Luminal B enrichment, reduced AR signaling, and loss of TP53/PTEN activity, supporting the clinical and biological validity of genomic risk refinement beyond conventional NCCN classification. Research Sponsor: None.

A phase 1, first-in-human (FIH) study evaluating the safety, pharmacokinetics, and efficacy of ABBV-969 in patients with metastatic castration-resistant prostate cancer (mCRPC).

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Background: Prostate-specific membrane antigen (PSMA) and six-transmembrane epithelial antigen of prostate 1 (STEAP1) are overexpressed in >80% of metastatic prostate cancer tumors. ABBV-969 is a first-in-class PSMA/STEAP1 dual-targeting antibody drug conjugate with a topoisomerase 1 inhibitor (Top1i) payload. We report results from the completed dose escalation part of the phase 1, FIH study (NCT06318273) evaluating ABBV-969 in patients (pts) with mCRPC. **Methods:** Pts were ≥ 18 years with confirmed metastatic prostate adenocarcinoma, had an ECOG performance score ≤ 1 , a serum prostate-specific antigen (PSA) level ≥ 1.0 ng/mL, and hemoglobin ≥ 9 g/dL at study entry. Pts received ≥ 1 novel hormone agent (NHA) and ≥ 1 taxane (unless unable to receive or declined taxane), and progressed on prior NHA. Pts received 1 mg/kg–12.5 mg/kg of ABBV-969 monotherapy every 3 weeks until disease progression or intolerable toxicity. Primary objective was to determine safety and tolerability. Secondary objectives were preliminary efficacy, pharmacokinetics, and recommended phase 2 dose. **Results:** As of Jan 2026, 49 pts with mCRPC received ABBV-969 in the dose escalation part of the study. Median follow-up was 11.1 months (95% CI, 8.4–13.2), and median number of prior lines was 5 (range 1–9). Pt demographics and safety results are shown in Table 1. Thirty-one (63%) pts had Grade (G) ≥ 3 TEAEs, primarily G3 anemia (n=24). Dose and exposure responses were observed, with durable PSA and objective responses noted at all dose levels ≥ 3 mg/kg. At dose levels ≥ 3 mg/kg, confirmed PSA50 and PSA90 responses were 67% (95% CI, 52–81) and 28% (95% CI, 15–44), respectively. Among 29 pts with RECIST-evaluable disease, the confirmed ORR, as assessed by investigator, was 45% (95% CI, 26–64). At data cut, 26 pts were receiving ongoing treatment. Radiographic PFS will be presented. **Conclusions:** ABBV-969 demonstrated promising antitumor activity and a manageable safety profile in heavily pretreated pts with mCRPC. Dose optimization is ongoing. Clinical trial information: NCT06318273. Research Sponsor: AbbVie Inc.

Pt demographics and safety.	
	Total N=49
Median age, years (range)	71 (57–84)
Median PSA, $\mu\text{g/L}$ (range)	74 (2–2879)
Disease location, n (%)	
Bone	43 (88)
Lymph node	20 (41)
Liver	8 (16)
Lung	7 (14)
Adrenal gland	2 (4)
Prior therapy, n (%) ^a	
Androgen-receptor pathway inhibitor	49 (100)
Docetaxel	41 (84)
Cabazitaxel	19 (39)
¹⁷⁷ Lu-PSMA-617	23 (47)
Any Grade TEAE of interest, n (%)	
Hematologic toxicity	38 (78)
Gastrointestinal toxicity	33 (67)
Salivary gland toxicity	6 (12)
TEAE leading to, n (%)	
Discontinuation ^b	3 (6)
Interruption	24 (49)
Reduction	16 (33)
TEAE leading to death, n (%) ^c	
Pneumonitis ^c	1 (2)
DLT events, n (%) ^d	3 (6)

^aOnly therapies of interest listed.

^bG3 pneumonitis and disease progression.

^cABBV-969-related.

^dAnemia at ≥ 8 mg/kg doses.

DLT, dose-limiting toxicity.

Phase 2 study of YL201, an anti-B7H3 antibody–drug conjugate (ADC), in heavily pretreated metastatic castration-resistant prostate cancer (mCRPC).

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Background: The treatment of mCRPC remains challenging, especially for patients who progressed on androgen receptor axis-targeted therapy (ARAT) with or without taxane-based chemotherapy. YL201 is a B7H3-targeting ADC with promising activity in advanced solid tumors. Here, we report the safety and preliminary efficacy of YL201 monotherapy in heavily pretreated mCRPC patients from a phase 2 study. **Methods:** Patients with mCRPC who had an ECOG PS of 0 or 1 and progressed on ≥ 1 prior line of ARAT and ≤ 2 lines of chemotherapy were enrolled and treated with YL201 intravenously Q3W at 2.0 or 2.4 mg/kg until disease progression or unacceptable toxicity. Primary endpoints were objective response rate (ORR) and radio-graphic progression-free survival (rPFS) per RECIST v1.1 and PCWG3 criteria. Secondary endpoints included PSA₅₀ response rate, duration of response (DoR), overall survival (OS), and safety. **Results:** As of 12 December 2025, 82 patients were enrolled (34 at 2.0 mg/kg; 48 at 2.4 mg/kg) with a median follow-up of 12.2 months (95% CI: 11.2–13.4). The median age was 67.0 years, 65.9% had an ECOG PS of 1, and 43.9% had visceral metastases (22.0% with liver metastasis) at study entry. Patients had a median of 4 prior line of therapy (range: 1–8), with 100% having received ARAT and 70.7% having received taxane-based chemotherapy. Across both dose levels, confirmed PSA₅₀ response rate was 38.5% (95% CI: 27.7–50.2), with a median duration of PSA response of 13.6 months (95% CI: 6.9–NR). Confirmed ORR was 29.5% (95% CI: 18.5–42.6), with a median DoR of 9.9 months (95% CI: 6.5–NR). Median rPFS was 9.1 months (95% CI: 7.4–12.0), while median OS remained immature. Higher PSA₅₀ response rate, ORR and rPFS were observed at 2.4 mg/kg compared with 2.0 mg/kg (48.9% vs. 24.2%, 33.3% vs. 24.0%, 11.8 vs. 9.0 months, respectively). Notably, in patients with baseline visceral metastases, YL201 still showed encouraging efficacy with a confirmed PSA₅₀ response rate of 54.5%, confirmed ORR of 28.6%, and median rPFS of 11.8 months at 2.4 mg/kg. Membrane B7H3 expression was detected in most tumor samples (median H-score: 185; range: 0–290), with no association observed between response and B7H3 expression level. Treatment-related adverse events (TRAEs) of grade ≥ 3 occurred in 43.9% of patients. The most common grade ≥ 3 TRAEs included neutropenia (29.3%), anemia (22.0%), leukopenia (18.3%), and thrombocytopenia (9.8%). No interstitial lung disease or pneumonitis was observed. The rate of treatment discontinuation due to TRAEs was 1.2%, and no treatment-related deaths were reported. **Conclusions:** YL201 showed promising antitumor activity and manageable safety profile in heavily pretreated mCRPC patients. These findings support further development of YL201 in mCRPC, especially for those who progressed after ARAT with or without taxane-based chemotherapy, and those with visceral metastases. Clinical trial information: NCT06241846. Research Sponsor: Medi-Link Therapeutics.

Phase 2 multicenter trial of chemoimmunotherapy for patients with neuroendocrine or aggressive variant metastatic prostate cancer (CHAMP).

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Background: Platinum-doublet chemotherapy is effective in pts with neuroendocrine small cell neuroendocrine or aggressive-variant prostate cancer (NEPC/AVPC), but responses have limited durability. PD-1/PD-L1 inhibition in small cell lung cancer with chemotherapy is standard of care, but chemoimmunotherapy has not been tested in patients with NEPC/AVPC. **Methods:** We conducted a multicenter, phase II trial evaluating cabazitaxel, carboplatin, ipilimumab, and nivolumab (NCT04709276) in patients with metastatic NEPC/AVPC defined by histologic, clinical, or molecular features. Ipilimumab was dosed at 1 mg/kg q6w and nivolumab 360 mg q3w w/ongoing ADT. Cabazitaxel 20-25 mg/m² + carboplatin AUC₄ with GCSF was given q3w up to 10 cycles but could be stopped early for response or toxicity, followed by maintenance immunotherapy. Primary endpoint was immune modified iRECIST/PCWG3 radiographic progression-free survival (rPFS), hypothesizing a 55% 6-mo rPFS rate for cabazitaxel/carboplatin (1-sided α 0.1, 85% power) based on historic data. Secondary endpoints: overall survival (OS), rPFS, objective responses, safety. **Results:** We enrolled 40 patients across 3 centers in the Department of Defense Prostate Cancer Clinical Trials Consortium from 7/2021-8/2025, including 12 (32%) with NEPC and 28 (68%) with AVPC, with 38 evaluable for efficacy. Median age was 65 yrs, median PSA 2 ng/dl (range 0-807), and 75% with any visceral metastases including 58% with liver and 33% with lung metastases. The % with elevated serum CEA, LDH, or CgA was 88%; 85% had prior ARPI and 70% prior chemo. With a median f/u of 17 mo, CHAMP met its primary endpoint of improving 6-mo rPFS vs. cabazi/carbo with a 6-mo PFS rate of 78% (90% CI 69-100%); median rPFS was 12 mo. See Table for efficacy. We observed 20 G3 (50%) and 7 G4 (18%) toxicities related to treatment on a per patient basis. Two patients are free of disease and off therapy at 30+ mo. Most common overall G3-4 toxicities were anemia (n=15), neutropenia (n=5), sepsis (n=5), thrombocytopenia (n=5), colitis (n=5), febrile neutropenia (n=4), and UTI (n=4), with no treatment-related deaths. **Conclusions:** Dual PD-1/CTLA4 immune checkpoint blockade with platinum doublet chemotherapy is effective in patients with AVPC/NEPC, resulting in greater efficacy than expected with historic platinum chemotherapy alone, and with acceptable toxicity given disease risk. These results support randomized controlled clinical trials of chemoimmunotherapy in patients with NEPC/AVPC. Clinical trial information: NCT04709276. Research Sponsor: Bristol-Myers-Squibb.

Primary Endpoint (n=38)	Outcome (95% CI)
6 mo PFS (%) by iRECIST/PCWG3 (1-sided 90% CI)	78% (69-100%)
Secondary Endpoints	
12 mo rPFS (%; 95% CI)	44% (29-69%)
PFS, median by iRECIST/PCWG3, mo	12 (9.6-17)
PFS, median by RECIST/PCWG3, mo	6.8 (4.3-9.2)
OS, median, mo	12 (9.6-17)
12-month OS (%)	46% (30-69%)
iRECIST Best Radiographic Response	
ORR (CR+PR) %	34%
CR	2.6%
PR	32%
SD	45%
iUPD/iCPD	13/8%

PROTRACT: A randomized phase II trial comparing ctDNA-guided biomarker directed therapy vs patient/clinician's choice for metastatic castration resistant prostate cancer (mCRPC) progressing after abiraterone plus prednisone (AAP).

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Background: A subset of mCRPC patients (pts) will benefit from enzalutamide (ENZA) following disease progression on AAP. Preliminary data suggests that higher plasma ctDNA/total cfDNA fraction (ctDNA%) post-AAP predicts poor response to ENZA but preserved sensitivity to docetaxel (DOC). We hypothesize that ctDNA%-guided selection of enzalutamide or docetaxel in chemotherapy-naïve mCRPC post-abiraterone will improve clinical outcomes versus patient/clinician's choice of treatment. **Methods:** A multi-centre, open-label, phase II trial randomized mCRPC pts progressing after AAP 1:1 to biomarker-directed therapy (Arm A: ctDNA% $\geq 2\%$ receives DOC; ctDNA% $< 2\%$ receives ENZA) or clinician's choice of ENZA or DOC (Arm B, ctDNA% blinded). Baseline ctDNA% was assessed at screening using somatic mutations and genome-wide ploidy models. At progression, eligible pts could cross over to the alternative therapy. The primary endpoint was progression-free survival (PFS) defined as the time from treatment initiation to first documented disease progression (clinical, radiological, or PSA) or death from any cause. PFS was estimated using the Kaplan-Meier method and compared between arms using the log-rank tests. Secondary endpoints included PSA50 response (PSA decline $\geq 50\%$ from baseline) and overall survival (OS). **Results:** Between October 2020 and June 2025, 56 pts were screened and 42 randomized 1:1 to Arm A (n=17) or Arm B (n=25). The trial was terminated due to slow accrual prior to the planned enrollment of 100 patients. At data cut-off (January 7, 2026), median follow-up was 38.0 months, and 94% (Arm A) and 92% (Arm B) had experienced disease progression or death. Baseline characteristics were balanced. ctDNA% $< 2\%$ was observed in 35.3% and 32% of pts in Arm A and B, respectively. In Arm A, 11 pts were assigned to and received DOC (ctDNA% $\geq 2\%$) and 6 pts to ENZA (ctDNA% $< 2\%$). In Arm B patient/clinician choice was DOC in 4 patients (3 pts with ctDNA% $\geq 2\%$) and ENZA in 21 patients (7 pts with ctDNA% $< 2\%$). PFS, OS and PSA50 all favoured biomarker directed therapy (Arm A) (Table). **Conclusions:** In this clinical utility study, ctDNA% to guide ENZA or DOC selection in patients previously treated with AAP led to superior PFS and OS compared to patient/clinician-selected therapy. These hypothesis-generating results illustrate the potential for ctDNA% as a predictive biomarker to assist in clinical decision making and support further studies. Clinical trial information: NCT04015622. Research Sponsor: Prostate Cancer Canada, Canadian Cancer Society.

Primary & secondary outcomes.

	Biomarker-Directed (Arm A, n=17)	Clinician's Choice (Arm B, n=25)	HR (95% CI) P-Value
Progression-Free Survival (PFS), Months, median (95% CI)	5.6 (3.2-8.2)	2.5 (1.5-3.7)	0.4 (0.2-0.8) $p = 0.01$
PSA50 Response (%)	52.9%	28.0%	$p = 0.12$
Overall Survival (OS), months, median (95% CI)	46.3 (12.2-NR)	15.3 (13.5-20.7)	0.4 (0.2-0.9) $p = 0.04$

Circulating tumor DNA–based clinical-genetic (CG) prognostic model for radio-graphic progression-free survival (rPFS) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): Analysis of Alliance A031201.

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Background: mCRPC is characterized by marked molecular heterogeneity and variable clinical outcomes. Circulating tumor DNA (ctDNA) profiling provides a noninvasive approach to capture tumor genomic alterations with potential prognostic value. We developed and validated a ctDNA-based prognostic model for rPFS using data from the Alliance A031201 (NCT01949337) trial, distinct from our published CG model of overall survival (Halabi et al. Eur Urol 2025). **Methods:** We analyzed ctDNA from 776 pts enrolled in the A031201 trial that randomized men with chemotherapy-naïve mCRPC to enzalutamide +/- abiraterone acetate and prednisone. Baseline cell free DNA samples from 776 pts were sequenced using the AR-ctDETECT assay. The primary endpoint of this analysis was rPFS. Proportional hazards model was used to assess the association of each genetic alterations and clinical variables with rPFS. Random survival forest (RSF) incorporating CG and clinical (C) variables only were trained and evaluated using 10-fold cross-validation. Model performance was assessed using integrated time-dependent area under the ROC curve (itAUC) and net reclassification improvement (NRI). **Results:** Higher ctDNA aneuploidy fraction, ctDNA positivity, and multiple pathogenic genomic alterations were associated with worse rPFS. Among prevalent alterations, AR enhancer gain and AR gain were strongly prognostic, with median rPFS of 13.7 vs 27.3 months (mos) and 13.5 vs 27.0 mos for pts with and without alterations, respectively. The rPFS prognostic model included gains in AR, AR enhancer, MYC, CCND1, and FOXA1, and losses in PTEN, TP53, and LRP1B based on RSF. PTEN loss, gains in AR enhancer, MYC, along with hemoglobin, PSA and alkaline phosphatase showed the largest contribution to risk prediction. Mean itAUC for C model was 0.66 (95% confidence interval [CI] 0.62–0.70), mean itAUC for CG model was 0.73 (95% CI: 0.69–0.77). At 22 mos (median rPFS), NRI comparing CG model with C model was 0.30 (95% CI: 0.19–0.36). Pts were stratified into low-, intermediate-, and poor-risk groups and showed markedly distinct rPFS outcomes, with median rPFS of 39.2, 25.2, and 12.8 mos, respectively. The hazard ratios for low vs poor risk was 0.25 (95% CI: 0.20–0.31) and for intermediate vs poor risk 0.46 (95% CI: 0.38–0.55). **Conclusions:** A ctDNA-based prognostic model integrating CG features robustly stratifies rPFS risk in pts with mCRPC treated with first line AR pathway inhibitor therapy. This approach may support individualized risk assessment and inform trial design around treatment intensification combinations and therapeutic decision-making. External validation in independent cohorts is warranted. **Support:** U10CA180821, U10CA180882; R01CA256157; R01CA174777; <https://acknowledgments.alliancefound.org>. Clinical trial information: NCT01949337. Research Sponsor: National Cancer Institute.

Canadian Cancer Trials Group (CCTG) study PR21 (PLUDO): Results of crossover treatment from a randomized trial of ^{177}Lu -PSMA-617 (LuP) vs docetaxel (DOC) in patients with metastatic castration-resistant prostate cancer (mCRPC).

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Background: The PLUDO trial randomized patients with mCRPC to receive either LuP or DOC, with cross-over permitted at radiographic progression (RP). At the primary analysis, there was no significant difference in the primary endpoint of 1st line radiographic progression free survival (rPFS) (HR 1.01, 90% CI: 0.77, 1.31). However, overall survival (OS) was in favor of patients randomized to receive docetaxel first (HR 1.64, 95% CI: 1.14, 2.35) (KN Chi, et al. ESMO Congress, 2025). To provide insights into potential reasons for the survival difference, we report the prespecified secondary objective of rPFS after cross-over therapy. **Methods:** Multi-centre open-label randomized phase II trial. 199 patients with chemotherapy-naïve, PSMA-PET positive mCRPC progressing after ARPI therapy were randomized 1:1 to receive either LU-P 7.4 GBq IV q6 weeks or DOC 75 mg/m² IV q3 weeks, with cross-over permitted at progression. rPFS₂ was measured from randomization to RP or death after cross-over therapy, “2nd line rPFS” was from time of start of cross-over therapy to RP or death, OS was defined from time of initial randomization to death, and “2nd line OS” was from time of cross-over therapy to death. **Results:** 159 patients had an rPFS event on 1st line therapy (LuP: n = 79, DOC: n = 80) including 24 deaths (LuP: n = 16, DOC: n = 8). At the time of 1st rPFS, there were no substantive differences between arms for grade 3-4 adverse events, but patients on LuP reported better quality of life (FACT-P). Of the 135 patients alive, 104 received cross-over therapy (LuP → DOC: 42, DOC → LuP: 62). There were no clinically relevant differences in baseline characteristics of patients who had cross-over therapy between treatment arms. OS was worse for patients that did not cross-over compared to those who did cross-over (LuP arm: HR 3.18 (95% CI 1.93, 7.42); DOC arm: HR 4.73 (95% CI 1.96, 11.38)). For the 104 patients who received both lines of therapy, there was no differences in efficacy outcomes for 2nd line rPFS, rPFS₂, OS, or 2nd line OS (TABLE). PSA decline ≥ 50% was higher with cross-over Doc than LuP (69% vs 40%, P = 0.004). There were 9 grade 3 adverse events related to cross-over therapy in each arm. **Conclusions:** In the PLUDO study, there was no difference in first-line or cross-over rPFS between LuP and DOC. In patients who received cross-over therapy, this analysis shows no OS difference, suggesting that imbalance in cross-over from LuP to Doc likely impacted the OS difference in the ITT population and emphasizes the importance of both treatments on efficacy outcomes. Clinical trial information: NCT04663997. Research Sponsor: Canadian Cancer Society; 707213; Novartis; Prostate Cancer Canada.

	LuP → DOC (median, months) n = 42	DOC → LuP (median, months) n = 62	HR (DOC → LuP/LuP → DOC)
2 nd line rPFS	4.8	5.4	0.86 (90% CI: 0.58, 1.26)
rPFS ₂	18.5	15.8	0.91 (90% CI: 0.61, 1.35)
2 nd line OS	8.1	8.3	0.94 (95% CI: 0.53-1.64)
OS	23.2	20.0	0.88 (95% CI: 0.50, 1.53)

Subgroup analyses by disease volume and *de novo*/recurrent mHSPC in the PSMAddition study of [¹⁷⁷Lu]Lu-PSMA-617.

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Background: In the phase 3 PSMAddition study (NCT04720157), combining [¹⁷⁷Lu]Lu-PSMA-617 (¹⁷⁷Lu-PSMA-617) with ADT + ARPI significantly improved rPFS in patients with PSMA+ mHSPC vs ADT + ARPI at rPFS interim analysis (data cut off Jan 13, 2025), with a HR of 0.72 (95% CI 0.58, 0.90; *p* = 0.002). **Methods:** Patients had treatment-naïve/minimally treated mHSPC diagnosed by CT/MRI/bone scan and ≥1 PSMA+ metastatic lesion on [⁶⁸Ga]Ga-PSMA-11 PET/CT. Patients were randomized 1:1 to ¹⁷⁷Lu-PSMA-617 (7.4 GBq ± 10% q6w, 6 cycles) + ADT + ARPI (¹⁷⁷Lu-PSMA-617 arm) or ADT + ARPI (control arm). The primary endpoint of rPFS (centrally assessed rPD per PCWG3/RECIST v1.1 or death) and selected secondary efficacy, safety, and patient-reported outcomes (PROs) were assessed in subgroups of high/low disease volume (DV) per CHARTED criteria (locally assessed by CT/MRI/bone scan; prespecified) and *de novo*/recurrent mHSPC (AJCC stage ≥/ < IVb; *post hoc*). **Results:** Of 572 patients randomized to the ¹⁷⁷Lu-PSMA-617 arm and 572 to the control arm, 68.0% and 68.2% had high DV, and 52.1% and 47.9% had *de novo* mHSPC. Efficacy and PRO HRs for the ¹⁷⁷Lu-PSMA-617 arm vs control arm were generally similar in the overall population and DV and mHSPC subgroups (rPFS HR 0.72–0.74; time to PSA progression HR 0.29–0.51) (Table). Incidences of AEs, grade ≥3 AEs, serious AEs, and selected safety topics of interest (cytopenias, dry mouth) were similar across subgroups within each treatment arm. **Conclusions:** In patients with PSMA+ mHSPC, combining ¹⁷⁷Lu-PSMA-617 with ADT + ARPI improved rPFS vs ADT + ARPI across high/low DV and *de novo*/recurrent mHSPC subgroups. Other efficacy outcomes, PROs, and the safety profile were generally consistent across subgroups. Clinical trial information: NCT04720157. Research Sponsor: Novartis.

Efficacy and PROs.

HR (95% CI) for ¹⁷⁷ Lu-PSMA-617 arm vs control arm	Overall N = 1144	High DV n = 779	Low DV n = 365	<i>De novo</i> mHSPC n = 572	Recurrent mHSPC n = 523
rPFS ^a	0.72 (0.58, 0.90)	0.72 (0.56, 0.92)	0.73 (0.42, 1.27)	0.74 (0.54, 1.01)	0.74 (0.53, 1.04)
PFS per investigator ^b	0.64 (0.51, 0.79)	0.61 (0.48, 0.78)	0.80 (0.46, 1.37)	0.65 (0.48, 0.88)	0.64 (0.46, 0.89)
Time to:					
PSA progression	0.42 (0.30, 0.59)	0.43 (0.31, 0.62)	0.29 (0.08, 1.05)	0.51 (0.32, 0.79)	0.35 (0.21, 0.60)
Symptomatic skeletal event	0.89 (0.62, 1.26)	0.93 (0.64, 1.37)	0.67 (0.27, 1.66)	0.97 (0.60, 1.57)	0.82 (0.48, 1.40)
mCRPC	0.70 (0.58, 0.84)	0.67 (0.54, 0.82)	0.87 (0.55, 1.37)	0.61 (0.47, 0.80)	0.75 (0.56, 1.00)
BPI-SF pain intensity worsening ^c	1.02 (0.87, 1.18)	0.98 (0.82, 1.18)	1.09 (0.83, 1.44)	1.06 (0.85, 1.31)	0.97 (0.78, 1.22)
FACT-P total score worsening ^c	1.14 (0.98, 1.33)	1.13 (0.94, 1.37)	1.16 (0.88, 1.53)	1.13 (0.90, 1.41)	1.16 (0.92, 1.46)
EQ-5D-5L worsening ^c	1.13 (0.97, 1.31)	1.04 (0.87, 1.25)	1.34 (1.01, 1.77)	1.17 (0.93, 1.45)	1.09 (0.87, 1.37)

N may differ across outcomes.

^arPD by BIRC or death.

^bComposite of radiographic, clinical, and PSA progression and death.

^cComposite with clinical progression and death.

Validation of prostate-specific antigen (PSA) decline among the Latin American subgroup of LIBERTAS: A phase 3 study of apalutamide (APA) plus continuous versus intermittent androgen deprivation therapy (ADT) in metastatic castration-sensitive prostate cancer (mCSPC).

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Background: APA in combination with continuous ADT showed rapid and deep PSA decline in participants (pts) with mCSPC in the TITAN study, and this deep PSA decline was associated with improved overall survival. LIBERTAS (NCT05884398), a global phase 3 study, is evaluating APA + intermittent ADT as an ADT de-escalation strategy for pts with mCSPC who achieve an undetectable PSA (< 0.2 ng/mL) after 6 months on APA + ADT. In the initial treatment phase of LIBERTAS, 6 months of APA + continuous ADT resulted in deep PSA responses in the majority of pts with mCSPC. **Methods:** Pts with mCSPC were eligible if they had ≤ 3 months of prior ADT, ECOG PS 0–1 and confirmed metastases by conventional or next-generation imaging. In the initial 6-month treatment phase, all pts received APA 240 mg/day + ADT. In the main treatment phase, pts with < 0.2 ng/mL were randomized 1:1 to APA 240 mg/day + intermittent or continuous ADT. Co-primary endpoints were radiographic progression-free survival (rPFS), measured by the 18-month event-free survival rate, and reduction of hot flash burden, measured by the 18-month severity-adjusted hot flash score. Here, we present an analysis of the Latin American (LATAM) subgroup evaluating PSA response results following the initial treatment phase. **Results:** From Dec 2023 to July 2024, 118 LATAM pts were enrolled (87 pts from 7 sites in Brazil, and 31 pts from 4 sites in Mexico). Racial distribution in LATAM pts was 60.2% White, 10.2% Black, 9.3% Multiple, and 17.8% other. LATAM pts were younger (median age 67 years [range: 48–86]) and had more advanced disease (89.0% with M1 disease at diagnosis; 39.8% with ECOG PS 1, 66.1% with high volume disease; median baseline PSA 22.95 ng/mL [IQR: 3.18–87.00]) compared with the overall study population. Among 109 pts who completed the 6-month initial treatment phase, 104 (95.4%) achieved a $\geq 50\%$ PSA decline (PSA50), 90 (82.6%) achieved a $\geq 90\%$ decline (PSA90), and 66 (60.6%) achieved PSA < 0.2 ng/mL (PSA0.2), of which 62 (56.9%) pts were randomized to the main treatment phase. Median time to response was 1.87 months for PSA50, 1.91 months for PSA90, and 3.14 months for PSA0.2. No new safety signals were observed in the LATAM subgroup. **Conclusions:** LATAM pts in LIBERTAS were younger on average and had more advanced disease compared with the overall study population. Despite having higher baseline PSA levels, LATAM pts with mCSPC demonstrated rapid and deep PSA responses to APA + ADT, consistent with the results from the global analysis. The safety profile of APA was consistent with previous studies. The LIBERTAS study remains on track for the primary readout. Clinical trial information: NCT05884398. Research Sponsor: None.

Real-world genetic testing patterns in prostate cancer assessed via artificial intelligence: Implications for NCCN guideline implementation.

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Background: Germline and somatic genomic testing in prostate cancer guide both targeted therapy selection and identification of heritable cancer risk. Although NCCN guidelines define testing eligibility based on disease risk and stage, real-world testing remains suboptimal. Population-level data indicate that only one-third of men with metastatic prostate cancer undergo genomic testing. As part of a larger effort to improve testing rates, we evaluated three consecutive years of prostate cancer care to quantify testing utilization and assessed artificial intelligence (AI) performance for risk stratification and testing eligibility. **Methods:** We conducted a retrospective chart review of patients with advanced prostate cancer treated at a large multi-site community oncology practice between 2023 and 2025. Clinical data were manually reviewed to assign disease stage, NCCN risk stratification, and eligibility for germline and somatic testing. In 2023, a rules-based AI applied explicit NCCN guideline logic (v1.2023). In 2024 and 2025, an untrained general-purpose AI model (ChatGPT 5.2) was provided NCCN guideline text (v1.2024 and v1.2025) and tasked with inferring risk category and testing eligibility. Primary outcomes included observed annual germline and somatic testing rates and AI concordance with manual review. Temporal trends in germline and somatic testing adoption were assessed using the Cochran-Armitage trend test. **Results:** Across 2023–2025, NCCN-indicated germline and somatic testing was inconsistently performed (Table 1), with significantly increasing rates from 2023 to 2025 (Cochran-Armitage trend test, germline $p < 0.001$, somatic $p < 0.001$). Testing outside of NCCN guidelines was ordered by clinicians in 10 (4%), 22 (9%), and 31 (18%) patients each year, respectively. **Conclusions:** In a large community oncology setting, NCCN-indicated germline and somatic testing for prostate cancer was frequently underutilized, despite significant improvement over time. Ongoing analyses seek to clarify which interventions contributed to increased testing rates and whether testing performed outside NCCN guidelines reflects broader clinical awareness of indications not consistently captured in structured data. AI-based guideline interpretation of NCCN guidelines demonstrated consistently high concordance with manual review and may offer a scalable approach to systematically identify patients eligible for genetic testing using structured data. Research Sponsor: AstraZeneca; Pfizer.

Year	Charts Reviewed	Germline Eligible	Germline Tested	Somatic Eligible*	Somatic Tested	AI Risk Stratification	AI Testing Recommendation Concordance
2023	259	194	54 (28%)	91	24 (26%)	Not assessed	Germline 97%; Somatic 100%
2024	255	195	82 (42%)	86	37 (43%)	235 / 255 (92%)	Germline 100%; Somatic 100%
2025	177	167	98 (59%)	62	50 (81%)	177 / 177 (100%)	Germline 100%; Somatic 100%

*Somatic testing was "recommended" for patients with metastatic disease per NCCN 2023 -2025.

Image-only and multimodal AI digital pathology biomarkers to demonstrate risk stratification across standard prostate cancer management strategies.

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Background: Reliable risk stratification across standard treatment pathways is essential for the clinical adoption of precision medicine biomarkers in localized prostate cancer. We previously developed and validated a multimodal artificial intelligence (MMAI) model that integrates digitized hematoxylin and eosin (H&E) prostate biopsy slides with clinical variables to prognosticate distant metastasis (DM) and prostate cancer specific mortality (PCSM). To evaluate the independent prognostic signal derived from routine histopathology alone without clinical variables, we built an Image-only artificial intelligence model. In this study, we validate the prognostic ability of the new Image-only and existing MMAI models in a multi-institutional cohort of nonmetastatic prostate cancer patients receiving guideline-concordant standard-of-care treatments. **Methods:** The Image-only model was trained to estimate the risk of 10-year distant metastasis (DM) without clinical inputs. Both the Image-only and MMAI models were evaluated in a cohort of men from 3 institutions with non-metastatic prostate cancer treated with active surveillance (AS), radical prostatectomy (RP), or radiation therapy (RT). The primary endpoint was 10-year risk of DM, with prostate cancer-specific mortality (PCSM) as a secondary endpoint. Prognostic associations were evaluated within each treatment subgroup using Fine-Gray models. **Results:** Among 886 patients with Image-only scores and 911 with MMAI scores, approximately 36% were managed with AS, 41% with RP, and 23% with RT. The Image-only model continuous raw scores were consistently associated with DM risk across treatment modalities, including AS (subdistribution hazard ratio [sHR] 2.38, $p < 0.001$), RP (1.99, $p < 0.001$), and RT (sHR 2.84, $p < 0.001$). Similarly, the Image-only model calibrated scores showed significant prognostic association with DM across all treatment groups. The MMAI showed consistent prognostic performance for DM using both calibrated and raw scores (raw scores: AS sHR 2.87, $p < 0.001$; RP sHR 2.12, $p < 0.001$; RT sHR 2.73, $p < 0.001$). Both Image-only and MMAI scores were significantly associated with PCSM despite low event rates. **Conclusions:** Both Image-only and MMAI biomarkers demonstrate consistent prognostic performance across standard prostate cancer management strategies, including AS, RP, and RT, supporting their utility for risk stratification regardless of ultimate treatment selection. These findings highlight the robustness of image-derived prognostic information and demonstrate that routinely available H&E pathology alone captures clinically meaningful risk information that generalizes across treatment contexts. Together, these results support the use of AI-based digital pathology biomarkers for prognostication in localized prostate cancer. Research Sponsor: Artera Inc.

AI-assisted preoperative communication in prostate cancer: A prospective, single-blinded, randomized phase II trial.

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Background: To evaluate whether AI-assisted preoperative communication reduced patient anxiety, and physician workload compared with standard preoperative communication in patients undergoing radical prostatectomy. **Methods:** We conducted a prospective, randomized, single-blinded, phase II trial in newly diagnosed prostate cancer patients undergoing radical surgery, excluding those with severe psychiatric or cognitive disorders. Upon hospital admission, patients were randomized at the room level to receive either standard or AI-assisted preoperative communication. After baseline assessment, the AI-assisted group received individualized responses generated by a locally deployed large language model-based AI system prior to routine physician-led face-to-face preoperative communication, while physicians remained blinded to group allocation. The primary outcomes were patient anxiety (GAD-7) and physician workload (NASA-TLX). Comparisons were conducted using non-parametric rank-sum tests. The trial was registered at ClinicalTrials.gov (NCT07082049). **Results:** Between April and November 2025, 268 patients were randomized to the control group (n = 130) or the AI-assisted group (n = 138). A total of 3,507 questions were collected (avg. 13.08 per patient). After routine preoperative communication, patients in the AI-assisted group reported lower anxiety levels than those in the control group (GAD-7 median [IQR], 3.5 [2.5–5.0] vs. 7.5 [6.5–9.0]; $P < 0.001$). Physician workload was also reduced in the AI-assisted group, as reflected by lower NASA-TLX scores (median [IQR], 37.0 [27.0–46.0] vs. 54.0 [35.0–73.0]; $P < 0.001$), accompanied by a substantial reduction in preoperative communication time (12.60 vs. 21.90 minutes; $P < 0.001$). Patients in the AI-assisted group reported more favorable emotional status, lower negative illness perceptions, and higher satisfaction, while exploratory analyses indicated that AI-assisted communication alone improved anxiety, emotional status, and disease-related perceptions prior to physician face-to-face preoperative communication. The observed reductions in physician workload and communication time suggest potential applicability in resource-constrained clinical settings where clinical manpower and consultation time are limited. **Conclusions:** AI-assisted preoperative communication reduced patient anxiety, and physician workload compared with standard communication, supporting its role as a supplementary approach to routine preoperative care in prostate cancer, including settings involving older adults and limited clinical resources. Clinical trial information: NCT07082049. Research Sponsor: National Nature Science Foundation of China; 82373355, 82303097; Shanghai Oriental Talent Program Top Project; BJKJ2024007; the Special Research Fund for Clinical Studies of Innovative Drugs after Market Launch of the Development Center for Medical Science and Technology National Health Commission of China; WKZX2024CX104201.

Implementation of serum microRNA-371a-3p testing for testicular germ-cell tumors in a pathology department: Real-world data from a comprehensive cancer center.

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Background: The classical serum tumor markers for testicular germ cell tumor (TGCT) patients show limited sensitivity and specificity in some clinical settings. In the last years, serum miR-371a-3p testing has been shown to have superior performance for the detection and follow-up of TGCT patients. A commercial test with IVD approval is already available for use in the clinic. In this work we demonstrate our experience with the clinical implementation of this liquid biopsy test, comparing its performance with the one of AFP, HCG and LDH. **Methods:** The M371 test (serum) was implemented at the Department of Pathology of our Comprehensive Cancer Center in August 2024, for patients presenting with testicular masses and for TGCT patients during follow-up. Simultaneous collection of AFP, HCG and LDH was performed at the different timepoints, following the guidelines for diagnosis and follow-up of TGCT patients. Blood was collected on the recommended Serum-Gel 7.5mL tubes and processed to serum within 3h of collection. The RTqPCR test and analysis followed the manufacturer's closed protocol (IVDR approved). Clinical charts and CT scans were reviewed to determine disease status, and results were correlated with histology. **Results:** A total of 128 M371 tests were performed at the Department of Pathology during 16 months, including several contexts of the disease (pre-orchietomy, follow-up, pre-RPLND, pre and post-chemotherapy). The mean turnaround time for the test (from receiving the blood sample to issuing the report) was of 5.6 days. The median patient age was 35 years (19–81 years). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were as follows: 0.43, 0.96, 0.76 and 0.85 for AFP; 0.57, 0.98, 0.89 and 0.88 for HCG; 0.37, 0.91, 0.55 and 0.82 for LDH; 0.80, 0.92, 0.77 and 0.93 for the combination of AFP+HCG+LDH; and 0.96, 0.96, 0.87 and 0.99 for M371 test alone. Additional collections/testing and subanalyses based on disease setting and histologic findings are ongoing. **Conclusions:** The M371 IVD serum test alone showed a superior diagnostic performance for detecting active TGCT in an unselected, consecutive cohort of TGCT patients representing different settings of the disease, when compared to the classical serum tumor markers AFP, HCG and LDH, isolated or in combination. The sensitivity of AFP, HCG and particularly LDH isolated (0.43, 0.57 and 0.37) were outperformed by the sensitivity of the M371 test (0.96). The high NPV of the M371 test (0.99) may aid in the decision of de-escalating intervention (treatment or follow-up measures) of young TGCT patients. These real-world data underscore the potential advantages of adding microRNA testing as an additional test to combine with classical serum tumor markers and imaging. Research Sponsor: None.

Comparative transcriptomic analysis of chemotherapy-naïve and post-chemotherapy germ cell tumors.

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Background: Cisplatin-based chemotherapy is highly effective in testicular germ cell tumors (GCTs); however, the presence of viable tumor after first-line chemotherapy is associated with chemoresistance and poor clinical outcome. The transcriptional programs distinguishing chemotherapy-naïve and post-chemotherapy viable GCTs remain incompletely characterized. **Methods:** Tumor samples from 50 GCT patients treated between 2010 and 2022 were analyzed, including 30 chemotherapy-naïve tumors and 20 post-chemotherapy viable GCTs resected from the retroperitoneum. Five normal testicular tissue samples served as controls. Formalin-fixed paraffin-embedded samples were profiled using the HTG EdgeSeq Oncology Biomarker Panel. Differential gene expression analysis was performed using DESeq2, adjusted for histology, with significance defined as adjusted p-value < 0.1 and |log2 fold change| > 1. Functional enrichment analysis was conducted to identify deregulated biological pathways. **Results:** Compared with normal testicular tissue, chemotherapy-naïve GCTs and post-chemotherapy viable GCTs exhibited 1,010 and 720 differentially expressed genes, respectively. Direct comparison between chemotherapy-naïve and post-chemotherapy tumors identified 424 differentially expressed genes. Post-chemotherapy viable GCTs demonstrated marked downregulation of genes associated with pluripotency and embryonal stem cell identity, including *POU5F1*, *UTF1*, *DPPA4*, and *PRDM14*. In contrast, post-chemotherapy tumors showed upregulation of immediate early stress response genes, inflammatory and cytokine signaling pathways, EGFR-related growth factor signaling, and metabolic stress adaptation. **Conclusions:** Post-chemotherapy viable GCTs are characterized by loss of pluripotent transcriptional programs and acquisition of stress-responsive, inflammatory, and adaptive signaling pathways. These transcriptional changes provide insight into the biology of chemotherapy resistance in GCTs and may have prognostic and therapeutic implications. Research Sponsor: Agency for research and development; 24-0168.

Genomic determinants of cisplatin resistance in germ cell tumors.

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Background: Cisplatin-based chemotherapy achieves complete remission in 70–80% of patients with germ cell tumors (GCTs), but a subset are cisplatin-resistant and progress after first-line therapy. Prior studies have linked *TP53* and *MDM2* alterations and chromosome 3p25.3 gain to cisplatin resistance and worse outcomes in GCT. We sought to validate this and identify additional genomic determinants of cisplatin response in a large GCT cohort. **Methods:** Patients who received first-line cisplatin-based chemotherapy for GCT of any primary site with genomic analysis of the tumor were eligible. Cisplatin resistance was defined as: (1) incomplete response to chemotherapy, (2) non-teratoma progression after chemotherapy, or (3) viable non-teratoma GCT at post-chemotherapy surgery; all other patients were considered sensitive. Next-generation sequencing was performed using the MSK-IMPACT assay and association between genomic alterations and resistance was assessed using Fisher's exact test. Cytoband analysis was completed using the FACETS algorithm to calculate chromosomal alterations, with a required cytoband coverage of 75%. The association between cytoband alterations and resistance was assessed using relative risk with a robust variance estimator. **Results:** The cohort of 556 patients included 79% testicular, 15% mediastinal, 4% ovarian, and 1.5% tumors of other primary site. 79% were nonseminomatous germ cell tumors and 21% pure seminoma. Among these, 336 (60%) were cisplatin-resistant. *TP53* mutations were more common in resistant than sensitive tumors (16% vs 2%), as were *MDM2* and *CRKL* amplifications (7% vs 1% and 4% vs < 1%, respectively). *KIT* was more frequently mutated in cisplatin-sensitive tumors (5% in resistant vs 14% in sensitive) (Table 1). *TP53* mutations occurred predominantly in mediastinal primary tumors (89%) whereas *MDM2* alterations were confined to testicular primaries. Of 472 patients who underwent cytoband 3p25.3 analysis, chromosome 3p25.3 gain was associated with cisplatin resistance (relative risk 1.23; 95% CI: 1.00, 1.49; $p = 0.04$). **Conclusions:** In this large GCT cohort, *TP53* and *MDM2* alterations and chromosome 3p25.3 gains were associated with cisplatin resistance, consistent with prior reports. We also found that *CRKL* amplifications were associated with cisplatin resistance whereas *KIT* mutations were associated with cisplatin sensitivity. These latter findings are the first reports of the association of these genes with cisplatin response and warrant further mechanistic investigation to define how these alterations influence cisplatin sensitivity. Research Sponsor: None.

Genomic alterations corresponding to cisplatin response in GCT.

Alteration	Resistant (n=336)	Sensitive (n=220)	p-value
<i>TP53</i> mutations	53 (16%)	4 (2%)	<0.01
<i>KIT</i> mutations	16 (5%)	31 (14%)	<0.01
<i>MDM2</i> amplifications	23 (7%)	2 (1%)	<0.01
<i>CRKL</i> amplifications	14 (4%)	1 (<1%)	<0.01

Prognostic significance of teratoma components in germ cell tumor patients undergoing high-dose chemotherapy and autologous stem cell transplantation.

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Background: The prognostic significance of a teratoma component in relapsed or refractory germ cell tumors (GCT) treated with high-dose chemotherapy followed by autologous stem cell transplantation (HDCT-ASCT) remains unclear. While teratoma has been extensively studied in earlier treatment lines, data specifically addressing its impact in the transplant setting are limited. Identification of factors influencing outcomes after HDCT is critical for patient selection and treatment optimization. **Methods:** This single-center retrospective study included 132 GCT patients who underwent autologous stem cell-supported HDCT. Primary tumor specimens were re-evaluated by an experienced pathologist for the presence of a teratoma component. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method and compared between teratoma-positive and teratoma-negative groups. Univariate Cox regression and predefined subgroup analyses were performed to identify factors associated with survival outcomes. **Results:** Baseline pathological data were available for 132 patients; 59 (44.7%) had a teratoma component and 73 (55.3%) did not. Baseline clinicopathological characteristics, including age, primary tumor site, stage, IGCCCG risk group, metastatic pattern, biomarker status, and response to first-line therapy, were comparable between groups. After a median follow-up of 55.6 months, median PFS was 6.8 months (95% CI, 4.1–9.6). Median PFS was significantly shorter in teratoma-positive patients compared with teratoma-negative patients (5.6 vs 10.0 months; log-rank $p = 0.011$). The 2-year PFS rates were 34% and 50%, respectively. Teratoma presence was associated with inferior PFS in univariate analysis (HR 1.77, 95% CI 1.13–2.77; $p = 0.013$). Median OS was not reached overall; median OS was 68.9 months in teratoma-positive patients and not reached in teratoma-negative patients, with no significant difference between groups ($p = 0.986$). The 2-year OS rates were similar (64% vs 67%). Subgroup analyses showed numerically poorer OS with teratoma across most strata, without statistical significance. **Conclusions:** In relapsed or refractory GCT patients undergoing HDCT, the presence of a teratoma component was associated with inferior disease control but not with a statistically significant OS disadvantage, possibly due to limited follow-up. Teratoma status may help identify patients requiring more intensive transplant strategies and early post-transplant treatment optimization. Prospective studies with longer follow-up are warranted. Research Sponsor: None.

Integrated clinical and genomic analysis of mediastinal germ cell tumors (GCT) with somatic transformation (SM): A multi-institutional cohort study.

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Background: SM of GCT is a rare but lethal entity largely described in the context of testicular primaries. The distinct clinical and genomic features of SM that arise from anterior medias-tinum are less defined. **Methods:** A multi-institutional study was conducted by integrating data from Indiana University and the MD Anderson Cancer Center, including patients(pts) with SM arising from mediastinal GCT treated between 2016 and 2025. Electronic health records were queried to obtain clinical, pathologic and genomic data when available. SM was classified as “de novo” if detected prior to disease relapse; all others were “evolved”. In the absence of elevated markers or concomitant GCT elements, isochromosome12p testing confirmed GCT ancestry. Descriptive statistics were used. Cox regression and Kaplan Meier analysis were used for overall survival(OS) and reverse KM for follow-up. OS measured from the time of transformation to date of last follow-up. The study was under protocol PA16-0736. **Results:** 40 pts were identified. All were male; median age at GCT diagnosis was 25 yrs (IQR:22-35); First detection of SM was by diagnostic biopsy in 14(35%) instances and surgical excision in 24(60%). Sarcoma was the most common histology detected in 33(82%), notably rhabdomyosarcoma and angiosarcoma-8(20%) each. More than one SM pathology in 6(15%) pts and hematolymphoid SM was detected in 4(10%). Of 23/40 (57%) pts with genomic testing, 17(74%) were performed on the primary specimens, 5(22%) on metastatic deposits and 1(4%) on peripheral blood. TP53 and PTEN/AKT pathway mutations were seen in 16(70%) and 14(61%) respectively. De novo SM was seen in 32(80%). 9(28%) had baseline metastatic disease. Elevated AFP and beta-hCG in 28/32(84%) and 14/32(44%); 6(19%) were marker negative. 24(75%) received conventional GCT regimens. All marker negative pts had histology-driven therapy. Response data in Table. 26(81%) received surgical consolidation. For full cohort, median follow-up was 2.9 yrs, 2yr OS- 62%(95%CI: 46.9-81.9) and 5yr OS- 52%(95%CI: 35.6-75.4). For de novo SM, surgical consolidation was associated with longer survival (mOS 8 yrs vs 0.6 yrs, HR-0.09, 95%CI:0.02-0.3, p-0.0003). **Conclusions:** The vast majority of mediastinal SM are sarcomas, that can be detected de novo. Conventional tumor markers are frequently elevated at presentation and may reflect concom-itant non-teratoma GCT. TP53 and PTEN/AKT pathway mutations characterize the most common alterations and can be detected in primary and metastatic specimens. Research Sponsor: None.

Response to first-line therapy	GCT Therapy (n= 24) (%)	Histology driven therapy (n=7) (%)
Complete Remission (without resection)	4 (17)	1 (14)
Partial Remission	8 (34)	3 (42)
Stable Disease	5 (22)	2 (29)
Progressive Disease	6 (26)	1 (14)
Not available	1 (4)	
Marker Response		
Elevated at presentation	23 (96)	1 (14)
Normalization of markers	15 (63)	1 (14)

Regional trends in testicular cancer burden among adolescents and young adults (15–39 years), 1990–2023: A Global Burden of Disease analysis.

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Background: Testicular cancer is the most common solid malignancy in adolescent and young adult (AYA) males. Contemporary long-term regional trends in incidence and health loss among AYAs remain incompletely described. We quantified trends in testicular cancer burden among ages 15–39 years from 1990–2023 across World Health Organization (WHO) regions. **Methods:** Using annual Global Burden of Disease (GBD) estimates (1990–2023) for ages 15–39 years, we assessed trends in incidence, prevalence, deaths, disability-adjusted life years (DALYs), years of life lost (YLLs), and years lived with disability (YLDs). For each WHO region and measure, we fit log-linear models ($\ln[\text{rate}] = \beta \times \text{year}$) and calculated annual average percent change (AAPC) as $100 \times (e^{\beta} - 1)$, with 95% confidence intervals (CI) derived from the regression. **Results:** Incidence showed an upward trend in all regions, ranging from 0.62%/year in the African Region (95% CI 0.28–0.96) to 3.15%/year in the Eastern Mediterranean Region (2.98–3.33). Prevalence rose across regions, highest in the South-East Asia Region (6.04%/year, 5.82–6.26) and Eastern Mediterranean Region (5.22%/year, 5.09–5.34). Mortality trends varied across regions. Deaths declined in the Western Pacific (–1.69%/year, –1.99 to –1.39), Europe (–1.43%/year, –1.49 to –1.36), and Africa (–0.89%/year, –1.20 to –0.58), were stable in South-East Asia (–0.07%/year, $p=0.44$), and increased in the Americas (1.68%/year, 1.49–1.87) and Eastern Mediterranean (0.42%/year, 0.32–0.51). DALYs and YLLs followed similar patterns (declining in Europe/Western Pacific, rising in the Americas). **Conclusions:** From 1990–2023, testicular cancer incidence and survivorship-related burden increased across all WHO regions among AYAs, while mortality-related metrics improved in Europe/Western Pacific but worsened in the Americas and Eastern Mediterranean. These findings support urgent investigation of drivers of rising incidence and targeted strategies to reduce regional inequities in timely diagnosis and curative treatment for AYAs. Research Sponsor: None.

Metabolic and inflammatory marker elevations and associations with hormone therapy usage in prostate cancer patients of the All of Us Research Program cohort.

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Background: The development of cardiovascular disease (CVD) involves an interplay of inflammatory and metabolic factors. While hormone therapy (HT) is associated with increased CVD risk in prostate cancer (PCa) patients, the underlying mechanism remains unclear. Prior studies suggest an association between hypogonadism and systemic inflammation, but the specific effect of HT is poorly understood. Utilizing the All of Us Research Program, we investigated the effects of HT on metabolic and inflammatory markers. **Methods:** Our study examined All of Us participants who were diagnosed with PCa and were either treated or not treated with HT (GnRH agonists, GnRH antagonists, and/or anti-androgens), as well as those who received HT for non-PCa indications. We used ANCOVA to evaluate the effect of HT on metabolic and inflammatory labs after adjusting for pre-PCa baseline values. Among HT-treated PCa patients without prior CVD (myocardial infarction, stroke, or heart failure), we used Gray's test to compare CVD time-to-event between participants with and without elevated inflammatory labs (CRP > 10, ESR > 20, or Ferritin > 300) after HT treatment. In the non-PCa cohort, paired T-tests compared pre-HT and post-HT values. **Results:** The study included 7124 participants with PCa (1480 with HT; 5644 controls) and 2683 participants without PCa who received HT. After adjustment for baseline values, HT usage was associated with increased HgbA1c ($P < 0.001$), HDL ($P < 0.001$), triglycerides ($P < 0.001$), ESR ($P = 0.006$), CRP ($P = 0.009$), and ferritin ($P = 0.006$). Similar trends were seen in the non-PCa cohort (Table). In our survival analysis, HT-treated PCa patients with elevated inflammatory labs had higher CVD risk ($P < 0.001$). **Conclusions:** Our study demonstrated associations between HT usage and metabolic dysregulation, while also suggesting a pro-inflammatory effect of HT in PCa patients. These trends reinforce prior studies and were similar among those without PCa, suggesting a drug-class effect. Our study also observed an increased risk of CVD among HT-treated PCa patients with elevated inflammatory labs. Future research should explore the role of HT associated inflammation in CVD, as well as identify targets for risk mitigation. Research Sponsor: None.

Lab	HT Treatment EMM (SE)	No HT Treatment EMM (SE)	P-value (ANCOVA)	Non-PCa Pre-HT Mean	Non-PCa Post-HT Mean	P-Value (Paired T-test)
HgbA1c (%)	6.34 (0.04)	6.15 (0.02)	$P < 0.001$	5.8	6.0	$P < 0.001$
LDL (mg/dL)	102 (1.10)	101 (0.55)	$P = 0.71$	103.0	107.6	$P < 0.001$
HDL (mg/dL)	52.0 (0.17)	49.7 (0.33)	$P < 0.001$	55.0	55.9	$P = 0.02$
Triglycerides (mg/dL)	136 (2.33)	127 (1.18)	$P < 0.001$	117.5	124.1	$P = 0.001$
CRP (mg/L)	45.7 (8.81)	24.9 (4.61)	$P = 0.009$	19.8	23.3	$P = 0.45$
ESR (mm/hr)	28.0 (2.27)	21.8 (1.19)	$P = 0.006$	27.1	30.2	$P = 0.02$
Ferritin (ng/mL)	303 (55.8)	267 (34.2)	$P = 0.006$	195.7	338.6	$P = 0.02$

EMM= Estimated Marginal Mean, SE = Standard Error.

Burden, mortality patterns, and treatment disparities of prostate cancer across G20 countries: Insights from the Global Burden of Disease 2023 study.

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Background: Prostate cancer is the leading male malignancy in G20 nations, yet cross-national disparities in detection, treatment, and outcomes remain insufficiently characterized. This study examines incidence, mortality, and treatment patterns across G20 countries, with attention to socioeconomic and health system factors. **Methods:** We analyzed prostate cancer incidence, mortality, and disability-adjusted life years (DALYs) in all 20 G20 member states from 1990 to 2023 using GBD 2023 data. Analysis focused on men aged ≥ 50 years. Age-standardized rates were calculated, and incidence-to-mortality ratios were used as a proxy for early detection and treatment access. Radical treatment rates (surgery, radiotherapy) and PSA screening availability were correlated with survival patterns. Country-level economic estimates included diagnostic, therapeutic, and end-of-life expenditures. **Results:** In 2023, G20 countries reported 3.24 million new prostate cancer cases and 512,000 deaths, resulting in 11.8 million DALYs. Age-standardized incidence rates ranged from 23.4 to 112.6 per 100,000 men—a 4.8-fold variation—strongly associated with national healthcare development index ($r = 0.78$, $p < 0.001$). High-income G20 nations reported incidence-to-mortality ratios between 4.2:1 and 5.8:1, while middle-income countries such as India, Indonesia, and Mexico ranged from 1.3:1 to 1.8:1. India and Indonesia together accounted for 24% of G20 prostate cancer deaths despite contributing only 18% of total incident cases. Radical treatment rates spanned from 8% in India to 68% in the USA, correlating with long-term survival trends. Average healthcare expenditure per prostate cancer death ranged from \$2,100 in low-resource settings to \$89,400 in high-income countries. Within high-income nations, men in the lowest socioeconomic quintile experienced 2.1 times higher mortality than those in the highest quintile. **Conclusions:** Marked disparities in prostate cancer burden and treatment access persist across G20 nations, shaped by income level and healthcare system capacity. Strategic expansion of PSA-based screening and curative treatment in middle-income settings could substantially reduce preventable deaths and narrow the outcome gap. Research Sponsor: None.

Real-world overall survival outcomes of lutetium (Lu¹⁷⁷) vipivotide tetraxetan treatment in prostate cancer.

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Background: After FDA approval on March 23, 2022, lutetium (Lu¹⁷⁷) vipivotide tetraxetan became an established treatment option for advanced prostate cancer, but real-world survival outcomes and prognostic factors remain incompletely described. **Methods:** We conducted a retrospective cohort study in Epic Cosmos with the largest to date reported cohort of patients with prostate cancer who initiated lutetium Lu¹⁷⁷ vipivotide tetraxetan after FDA approval to Dec 20, 2025, ensuring at least one month of follow-up prior to the query date. OS was measured from the medication start date to death, or censoring at last encounter. Kaplan–Meier methods were used for survival analysis. Univariable Cox proportional hazards models, adjusted for false discovery rate (FDR), were used to assess associations between OS and clinical variables. **Results:** The cohort included 6464 patients with a median age of 74.0 years (IQR: 38–100). The cohort was predominantly White (75.2%) and Black/African American (19.9%). Kaplan–Meier analysis showed OS probabilities of 85.4%, 67.2%, 42.8%, and 23.8% at 6, 12, 24, and 36 months, respectively, comparable to results reported in the Phase 3 VISION trial. Worse survival was significantly associated with a history of tobacco use (HR 1.22 [1.11–1.33], FDR <0.01) and higher Charlson Comorbidity Index scores (HR 1.04 [95% CI 1.02–1.06], FDR <0.01). Conversely, higher BMI (HR 0.98 [0.97–0.99], FDR <0.01) was associated with improved survival. Baseline laboratory markers of nutritional and hematologic reserve were strongly protective, including higher Albumin (HR 0.39 [0.35–0.43], FDR <0.01), Total Protein (HR 0.81 [0.74–0.89], FDR <0.01), Hemoglobin (HR 0.77 [0.75–0.79], FDR <0.01), RBC count (HR 0.53 [0.49–0.57], FDR <0.01), and MCHC (HR 0.88 [0.86–0.91], FDR <0.01). Inflammatory and immune markers showed distinct prognostic value: higher Eosinophils (HR 0.38 [0.25–0.58], FDR <0.01) and Lymphocytes (HR 0.69 [0.64–0.76], FDR <0.01) were associated with better outcomes, while higher Basophil-to-Lymphocyte Ratio (HR 2.10 [1.17–3.78], FDR = 0.02), RDW (HR 1.16 [1.14–1.19], FDR <0.01), and Neutrophils (HR 1.06 [1.04–1.08], FDR <0.01) were associated with worse survival. Higher electrolytes (Sodium, Chloride, Potassium, Bicarbonate) were generally associated with lower hazard, likely reflecting better physiologic homeostasis. **Conclusions:** In this large real-world cohort of prostate cancer patients treated with Lu¹⁷⁷ vipivotide tetraxetan, overall survival was strongly influenced by tobacco use, comorbidity burden, and baseline laboratory markers reflecting nutritional status, hematological reserves, and immunity. These findings highlight the importance of physiologic reserve and inflammatory state in shaping outcomes with this radioligand therapy and may inform risk stratification and care strategies in routine clinical practice. Research Sponsor: Pelotonia Institute for Immuno-Oncology (PIIO) Recruitment Startup Fund; The Ohio State University Comprehensive Cancer Center (OSUCCC).

Efficacy and safety of disitamab vedotin combined with toripalimab for cisplatin-refractory advanced penile cancer: A prospective single-center study (SAVE).

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Background: Patients with advanced penile cancer progressing on cisplatin-based chemotherapy have limited options. Anti-EGFR therapy has not demonstrated significant survival benefit, and immune checkpoint inhibitors (ICIs) remain uncommon. Preclinical evidence suggests HER-2-targeted antibody-drug conjugates (ADCs) may synergize with ICIs by redirecting immune cells to the tumor microenvironment and overcoming immunosuppression. The HER-2 ADC (Disitamab Vedotin, DV) has shown preclinical activity in HER-2-positive and cisplatin-resistant penile cancer models. This study evaluated DV plus a PD-1 inhibitor (Toripalimab, T) in the cisplatin-resistant and advanced penile cancer patients. **Methods:** In this single-arm prospective study, patients received DV (2.0 mg/kg every 2–3 weeks) plus T (240 mg every 3 weeks) until progression or unacceptable toxicity. Tumor assessments tested by CT/MRI were performed every 8–12 weeks for RECIST v1.1. PD-L1 by combined positive score (CPS), tumor mutational burden (TMB) and HER-2 expression were analyzed. Follow-up continued until death or December 31, 2025. **Results:** Eight patients (median age 52 years; range 38–66) were enrolled, all previously treated with ≥ 4 cycles of cisplatin chemotherapy and 3 had received ICIs as second-line therapy (1 with ICIs plus cetuximab). Baseline staging included T4 (n = 2), N3 (n = 7), and M1 (n = 5); all target lesions were > 5 cm (perineal/inguinopelvic). After ≥ 3 treatment cycles and first scan at 8 weeks, best responses were partial response (PR) in 3 patients (1 patient achieved at first assessment, with ongoing response at 18 months and conversion of ctDNA from positive to negative; 1 with sustained response for 17 months, accompanied by reduction in circulating tumor cells; 1 with PR followed by treatment discontinuation and survival of 4 months), stable disease (SD) in 1, and progressive disease (PD) in 4 (median overall survival 5 months). Objective response rate (ORR) was 37.5% (3/8) and disease control rate (DCR) 50% (4/8). Median PFS and mOS were 3 and 5 months, respectively (Kaplan-Meier estimate). One grade ≥ 3 adverse event occurred (immune-mediated colitis with hematochezia). Grade 1–2 toxicities included leukopenia (n = 2), infusion-related fever (n = 1), sinus tachycardia (n = 1), fatigue (n = 6), rash (n = 1), and peripheral neuropathy (n = 5). Notably, HER-2 expression was assessed as negative in all patients. The patient with clearance of ctDNA had high TMB but low PD-L1 expression; others evaluable tumors had PD-L1 CPS > 40 (TMB not assessed). **Conclusions:** The combination of DV and T shows promising antitumor activity and a manageable safety profile in cisplatin-refractory advanced penile cancer patients, independent of HER-2 or PD-L1 status. These findings support further evaluation in this patients with high unmet clinical need. Clinical trial information: ChiCTR2400086605. Research Sponsor: None.

Spatial immune architecture as used to define progression and treatment response in penile squamous cell carcinoma.

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Background: Penile squamous cell carcinoma (PSCC) is a rare, aggressive malignancy with limited treatment options and poor outcomes. Although immunotherapy has shown activity in a subset of patients, the spatial immune mechanisms underlying disease progression and treatment resistance remain unknown. We hypothesized that clinical behavior in PSCC is driven by spatial organization of the tumor microenvironment (TME), rather than immune cell abundance alone. **Methods:** We conducted the first and largest longitudinal, multi-omics study of PSCC, integrating spatial transcriptomics (NanoString CosMx 6K panel) and single-cell RNA sequencing across 81 patients spanning all disease stages. Spatial profiling was performed on a tissue microarray of 35 primary tumors from 31 patients, capturing >390,000 spatially resolved cells. Patients were stratified by progression status, HPV, stage, and chemotherapy response (n=12) per RECIST 1.1. Spatial architecture was quantified using neighborhood Enrichment Analyses, Spatial cell-cell proximity and Ripley K AUC analyses. **Results:** Two distinct and clinically divergent TME architectures were identified. Tumors with favorable clinical behavior exhibited organized, antigen-driven immune surveillance. HPV-positive (n=18) and non-progressed tumors (n=17) showed coordinated neighborhoods involving myeloid cells, dendritic cells, T cells, and endothelium. Proliferative tumor programs were spatially proximal to DCs, and effector CD8 T cells maintained close coupling to tumor states, with preserved CD8-DC interactions. In contrast, HPV-negative (n=17), progressed (n=18), and chemotherapy non-responders (n=4) converged on a dysregulated inflammatory state characterized by B cell-macrophage and CAF-associated neighborhoods, EMT-hypoxia tumor programs, and immune-stromal self-clustering. These tumors showed reduced tumor-directed immune engagement and loss of organized immune domains. Notably, chemotherapy non-responders were not immune-depleted but instead exhibited dense innate and antigen-presenting cell infiltrates that were spatially confined to stromal and vascular compartments, with limited tumor-directed immune engagement. **Conclusions:** This study establishes the first spatially resolved atlas of PSCC, integrating spatial and single-cell multi-omics to uncover distinct immune and stromal architectures linked to progression and therapy resistance. Distinct TME architectures define progression and treatment resistance, supporting spatial biomarkers for patient stratification and therapeutic optimization. Research Sponsor: None.

HRS-1167 (M9466), a PARP1 inhibitor, combined with abiraterone acetate and prednisone in metastatic castration-resistant prostate cancer: A phase 1b/2 study.

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Background: PARP inhibitors combined with novel hormonal agents (NHAs) have shown improved progression-free survival in metastatic prostate cancer compared to NHA alone. HRS-1167 (M9466) is a novel highly selective PARP1 inhibitor with established antitumor activity in advanced solid tumors. This multicenter, open-label, dose-finding and efficacy expansion phase 1b/2 study assessed the safety, tolerability and preliminary efficacy of HRS-1167 combined with AA-P in mCRPC (ClinicalTrials.gov, NCT06689163). **Methods:** Chinese adult mCRPC patients with homologous recombination repair mutations who were previously treated were enrolled. Eligible patients received oral HRS-1167 at 30 mg QD or 50 mg QD, combined with AA-P (abiraterone acetate 300 mg QD; prednisone 5 mg BID). Primary objectives were safety and tolerability. **Results:** As of Oct 31, 2025, 58 patients were enrolled and treated (HRS-1167 30 mg, n = 33; HRS-1167 50 mg, n = 25; prior NHA, 100%; BRCA mutation, 44.8%). Median follow-up was 3.0 months and 6.2 months in the 30 mg and 50 mg cohorts. Preliminary efficacy was summarized in the Table. Among patients with evaluable efficacy (n = 47), prostate-specific antigen response (PSA50) rate was 36.4% (8/22) in the 30 mg cohort and 52.0% (13/25) in the 50 mg cohort. Confirmed objective response rate (cORR) was 37.5% and 14.3%, and disease control rate (DCR) was 81.8% and 92.0%, respectively. HRS-1167 plus AA-P demonstrated particularly encouraging efficacy in patients with BRCA mutations: PSA50 rate was 100% (6/6) in the 30 mg cohort and 81.8% (9/11) in the 50 mg cohort, and cORR was 100% (2/2) and 33.3% (1/3), respectively. DCR was 100% in the BRCA-mutated subgroup. Treatment-emergent adverse events (TEAEs) were reported by 26 (78.8%) and 25 (100%) patients in the 30 mg and 50 mg cohorts (grade ≥ 3 , 18.2% and 44.0%; serious, 9.1% and 32.0%). There were no TEAEs leading to death. The most common ($\geq 5\%$ of patients) grade ≥ 3 TEAEs were hematologic toxicities (anemia, 9.1% and 24.0%; decreased platelet count, 6.1% and 8.0%; decreased white blood cell count, 0% and 12.0%; decreased neutrophil count, 3.0% and 8.0%). **Conclusions:** HRS-1167 combined with AA-P showed promising efficacy in patients with mCRPC, especially those with BRCA mutations. The combination was well-tolerated with no new safety signals identified. Clinical trial information: NCT06689163. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

	Overall		BRCAm	
	30 mg (N = 22)	50 mg (N = 25)	30 mg (N = 6)	50 mg (N = 11)
PSA50, n (%)	8 (36.4)	13 (52.0)	6 (100)	9 (81.8)
Time to PSA progression, months, median (95% CI)	NR (3.7, NR)	6.5 (5.5, NR)	NR (4.6, NR)	6.5 (3.8, NR)
cORR, n/N* (%)	3/8 (37.5)	1/7 (14.3)	2/2 (100)	1/3 (33.3)
DCR, n (%)	18 (81.8)	23 (92.0)	6 (100)	11 (100)

N = efficacy evaluable patients; N* = patients with target lesions at baseline. PSA and tumor responses were confirmed.

PSA, prostate-specific antigen; cORR, confirmed objective response rate; DCR, disease control rate; NR, not reached.

Evaluation of the safety, efficacy and dosimetry of TRC003 in metastatic castration-resistant prostate cancer: A prospective, open-label, single-arm study.

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Background: TRC003 (also named as ^{225}Ac -PSMA-313) is a novel molecule of targeted alpha therapy (TAT) that administers alpha-particle radiation to cancer cells expressing Prostate Specific Membrane Antigen (PSMA). In this study, we plan to investigate preliminary safety, efficacy and dosimetry of TRC003 in patients with metastatic castration-resistant prostate cancer (mCRPC). **Methods:** This is a prospective, open-label, single-arm, single center study in accordance with ICH GCP guidelines. The patients with progressive PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibitors (ARPIs) and/or taxane-based chemotherapy were recruited and received TRC003 treatment intravenously at 200 μCi (7.4 MBq) doses administered every 8 weeks per cycle for 4 cycles followed by expanded 4 cycle treatment if the participants continued to be benefit from the treatment. Adverse events, ORR, PSA response, bPFS, rPFS and OS were evaluated. In addition, the SPECT images were acquired with noncircular orbit, 120 project views over 360° at 4, 24, 48 and 96 hours after administration for dosimetry analysis. **Results:** From Feb 2024 to Jan 2026, 15 patients were included with an average age of 67.1 yr and median baseline PSA of 98.6 ng/mL. 11 (73.3%) participants received ARPI and taxane-based chemotherapies while 4 (26.7%) participants received only ARPI previously. Median baseline SUVmax and SUVmean on PSMA-PET were 32.7 (14.7–60.26) and 18.2 (9.51–34.73), respectively. A total of 63 cycles of TRC003 were administered, with a median of 4 cycles per patient. The most common AE was anemia (80%) and dry mouth (73.3%). Grade 3 treatment-related adverse events occurred as anemia (20%), lymphocytopenia (13.3%), weight loss (13.3%), thrombocytopenia (6.7%), and vomiting (6.7%). No treatment-related Grade ≥ 4 AE were observed. No kidney related toxicities were observed. The ORR of all patients was 45.5%, whereas the ORR reached 57.1% in the subset of patients who had received prior treatment of ARPIs and taxanes. The median tumor absorbed dose was 2.40 ± 3.33 Gy (soft lesions: 5.03 ± 5.51 vs bone: 1.65 ± 2.19 Gy). The absorbed doses of kidneys, liver and spleen were 1.56 ± 0.38 , 1.07 ± 0.19 and 0.54 ± 0.29 Gy, respectively. The absorbed dose coefficients of tumors, kidney and liver were 0.36 ± 0.50 (soft lesions 0.75 ± 0.82 vs bone 0.25 ± 0.33), 0.23 ± 0.07 , 0.16 ± 0.03 Gy/MBq. **Conclusions:** TRC003 was safe and well-tolerated, and exhibited efficacy for mCRPC patients who were resistant to ARPI or chemotherapy. Overall TRC003 is a promising radiopharmaceutical agent for the treatment of mCRPC. Clinical trial information: ChiCTR2400083275. Research Sponsor: C-Ray therapeutics.

Safety and preliminary efficacy of M9466 (HRS-1167) in combination with abir-
aterone acetate and prednisone/prednisolone (AA-P) in patients (pts) with meta-
static prostate cancer in the phase 1 DDRiver 501 study.

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Background: M9466 (HRS-1167) is a highly potent, selective next-generation PARP1 inhibitor being investigated in pts with locally advanced/metastatic solid tumors. Here we report safety and preliminary efficacy data from Module 3 of the DDRiver 501 study, a Phase 1, open-label, global multicenter study, evaluating M9466 with AA-P in pts with metastatic prostate cancer (NCT06421935). **Methods:** DDRiver 501 Module 3 enrolled eligible pts with metastatic castration-resistant prostate cancer (mCRPC) or metastatic hormone-sensitive prostate cancer (mHSPC), irrespective of prior anticancer therapy received. Pts received M9466 (either 50 or 100 mg once-daily) with AA-P until disease progression. Primary objective was safety. Additional objectives included efficacy (objective response rate [ORR], PSA50 [confirmed decrease in prostate-specific antigen levels of >50% from baseline]), pharmacokinetics (PK), molecular responses (e.g. >50% reduction from baseline of methylation-based tumor fraction in circulating tumor DNA [ctDNA]) and tumor genetic profiling. **Results:** As of Nov 21, 2025, Module 3 enrolment was complete (N=21; M9466 50 mg n=10, 100 mg n=11; mHSPC n=1, mCRPC n=20; prior treatment included: PARP inhibitors n=0, androgen receptor pathway inhibitors [ARPI] n=21). Thirteen (62%) pts carried HRR gene mutations, including four (19.0%) with BRCA1/2 mutations, by ctDNA analysis. Pts received M9466 for a median (range) of 18.1 (6.0–30.1) and 26.9 (6.0–42.0) weeks (50 and 100 mg arms respectively). Safety outcomes are presented (table). No dose-limiting toxicities or serious treatment-related adverse events to any study intervention were observed. Across pts with baseline RECIST measurable disease, confirmed ORR was 18.8% (3/16, 95% CI: 4.0, 45.6). Two of the three responders had RAD50 loss of function mutations. In pts with baseline PSA ≥2 ng/mL, 3/17 (17.6%) achieved a PSA50 response. Molecular response and PK data will also be presented. **Conclusions:** Preliminary data from DDRiver 501 Module 3 demonstrate M9466 with AA-P is generally well tolerated and demonstrates antitumor activity in ARPI-pretreated pts with mHSPC/mCRPC. Clinical trial information: NCT06421935. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Safety overview.		
n (%)	M9466 50 mg (n=10)	M9466 100 mg (n=11)
Any TEAE	9 (90.0)	11 (100)
TEAEs (>25% of total pts)		
Anemia	7 (70.0)	9 (81.8)
Fatigue	6 (60.0)	2 (18.2)
Platelet count decreased	2 (20.0)	5 (45.5)
Neutrophil count decreased	3 (30.0)	3 (27.3)
Any ≥Grade 3 TEAE	4 (40.0)	5 (45.5)
≥Grade 3 TEAEs (≥n=2 of total pts)		
Anemia	2 (20.0)	5 (45.5)
Platelet count decreased	1 (10.0)	1 (9.1)
Neutrophil count decreased	1 (10.0)	1 (9.1)
M9466-related TEAEs leading to:		
Discontinuation	0	1 (9.1)*
Reduction	2 (20.0)	4 (36.4)
Interruption	4 (40.0)	4 (36.4)

*Due to anemia. TEAE, treatment-emergent adverse events.

Cell-free DNA nucleosome and genomic signatures as predictors of outcomes with radium-223 in metastatic castration-resistant prostate cancer.

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Background: Radium-223 (Ra-223) is a bone-seeking alpha emitter that induces double-stranded DNA breaks. Previous studies have shown Ra-223 can prolong survival of men with mCRPC with symptomatic bone metastases and no visceral metastases. However, clinical outcomes are heterogeneous, and predictive biomarkers for lack of benefit or progression with visceral disease are lacking. We evaluated whether genomic and epigenetic features derived from cell-free DNA (cfDNA) could identify tumor characteristics associated with favorable or unfavorable outcomes with Ra-223 therapy. **Methods:** Pre-treatment plasma cfDNA was analyzed from 137 mCRPC patients who received Ra-223. Ultra-low pass and deep whole genome sequencing were performed. Tumor fraction and copy number alterations were estimated using ichorCNA. Transcription factor (TF) activity was derived by nucleosome profiling of cfDNA fragments around transcription starts sites (TSS) and TF binding sites using the tools Griffin and TritonNP. Genomic and epigenetic features were associated with clinical outcomes including completion of six Ra-223 cycles, overall survival, and development of new nodal, visceral, or liver metastases. A multimodal binary classifier integrating copy number variation and TF activity was constructed using LASSO feature selection and XGBoost with repeated, nested 5-fold cross-validation. External validation was performed using independent cohorts of mCRPC patients treated with docetaxel (n=46) or other agents (n=142) for the prediction of new metastatic involvement. **Results:** Higher pre-treatment tumor fraction and TF activity at specific loci including HIF3A, ZNF770, and PRDM6 were associated with adverse outcomes. A binary classifier predicting completion of Ra-223 demonstrated strong discrimination in cross-validation, with similar performance for prediction of liver metastasis progression. External validation in independent cohorts demonstrated moderate discrimination, supporting generalizability across treatment contexts. **Conclusions:** Our findings demonstrate that analysis of cfDNA-derived genomic and epigenomic features can identify biologically relevant tumor characteristics associated with benefit from Ra-223 in mCRPC. These findings support the development of minimally invasive biomarkers to refine patient selection and risk stratification. Our ongoing analyses look to integrate mutations, amplifications, and deletions in key disease-related genes to further explore tumor genotype-phenotype associations with Ra-223 outcomes. Research Sponsor: Dana-Farber Cancer Institute; Fred Hutch Cancer Center; Bayer.

Quality of life analysis from a multicenter, randomized, phase 2, investigator-initiated ETCTN trial of olaparib + radium-223 versus radium-223 in metastatic castration-resistant prostate cancer with bone metastases (COMRADE).

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Background: Radium-223 is an α -emitting radioisotope that improves overall survival in men with metastatic castration resistant prostate cancer (mCRPC) and bone metastases (BM). In the ALSYMPCA trial, radium-223 was also associated with improved quality of life (QOL), delayed time to first opioid use, and pain palliation. We previously reported superior radiographic progression free survival (rPFS) with the addition of olaparib to radium-223 in the randomized phase 2 COMRADE study (NCT03317391). We now report patient-reported QOL outcomes from the trial. **Methods:** Patients were randomized 1:1 to olaparib 200 mg twice daily plus radium-223 (Arm A) or radium-223 alone (Arm B). QOL was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Brief Pain Inventory (BPI) at baseline and every 12 weeks. Mixed-effects ANCOVA models assessed treatment effects on QOL changes from baseline, adjusting for baseline score, timepoint, age, and Eastern Cooperative Oncology Group performance status. Least-squares (LS) mean changes were reported for each arm with between-arm differences and 95% confidence intervals. Analysis was limited to patients with baseline and ≥ 1 post-baseline assessment within 24 weeks. **Results:** Of 114 treated patients, 74 (65%) were evaluable for QOL analysis (Arm A, $n = 40$; Arm B, $n = 34$), including 71 (62%) for FACT-P and 72 (63%) for BPI pain severity and pain interference. Baseline characteristics were well balanced: median age was 70 and 72 years, ECOG PS 1 was present in 60% and 62%, prior docetaxel was received by 55% and 50%, > 20 bone metastases were present in 45% and 47%, and pain medication use at baseline was reported in 60% and 72% of patients in Arms A and B, respectively. There were no significant differences in LS mean change from baseline in FACT-P total score between arms at week 12 (Arm A: -5.09 vs Arm B: -0.23 ; difference -4.87 , 95% CI -13.4 to 3.62) or week 24 (Arm A: -1.41 vs Arm B: -3.20 ; difference 1.79 , 95% CI -8.28 to 11.9). Similarly, no significant between-arm differences were observed in LS mean changes in BPI pain severity at week 12 (difference 0.44 , 95% CI -0.44 to 1.33) or week 24 (difference -0.20 , 95% CI -1.32 to 0.93). Arm B showed greater improvement in BPI pain interference at week 12 (LS mean change: Arm A $+0.21$ vs Arm B -0.88 ; difference 1.09 , 95% CI 0.14 to 2.05), but this difference was not sustained at week 24 (difference -0.27 , 95% CI -1.37 to 0.82). **Conclusions:** In this phase 2 trial, the addition of olaparib to radium-223 achieved superior rPFS without significant detriment to patient-reported QOL or pain compared to radium-223 alone, supporting the tolerability of this combination in mCRPC patients with BM. Clinical trial information: NCT03317391. Research Sponsor: National Cancer Institute.

Clinical validation of circulating tumor cell synaptophysin and androgen receptor expression in metastatic prostate cancer phenotypes.

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Background: Chronic exposure to androgen receptor (AR) targeted therapies can drive lineage plasticity, promoting the emergence of neuroendocrine (NE) prostate cancer (NEPC) and treatment resistance. NEPC is characterized by a phenotypic shift, with loss of AR expression and emergence of markers (e.g., synaptophysin, SYP). To definitively diagnose NEPC, a metastatic biopsy is typically required; however, there are numerous barriers to obtaining a timely tissue diagnosis. As such, there is an unmet need for blood-based assays that can accurately identify treatment-emergent NEPC. In this study, we evaluate concordance between circulating tumor cell (CTC) SYP and AR expression patterns in patients with and without evidence of NE differentiation on tissue histology. **Methods:** Blood for CTC analysis was prospectively collected from patients with advanced prostate cancer. Patients were retrospectively assigned to either an adenocarcinoma (AR-positive) or NE differentiated (SYP-positive) group based on clinical and patho-genomic factors. Amphicrine PC was included in NE differentiated cohort. The RareCyte system was used to generate slides for CTC-based immunofluorescent (IF) analysis for SYP and AR. Associations between CTC SYP and AR expression, PSA at time of CTC collection, and overall survival (OS) were assessed for patients with ≥ 5 CTCs using Wilcoxon rank-sum test, Fisher's exact test, and Kaplan-Meier analyses. **Results:** We enrolled 52 patients with metastatic castration-resistant prostate cancer (mCRPC); 26 were classified as NE differentiated and 26 as AR-positive adenocarcinoma. Median time between biopsy and CTC collection was 10.6 months (IQR 4.1–34.3) and 19.4 months (IQR 3.5–66.4) for the NE differentiated and AR-positive adenocarcinoma cohorts respectively. NE differentiated patients had a significantly higher fraction of SYP-positive CTCs (median 28.6 % vs 0%, $p = 0.0084$), whereas patients in the adenocarcinoma cohort had a higher fraction of AR-positive CTCs (median 96.7% vs 0.0%, $p = 0.0004$). Phenotype classification based on high AR or SYP expression ($> 80\%$ of CTCs positive) significantly differentiated cohorts and was strongly associated with tissue histology ($p = 0.0048$). PSA level at the time of CTC collection was significantly lower in the NE differentiated cohort (median 3.8 vs 486.9 ng/mL, $p = 0.0001$). There was no difference in OS from time of diagnosis or time of metastasis between groups. **Conclusions:** SYP and AR CTC expression demonstrated strong concordance with tissue histology and established clinical features of NEPC and AR-positive adenocarcinoma. These early findings support the feasibility of CTC expression profiling to identify NE biomarker expression. However, results are only hypothesis-generating and prospective validation with matched tissue biopsy in a larger cohort with adequate follow up is warranted. Research Sponsor: None.

Impact of baseline demographics on therapy management in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with talazoparib (TALA) + enzalutamide (ENZA) in the TALAPRO-2 study: Extended follow-up.

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Background: The randomized, Phase 3 TALAPRO-2 trial showed improved radiographic progression-free survival (rPFS) and overall survival (OS) in pts with mCRPC treated with TALA + ENZA vs placebo + ENZA in two cohorts: unselected and homologous recombination repair (HRR)-deficient pts. Median TALA duration of treatment (DoT) was 19.7 mo (unselected) and 20.3 mo (HRR-deficient). Study protocol required dose reduction for pts with reported Grade 3 or 4 hematologic adverse events (AEs); 55% of pts in both cohorts had a TALA dose reduction due to AEs at final analysis. We analyze the impact of baseline demographics on TALA dose reductions and clinical outcomes in the TALA + ENZA arm. **Methods:** Pts in the TALA + ENZA arm received TALA 0.5 mg (in case of moderate renal impairment [30–59 mL/min/1.73 m²] 0.35 mg) + ENZA 160 mg PO QD. Time-to-event endpoints were summarized by the Kaplan–Meier method and compared by log-rank test. **Results:** In both cohorts, pts with a TALA dose reduction due to any cause (AEs and other reasons) were more likely to be older, be of Asian ethnicity, have lower bodyweight (BW), and have mild renal impairment vs pts without a TALA dose reduction (Table). Fewer pts with a TALA dose reduction than without discontinued treatment before wk 16 in the unselected (6.1% vs 20.0%) and HRR-deficient (2.7% vs 13.8%) cohorts. Median TALA DoT was longer in pts with a TALA dose reduction in the unselected cohort and similar between groups in the HRR-deficient cohort (Table). No clinically meaningful differences were observed in rPFS or OS in pts with a TALA dose reduction vs without in both cohorts (unselected: rPFS HR 0.94; 95% CI 0.70–1.25; OS HR 0.90; 95% CI 0.68–1.20; HRR-deficient: rPFS HR 0.96; 95% CI 0.64–1.44; OS HR 0.98; 95% CI 0.64–1.49; Table). **Conclusions:** Pts with specific baseline demographics (older, Asian ethnicity, lower BW, mild renal impairment) were more likely to have a TALA dose reduction. TALA dose reduction did not negatively impact TALA DoT or efficacy in pts who received TALA + ENZA in the TALAPRO-2 trial. Clinical trial information: NCT03395197. Research Sponsor: This study was funded by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide.

	Unselected with dose reduction (n=228)	Unselected without dose reduction (n=170)	HRR-deficient with dose reduction (n=111)	HRR-deficient without dose reduction (n=87)
Median age (range), y	73.0 (52–90)	70.0 (41–87)	73.0 (53–90)	68.0 (41–88)
White, %	53.1	70.0	60.4	78.2
Black/African American, %	2.6	2.9	3.6	2.3
Asian, %	39.5	21.2	31.5	11.5
Median weight (range), kg	75.0 (45–169)	85.0 (59–155)	78.0 (45–118)	85.0 (60–135)
Mild renal impairment (60–89 mL/min/1.73 m ²), %	52.2	36.5	59.5	34.5
Median TALA DoT (range), mo	23.0 (1.9–67.4)	15.2 (0.1–58.6)	20.3 (2.6–61.1)	20.8 (0.3–58.6)
Median rPFS (95% CI), mo	33.1 (27.4–41.4)	33.0 (22.3–41.4)	33.1 (24.3–38.5)	30.2 (18.1–46.7)
Median OS (95% CI), mo	46.9 (40–53.3)	45.1 (30.7–57.2)	41.9 (35.4–not reached [NR])	48.4 (31.5–NR)

Genomic landscape of *TP53* Y220C–mutated clinically advanced prostate carcinoma (CAPC).

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Background: The *TP53* Y220C base substitution mutation has become a significant therapeutic target with the development of reactivator drugs that restore TP53 function with a regulatory function in the cell cycle. However, its real-world prevalence and associated genomic landscape is not established in CAPC. Data on concurrent genomic alterations (GA) may guide the development of combinatorial therapeutic strategies. **Methods:** 26,156 cases of CAPC underwent hybrid capture-based comprehensive genomic profiling (CGP) to study all classes of GA including base substitutions, short insertions, deletions, copy number changes, rearrangements and fusions. Microsatellite instability (MSI) status and tumor mutation burden (TMB) were determined from the sequencing data; comparisons utilized the Fisher Exact method. **Results:** 144 CAPC (0.6%) of CAPC cases featured *TP53* Y220C mutation (*TP53* Y220C+). Patients with *TP53* Y220C+ CAPC had slightly higher median age (70.0 vs 68.2; $p = 0.020$) and numerically lower frequency of *TMPRSS2* GA (33.0% vs 39.4%; Not significant (NS)). GA potentially associated with CAPC primary hormonal-based therapy response more frequently found in *TP53* Y220C+ cases included *SPOP* (10.5% vs 1.4%; $p < 0.0001$) with *AR* GA (13.6% vs 11.3%; NS) being similar in both groups. GA linked to PARP inhibitor response slightly more frequent in *TP53* Y220C+ cases included *BRCA2* GA (8.7% vs 3.5%; $p = 0.0003$) and *ATM* GA (5.9% vs 4.2%; NS). GA in *RAD21* were slightly higher in *TP53* Y220C- CAPC (14.8% vs 8.3%; $p = 0.029$). GA in *PIK3CA* (6.6% vs 7.0%) and *PTEN* (32.4% vs 34.5%) were similar in the two groups. Biomarkers likely associated with benefit with anti-PD1/L1 agents were very low in both groups, included higher frequency of *CDK12* GA (5.4% vs 0.7%; $p < 0.0001$) in *TP53* Y220C+ cases and higher frequencies of MSI-High status (2.7% vs 0.0%; $p = 0.045$), mean TMB (3.8 vs 2.1 mutations/Mb; $p < 0.0001$) and TMB > 10 mutations/MB (4.4% vs 0.0%; $p = 0.010$) in *TP53* Y220C- cases. **Conclusions:** *TP53* Y220C is a rare finding in CAPC, but it may offer a potential therapeutic avenue for these patients whose tumors feature such a mutation. In addition, *TP53* Y220C+ cases appear to be genomically relatively distinct from *TP53* Y220C- CAPC cases and may feature genomic signatures that could influence treatment selection and trial design. Study limitations include a retrospective, descriptive design, a lack of clinical data annotation, and selection and confounding biases, so our findings are hypothesis-generating. Research Sponsor: None.

Selective GA in *TP53* Y220C+ vs *TP53* Y220C- in patients with CAPC.

	<i>TP53</i> Y220C+ CAPC (144 cases)	<i>TP53</i> Y220C- CAPC (26,012 cases)	P Value
Median Age (yrs)	70 (46-89+)	68 (35-89+)	
<i>TP53</i> (all)	100.0%	39.7%	<0.0001
<i>TP53</i> (non-Y220C)	7.6%	39.7%	<0.0001
<i>SPOP</i>	10.5%	1.4%	<0.0001
<i>BRCA2</i>	8.7%	3.5%	0.0003
<i>CDK12</i>	5.4%	0.7%	<0.0001
<i>APC</i>	9.1%	4.2%	0.0004
MSI-High	0.0%	2.7%	0.045
Mean TMB	2.1	3.8	<0.0001

Clonal hematopoiesis-related outcomes associated with radioligand therapy in prostate cancer: A “real-world” analysis.

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Background: Radioligand therapy with radium-223 (Rad) and lutetium-177 (Plu) demonstrates notable hematologic toxicities in patients (pts) with prostate cancer (PC), including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Delivery of ionizing radiation to the bone microenvironment is a known risk factor for accelerating clonal hematopoiesis, although the incidence of clonal cytopenias with these agents is not well characterized. We hypothesized that pts treated with Rad and/or Plu would have higher risk of clonal cytopenia of undetermined significance (CCUS) vs matched controls in the “real-world”. **Methods:** We performed a retrospective study using de-identified aggregate data from the TriNetX US Research Collaborative Network from January 2010 to December 2025. Adult males with PC who received ≥ 1 administration of Plu and/or Rad were included; pts with prior myeloid malignancy were excluded. Primary outcomes were incidence of CCUS and MDS. Propensity score matching (PSM) was performed based on age, race, prior diagnosis of leukopenia, anemia, thrombocytopenia, or pancytopenia. Risk ratios (RR) with 95% confidence intervals (CI) were calculated. **Results:** We identified 2,569 pts treated with Plu alone and 2,007 treated with Rad alone and compared them with pts with advanced PC without exposure to either agent (unexposed control) (Table 1). After PSM, the incident risk of CCUS was greater in Rad-exposed pts (RR 2.62, 95% CI 1.45 – 4.73, $p < 0.001$) while Plu was not associated with a significant increase in CCUS or MDS. Direct comparison after PSM ($n=1,433$) demonstrated lower risk of pancytopenia (RR 0.46, 95% CI 0.37 – 0.56, $p < 0.001$) and CCUS (RR 0.41, 95% CI 0.20 – 0.81, $p=0.008$) in Plu vs Rad. In unadjusted analysis, pts receiving both Plu and Rad had increased incidence of CCUS vs Plu alone (RR= 3.64, 95% CI 1.87 – 7.07, $p < 0.001$) and higher risk of MDS vs either agent alone. **Conclusions:** This “real-world” analysis demonstrates that compared with unexposed controls, Rad – but not Plu – is associated with an increased risk of CCUS. Treatment with Plu and Rad portends a higher risk of CCUS than Plu alone, as well higher risk of MDS than either drug alone. Study limitations include its retrospective nature, missing/ unknown data (e.g. bone marrow and mutation analysis), and potential selection and confounding biases. As treatment sequencing evolves for pts with metastatic PC, further evaluation of clonal hematopoiesis, MDS/AML with adequate sample size and follow up in this population is warranted. Research Sponsor: None.

¹⁷⁷ Lu-PSMA-617				
	Exposed (n = 2,569)	Unexposed (n = 2,569)	Risk Ratio (95% CI)	p-value
CCUS	1.03% (26)	0.67% (17)	1.54 (0.84 – 2.82)	0.16
MDS	0.94% (24)	0.55% (14)	1.72 (0.89 – 3.32)	0.10
Radium-223				
	Exposed (n = 2,007)	Unexposed (n = 2,007)	Risk Ratio (95% CI)	p-value
CCUS	1.97% (39)	0.75 (15)	2.62 (1.45 – 4.73)	<0.001
MDS	0.85% (17)	0.75% (15)	1.13 (0.57 – 2.26)	0.72

Safety and efficacy of QLC5508 (MHB088C) in heavily-treated patients with metastatic castration-resistant prostate cancer: Updated data from a phase 1/2 trial.

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Background: QLC5508 (MHB088C), a novel B7-H3-targeted antibody-drug conjugate with high cell-binding activity and internalization rate, contains SuperTopoi payload which is 5 to 10 times more potent than Dxd. The preliminary data of a phase 1 study indicated the promising anti-tumor activity and tolerability of QLC5508 in patients (pts) with solid tumors, including metastatic castration-resistant prostate cancer (mCRPC). Here we report the updated results of efficacy and safety in pts with mCRPC. **Methods:** This multi-center phase 1/2 trial consisted of dose-escalation stage and dose-expansion stage. In dose-escalation stage, QLC5508 was administered via intravenous infusion at dosage ranging from 0.8 mg/kg to 4.0 mg/kg every two (Q2W) or three weeks (Q3W) in pts with various advanced solid tumors. Then, pts with mCRPC were recruited if they failed or intolerable to standard treatment, including second-generation androgen receptor pathway inhibitors (ARPIs) and/or taxane-based chemotherapy. Dose levels of 1.6 mg/kg Q2W, 2.0 mg/kg Q2W, and 2.4 mg/kg Q3W were selected. The primary endpoints were safety and tolerability. The secondary endpoints were objective response rate (ORR), disease control rate (DCR), and radiological progression-free survival (rPFS) per RECIST v1.1 and PCWG3, and prostate-specific antigen (PSA) response rate. **Results:** As of Nov 30, 2025, 59 pts were enrolled (≥ 3 lines of prior treatment: 74.6%; ≥ 3 lines of prior second-generation ARPIs: 28.8%; prior taxane: 84.7%; ≥ 2 lines of prior taxane: 16.9%). Grade ≥ 3 treatment-emergent adverse events (TEAEs) with incidence of $> 20\%$ were neutrophil count decreased (25.4%), anemia (23.7%), and white blood cell decreased (20.3%). Grade ≥ 3 gastrointestinal TEAEs occurred in two (3.4%) pts, both unrelated to the treatment. Intestinal lung disease occurred in one (1.7%) patient from 1.6 mg/kg Q2W dose level. TEAEs leading to treatment discontinuation and dose reduction occurred in one (1.7%) and six (10.2%) pts, respectively. The median rPFS was not reached (95% confidence interval [CI], 13.11-not evaluable [NE]), and the 12-month rPFS rate was 71.7% (95% CI, 52.55%-84.26%). In 38 pts at 2.0 mg/kg Q2W dose level, the median rPFS was not reached (95% CI, 13.11-NE), and 12-month rPFS rate was 78.6% (95% CI, 50.67%-91.80%). In 31 pts at 2.0 mg/kg Q2W dose level who had received prior second-generation ARPIs and taxane, the median rPFS was 13.11 months (95% CI, NE-NE). In 31 pts with target lesion at baseline, confirmed ORR and DCR was 22.6% (95% CI, 9.6%-41.1%) and 96.8% (95% CI, 83.3%-99.9%), respectively. Thirteen pts (22.8%) achieved PSA₅₀ response. **Conclusions:** QLC5508 showed prolonged rPFS as well as manageable safety profile in heavily treated pts with mCRPC. A phase 3 study is currently being planned. Clinical trial information: NCT07102004. Research Sponsor: Qilu Pharmaceutical Co., Ltd.; Minghui Pharmaceutical.

Phase 1, multicenter, open-label study of HSK46575 in patients with metastatic castration-resistant prostate cancer progressing after next-generation hormonal agents and chemotherapy.

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Background: The development and progression of prostate cancer are regulated by steroid hormones. HSK46575 Tablet is a novel oral small-molecule inhibitor of cytochrome P450 11A1 (CYP11A1), which can block the production of all downstream steroid hormones and their precursors, thereby reducing the activation of the androgen receptor (AR) signaling pathway and inhibiting tumor progression. Herein, we report the safety and efficacy of HSK46575 in patients with metastatic castration-resistant prostate cancer (mCRPC). **Methods:** This multicenter, open - label Phase I clinical trial had two parts: Phase Ia (dose escalation and expansion) and Phase Ib (dose optimization). Eligible patients were mCRPC patients who failed at least one NHA treatment and either failed, were intolerant to, or refused at least one line of chemotherapy. Phase Ia's dose escalation used a "3 + 3" design to explore four doses (3 mg, 10 mg, 30 mg, 60 mg), and dose expansion was done at 30 mg due to good safety and preliminary efficacy. The primary endpoints were safety and the recommended Phase II dose (RP2D). **Results:** As of November 4, 2025, 27 subjects were enrolled, with a median follow-up of 3.7 months and a median age of 68 years (range: 51-82 years). Among them, 15 (55.6%) had AR ligand -binding domain (AR-LBD) mutations, and 12 (44.4%) had received taxane-based chemotherapy before. No dose-limiting toxicities were observed in any dose group. Treatment-related adverse events (TRAEs) occurred in 18 subjects (66.7%), most of which were Grade 1-2. The most common TRAEs were alanine aminotransferase elevation (18.5%), sinus bradycardia (11.1%), and nausea (11.1%). No adverse events leading to permanent treatment discontinuation or death were observed. Prostate-specific antigen (PSA) assessment was available for 26 subjects, with PSA response rates confirmed after at least 3 weeks. The PSA₃₀ and PSA₅₀ response rates were 42.3% and 34.6% in the total population, 71.4% and 57.1% in AR-LBD mutant subjects (n = 14), and 75% and 58.3% in the 30 mg dose group with AR-LBD mutations (n = 12). The PSA₅₀ response rate was 12.5% (1/8) in the 30 mg dose group with AR-LBD wild-type. Fourteen subjects were eligible for soft tissue assessment, 8 of whom had AR-LBD mutations. One partial response (PR) was seen during treatment in an AR-LBD mutant patient in the 30 mg dose group, leading to an objective response rate (ORR) of 14.3% in this population. The radiographic progression-free survival (rPFS) has not been reached. The 6-month rPFS rates were 67.5% in the total population and 76.2% in the AR - LBD mutation population. **Conclusions:** HSK46575 shows a manageable safety profile and preliminary antitumor activity, especially in the population with AR - LBD mutations. These findings support further exploration in the mCRPC population. Clinical trial information: NCT07007910. Research Sponsor: None.

Integrated clinical and molecular characterization of WNT pathway alterations in metastatic castration-resistant prostate cancer (mCRPC) liver metastases (mets).

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Background: mCRPC patients (pts) with liver mets (LM) have an aggressive clinical course and poor response to established treatments. LM frequently exhibit low PSMA expression, limiting the utility of PSMA-targeted therapies. The mechanisms driving hepatic organotropism and therapy resistance in advanced disease are poorly understood. **Methods:** We analyzed metastatic biopsies with matched transcriptional and genomic profiling from 4 independent mCRPC cohorts from the Stand Up To Cancer/Prostate Cancer Foundation (SU2C/PCF) West Coast Dream Team, SU2C/PCF East Coast Dream Team, University of Washington rapid autopsy program, and Weill Cornell Medicine. Tumors were classified by *FOLH1* gene expression tertile and by androgen receptor (AR) and neuroendocrine (NE) gene signature expression. Individual cohorts were assessed for differential gene expression and validated between cohorts. Cohorts were pooled for genomic and survival analyses. Multivariable Cox proportional hazard models were used to assess outcomes. **Results:** 595 mCRPC biopsies were analyzed, comprising 88 (15%) liver, 130 (22%) non-liver visceral, 166 (28%) bone, and 211 (35%) lymph node mets. 54% of pts had prior androgen receptor pathway inhibitor (ARPI) exposure and 29% had prior taxane chemotherapy. LM had lower *FOLH1* expression ($\log_2FC = -1.5$, $q < 0.001$) than non-LM. Amongst *FOLH1*-low LM, 32% had elevated NE gene expression, with high histological concordance (80% NE prostate cancer [NEPC], 9% adenocarcinoma with NE features). WNT pathway mutations in *APC* or *CTNNB1* were enriched in LM compared to non-LM (20% vs. 10%, $p = 0.01$) and *FOLH1*-low compared to *FOLH1*-high mets (16% vs. 6%, $p = 0.006$). Notably, in *FOLH1*-low LM, *APC* mutations were exclusively found in tumors with low NE gene expression (28% vs. 0%, $p = 0.02$). In contrast, NE LM were enriched for alterations in *RB1* (71% vs. 15%, $p < 0.001$) and homologous recombination repair genes (41% vs. 15%, $p = 0.04$). Compared to NE LM, non-NE *FOLH1*-low LM demonstrated persistence of AR signaling, enrichment for inferred β -catenin transcription factor activity, and upregulation of adaptive metabolic pathways including HIF-1 α mediated hypoxia signaling and unfolded protein response. β -catenin downstream targets including *CCND1*, *MYC*, *MSX2*, *AXIN2*, and *LEF1* were transcriptionally upregulated, while AR targets *STEAP1* and *KLK2* remained highly expressed. In the overall cohort, WNT pathway mutations were associated with shorter treatment duration on first-line ARPI (HR 2.2, 95% CI 1.04–4.8, $p = 0.03$) and inferior overall survival from start of first-line ARPI (HR 1.7, 95% CI 1.04–2.7, $p = 0.03$). **Conclusions:** WNT pathway alterations are enriched in a clinically aggressive PSMA-low subset of non-NE mCRPC that maintains luminal markers, suggesting distinct clonal evolution from NEPC and clinical actionability with emerging therapies. Research Sponsor: Prostate Cancer Foundation.

Phase I dose-escalation results of ^{177}Lu -NYM032 in patients with progressive metastatic castration-resistant prostate cancer (mCRPC).

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Background: ^{177}Lu -NYM032 is a novel prostate-specific membrane antigen (PSMA)-targeted radioconjugate with optimized properties. Phase I dose-escalation study evaluated its safety, tolerability, pharmacokinetics, radiation dosimetry and preliminary antitumor activity in patients with mCRPC. **Methods:** Eligible patients had PSMA-positive mCRPC confirmed by ^{68}Ga -NYM032 PET/CT, no discordant lesions on ^{18}F -FDG PET/CT, progression after ≥ 1 AR-targeted therapy and 1–2 prior taxane regimens (or unsuitability/refusal), ECOG 0–2, and no prior radioisotope therapy. A modified 3+3 dose-escalation design was used (^{177}Lu -NYM032: 1.9–7.4 GBq). Pharmacokinetics and dosimetry were evaluated using sequential blood samples and SPECT/CT imaging post-administration (Cycle 1: 2h, 24h, 48h, 7d, 14d; Cycles 2–4: 48h). Primary objectives were safety and maximum tolerated dose (MTD); secondary objectives included pharmacokinetics, dosimetry, and antitumor activity. **Results:** Eleven patients were enrolled across four dose levels: 1.9 GBq (n = 1), 3.7 GBq (n = 4), 5.55 GBq (n = 3), and 7.4 GBq (n = 3). Ten patients completed the study and one patient (3.7GBq) withdrew consent and discontinued the study prior to DLT evaluation. Ten Patients received 2–6 treatment cycles (at 6-week intervals) of ^{177}Lu -NYM032. Four patients were administered up to 6 cycles at 7.4 GBq per cycle, reaching a total cumulative activity of 44 GBq. Treatment was well tolerated; with most treatment-emergent adverse events being grade 1–2. Grade ≥ 3 TEAEs related to ^{177}Lu -NYM032 were limited to anemia, decreased lymphocyte count, and hypokalemia. No dose-limiting toxicities were observed. Clearance of ^{177}Lu -NYM032 from the kidney occurs rapidly (half-life: 18.37–38.66 hours). Physiological distribution of the radiopharmaceutical was observed including in the salivary glands, lacrimal glands, liver, spleen, kidneys, and intestines—consistent with known PSMA expression patterns. While the mean tumor absorption dose (7.73 Gy/GBq in cycle 1) decreased over time, mean absorbed doses per cycle to kidneys and salivary glands remained relatively stable across the administered dose range (1.9–7.4 GBq): kidney doses were 0.47–0.64 Gy/GBq in cycle 1 and 0.42–0.63 Gy/GBq in cycles 2–4; salivary gland doses were 0.42–1.34 Gy/GBq in cycle 1 and 0.43–0.83 Gy/GBq in cycles 2–4. Among 10 evaluable patients, objective response rate was 20% and disease control rate was 80%. Of 3 RECIST v1.1 measurable, 2 (66.7%) partial responded, 1 (33.3%) stable. PSA50 and PSA90 responses were observed in 60.0% and 20.0% of patients, respectively. Median rPFS was 6.5 months; median overall survival was not reached. **Conclusions:** ^{177}Lu -NYM032 demonstrated a favorable safety profile and promising antitumor activity in patients with mCRPC, supporting further evaluation in Phase II studies. Clinical trial information: NCT06383052. Research Sponsor: None.

ProTACT: Preliminary data from a first-in-human, phase 1 study evaluating the safety, tolerability, and anti-tumor activity of [²²⁵Ac]Ac-FL-020, a PSMA-targeted radioconjugate, in patients with mCRPC.

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Background: [²²⁵Ac]Ac-FL-020 is a next-generation, prostate-specific membrane antigen (PSMA) alpha radioconjugate developed using the proprietary UniRDC linker-chelator technology designed to optimize biodistribution. [²²⁵Ac]Ac-FL-020 is intended for treating patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and aims to enhance tumor uptake while sparing radiosensitive organs, such as salivary glands, thus potentially leading to an improved therapeutic window. **Methods:** ProTACT (FL-020-001) is a first-in-human, open-label, multicenter Phase 1 study investigating the safety, tolerability, and preliminary anti-tumor activity of [²²⁵Ac]Ac-FL-020 in pts with advanced PSMA-positive mCRPC. This study consists of: Bayesian dose escalation (Part 1) and dose expansion (Part 2). Eligible pts must have: histologically confirmed mCRPC, evidence of disease progression, and ≥ 1 PSMA-positron emission tomography positive lesion (uptake higher than liver). Prior androgen receptor signaling inhibitors or CYP17 inhibitors and ≥ 1 taxane-based chemotherapy is required, unless declined by the pt. Prior Lu-177 is allowed. Pts with extensive PSMA-negative disease are excluded. Dose cohorts of 1 to 3 pts (for Cohorts 1 and 2) and dose cohorts of 3 to 6 pts (for Cohorts 3+) will evaluate ascending dose levels from 1 to 10 MBq (intravenous; every 6 weeks; x 6 cycles) to determine the maximum tolerated dose and/or recommended Phase 2 dose (RP2D). Once the RP2D is established, 18 additional pts will be enrolled in Part 2 to further assess safety and early signals of efficacy. **Results:** As of 2 Jan 2026, 15 eligible pts have received [²²⁵Ac]Ac-FL-020 (maximum dose/cycle: 5 MBq). No dose-limiting toxicities have been observed. Most frequent adverse events (AEs) were fatigue (10 pts), nausea and dry mouth (7 pts each), constipation and anemia (4 pts each). Grade (G)3+ AEs were reported for 6 pts, all G3+ AEs occurred in one pt each. One pt at 1 MBq had G3 anemia and 1 pt at 5 MBq had G3 anemia and G3 thrombocytopenia, both considered related to disease progression with bone marrow infiltration and unrelated to [²²⁵Ac]Ac-FL-020. As of the cutoff date, 11 pts remain on treatment and 4 pts discontinued treatment prematurely, 3 due to disease progression and 1 due to G2 dry mouth. Another 6 pts reported dry mouth, all were G1. No renal toxicities or decline in renal function was observed. As of 6 Jan 2026, 1 of 3 pts at 3 MBq showed a reduction in baseline prostate-specific antigen (PSA) $> 80\%$ after 3 cycles and 2 of 6 pts at 5 MBq showed a reduction in PSA $> 50\%$ after 1 cycle. **Conclusions:** These initial findings support the feasibility and tolerability of [²²⁵Ac]Ac-FL-020 administration in heavily pretreated pts with mCRPC with a few notable PSA responses. The RP2D has not yet been reached, and dose escalation continues. Clinical trial information: NCT06492122. Research Sponsor: Full-Life Technologies.

Analysis of genomic and clinical predictors of overall survival and PSA response: Results from the PRECISION registry.

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Background: Outcomes in advanced prostate cancer vary substantially according to clinical and genomic characteristics among patients with metastatic castration-resistant prostate cancer (mCRPC). We sought to identify predictors of overall survival (OS) and prostate-specific antigen (PSA) response using data from the PRECISION real-world registry of mCRPC patients treated with poly(ADP-ribose) polymerase inhibitors (PARPi). **Methods:** Patient-level data from five centers (Dana Farber Cancer Institute, Thomas Jefferson University, University of British Columbia, University of Washington, Yale University) were aggregated, including demographics, clinical characteristics, genomic alterations, treatments, and clinical outcomes. OS was defined as the time from the first date of PARPi treatment to death or the last date the patient was known to be alive. PSA response was defined as a confirmed $\geq 50\%$ decline from the PSA level measured closest to the start of PARPi treatment. Ten candidate variables per endpoint were selected via a random forest-based feature selection. Cox models stratified by study were used for OS, and logistic regression models with study included as an additional covariate were used for PSA response. Similarly, non-*BRCA* mutation status was defined as the presence of any observed mutation in genes other than *BRCA*, including *ATM*, *CHEK2*, *MSH2*, *PALB2*, *BRIP1*, and *BARD1*. **Results:** The combined dataset included $n = 327$ patients, with heterogeneity in baseline characteristics and treatments across studies. The prevalence of *BRCA* (*BRCA1* or *BRCA2*) and non-*BRCA* mutations was 39% and 37% respectively. Median OS for patients with *BRCA* mutations was 21 months (95% CI: 16–28), compared with 15 months (95% CI: 14–18) for those without *BRCA* mutations. No difference in median OS was observed between patients with and without non-*BRCA* mutations: 16 months (95% CI: 14–22) and 17 months (15–21), respectively. Cox models identified age, N stage, PSMA-lutetium therapy, PARPi use within a clinical trial, prior taxane treatment (docetaxel or cabazitaxel), and *BRCA* as important predictors of OS. The corresponding hazard ratios with 95% confidence intervals are shown in the table below. **Conclusions:** These results from real-world data highlight the importance of incorporating genomic information and treatment-specific variables when predicting outcomes in advanced prostate cancer and demonstrate the utility of multi-study integrative analyses. Research Sponsor: Prostate Cancer Foundation.

Predictor	Hazard Ratio (95% CI)
Age	1.02 (1.01–1.04)
N stage	1.91 (1.18–3.12)
PSMA-lutetium therapy	0.35 (0.20–0.62)
PARPi use (within clinical trial)	0.68 (0.48–0.98)
Prior taxane treatment (docetaxel or cabazitaxel)	1.44 (1.02–2.02)
<i>BRCA</i> mutation	0.50 (0.36–0.69)

Association between smoking, tumor genetics, and outcomes in men with metastatic prostate cancer.

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Background: Smoking has been associated with increased metastatic prostate cancer (mPC) mortality, but the mechanisms behind this association are largely unknown. We hypothesized that smoking promotes genetic alterations associated with aggressive disease and/or the transformation to neuroendocrine prostate cancer (NEPC). **Methods:** We utilized the Prostate Cancer Precision Medicine Multi-institutional Collaborative Effort (PROMISE) clinical genomic database for this retrospective analysis. We examined associations between patient characteristics and tumor genetic data with smoking exposure at diagnosis (current, former, never and pack years) and with clinical outcomes, including overall survival (OS) from diagnosis, OS from metastasis, and NEPC status. Patients with unknown smoking status or incomplete/empty/insufficient NGS entries were excluded from analysis. **Results:** We identified 2353 men with mPC and next generation somatic tumor sequencing available for analysis in PROMISE, including 8.1% current, 39.5% former, and 52.4% never smokers. Current smokers were more likely to be younger, present with metastatic (M1 or N1) disease at diagnosis, and were less likely to have prior local therapy (all $p < 0.001$). Current smoking was associated with worse OS from diagnosis (99.9 mo in current vs 137 mo in former, and 139.4 mo in never smokers; $p = 0.008$), which remained significant after adjusting for disease characteristics (HR 1.27 95% CI 1.01–1.59). No differences in OS from metastasis were observed for amongst the three groups (current 68.1mo, former 60.3 mo, and never 64.2 mo; $p = 0.86$). We also found no difference in the percentage of NEPC at initial diagnosis or at any time between current, former, and never smokers ($p = 0.8$). However, positive associations were observed between smoking status and genetic alterations in SPOP (current: 15%, former 6.7%, never 3.8%; $p = 0.018$), FGFR1 (current 10%, former 0.4%, never 1.1% $p = 0.001$), and ARID1A (current 5.1%, former 2.2%, never 0.4%; $p = 0.035$) in mHSPC. No other associations between smoking status and genes of interest were identified. **Conclusions:** Active smoking is associated with worse overall and prostate cancer specific survival as compared to never/former smoking and was associated with specific tumor genetic alterations but not small cell/NEPC transformation. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

Association of tumor genetics with smoking status; alterations detected in hormone sensitive tissue only.

Characteristic	Current N = 39 [†]	Former N = 224 [†]	Never N = 264 [†]	p-value
TP53	17 (44%)	79 (35%)	100 (38%)	0.58
RB1	3 (7.7%)	11 (4.9%)	17 (6.4%)	0.59
PTEN	8 (21%)	55 (25%)	60 (23%)	0.81
BRCA2	8 (21%)	20 (8.9%)	35 (13%)	0.07
MYC	3 (7.7%)	18 (8.0%)	11 (4.2%)	0.15
SPOP	6 (15%)	15 (6.7%)	10 (3.8%)	0.02
FGFR1	4 (10%)	1 (0.4%)	3 (1.1%)	0.001
ARID1A	2 (5.1%)	5 (2.2%)	1 (0.4%)	0.04
PIK3CA	2 (5.1%)	9 (4.0%)	13 (4.9%)	0.80

[†]n (%).

Regional disparities in prostate cancer mortality in the African Union: A retrospective analysis (1980-2023).

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Background: Prostate cancer represents a substantial health burden among men in Africa and is an important contributor to cancer-related mortality, with considerable variation observed across African regions. This study uses data from the Global Burden of Disease (GBD) project to evaluate regional variations in prostate cancer age-standardized death rates (ASDR) from 1980 to 2023. **Methods:** Prostate cancer mortality data were extracted from the GBD 2023 database for the period 1980–2023. Age-standardized death rates (ASDRs) per 100,000 population were obtained for African regions as defined by the GBD classification, including Northern Africa, Central Africa, Eastern Africa, Western Africa, Southern Africa and the African Union aggregate. Temporal patterns from 1980 to 2023 were evaluated using joinpoint regression analysis, and average annual percentage change (AAPC) estimates were calculated to quantify long-term trends. Statistical significance was determined using corresponding p-values (less than 0.05) and 95% confidence intervals. **Results:** From 1980 to 2023, a gradual rise in the ASDR per 100,000 was observed in the African Union with substantial regional variations. It gradually increased from 8.78 per 100,000 in 1980 to 11.44 per 100,000 in 2023 (AAPC: 0.68; 95% CI: 0.51 to 0.84; $p < 0.000001$). The highest ASDR were observed in Central Africa. It increased from 13.72 per 100,000 in 1980 to 18.63 per 100,000 in 2023 (AAPC: 0.77; 95% CI: 0.62 to 0.91; $p < 0.000001$). This was followed by Western Africa increasing from 10.64 per 100,000 in 1980 to 16.06 per 100,000 in 2023 (AAPC: 0.96; 95% CI: 0.82 to 1.09; $p < 0.000001$). A slight increase was also observed in Southern Africa rising from 10.70 in 1980 to 12.07 (AAPC: 0.26; 95% CI: -0.0045 to 0.543; $p < 0.053$). Eastern Africa showed a slight increase in ASDR from 8.95 per 100,000 in 1980 to 10.36 per 100,000 in 2023 (AAPC: 0.43; 95% CI: 0.24 to 0.62; $p < 0.000009$). Northern Africa had consistently the lowest ASDR. It rose from 2.35 per 100,000 in 1980 to 4.32 per 100,000 in 2023 (AAPC: 1.41; 95% CI: 1.27 to 1.56; $p < 0.000001$). **Conclusions:** Prostate cancer remains the leading cause of cancer-related death among men in the African Union, particularly in Central Africa. High mortality is driven by limited healthcare access and late-stage diagnosis. Strengthening screening programs and improving specialized care can reduce this rising burden. Research Sponsor: None.

Trends in age standardized death rate (ASDR) per 100,000 due to prostate cancer in the African Union.			
Region	ASDR 1980 (per 100,000)	ASDR 2023 (per 100,000)	AAPC (95% CI)
African Union	8.79	11.45	0.68* (0.51 - 0.84)
Central Africa	13.72	18.63	0.77* (0.62 - 0.92)
Eastern Africa	8.95	10.36	0.44* (0.24 - 0.63)
Northern Africa	2.35	4.33	1.42* (1.27 - 1.57)
Southern Africa	10.70	12.08	0.26* (-0.01 -0.54)
Western Africa	10.64	16.06	0.96* (0.82 - 1.10)

AAPC = Average Annual Percentage Change; * $p < 0.05$.

Impact of prior treatment setting on the efficacy of rucaparib vs physician's choice in *BRCA*-mutated castration-resistant prostate cancer (mCRPC) in TRITON3.

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Background: Rucaparib significantly improved radiographic progression-free survival (rPFS) versus physician's choice of docetaxel or an androgen-receptor pathway inhibitor (ARPI) (abiraterone or enzalutamide) in men with *BRCA* mutations who were chemotherapy-naïve in the mCRPC setting and had received one prior ARPI in the phase 3 TRITON3 trial (NCT02975934). This post-hoc analysis evaluated whether the timing of prior ARPI therapy impacted the efficacy of rucaparib. **Methods:** Patients were randomized 2:1 to rucaparib (600 mg BID) or physician's choice of docetaxel or ARPI, after progression on 1 prior second-generation ARPI in any setting. The primary endpoint was rPFS. Outcomes were analyzed according to whether patients received the prior ARPI in the metastatic castration sensitive (mCSPC) or castration resistant (mCRPC) setting. Data cutoff was August 25, 2022. **Results:** Of the 302 *BRCA*1/2 patients, 68 received prior ARPI in the mCSPC setting (42 rucaparib; 26 physician's choice) and 234 in the mCRPC setting (159 rucaparib; 75 physician's choice). Baseline characteristics were generally similar. Prior treatments in the mCSPC and mCRPC groups, respectively, included abiraterone (73.5% vs 53.0%), enzalutamide (29.4% vs 48.3%), and docetaxel (17.6% vs 24.8%). Median rPFS favored rucaparib over physician's choice in both groups (mCSPC: 13.6 vs 8.2 months; HR 0.60 [95% CI, 0.32–1.15]; mCRPC: 11.2 vs 5.8 months; HR 0.43 [95% CI, 0.30–0.61]). Median OS was similar between treatments in both settings (mCSPC: 23.2 vs 21.7 months; HR 0.81 [95% CI, 0.47–1.41]; mCRPC: 23.2 vs 21.0 months; HR 0.91 [95% CI, 0.66–1.25]). Treatment-related adverse events occurred at comparable rates (89.6% vs 86.1%). **Conclusions:** Rucaparib demonstrated efficacy in patients with *BRCA*-mutated mCRPC, regardless of whether prior ARPI was administered in the mCSPC or mCRPC setting. Clinical trial information: NCT02975934. Research Sponsor: Clovis Oncology and pharmaand GmbH.

Phase 1b/2 study of pembrolizumab plus lenvatinib or pembrolizumab coformulated with vibostolimab in participants (pts) with metastatic neuroendocrine prostate cancer (NEPC): KEYNOTE-365 cohorts F and H.

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Background: Effective therapy for NEPC is an unmet need due to poor prognosis and no established standard of care. The phase 1b/2 KEYNOTE-365 study (NCT02861573) evaluated the efficacy and safety of pembrolizumab (pembro) + lenvatinib (lenva; cohort F) or coformulated pembro/vibostolimab (vibo; cohort H) in pts with NEPC. **Methods:** Pts with pathologically confirmed treatment-emergent neuroendocrine (t-NE) or de novo metastatic NEPC (small cell carcinoma, large cell neuroendocrine carcinoma, or mixed morphology per central review), progression ≤ 6 mo before screening, and an ECOG PS of 0 or 1 were enrolled. Prior androgen deprivation therapy for metastatic disease was required for pts with t-NE. Prior chemotherapy regimens (≤ 2) for metastatic castration-resistant prostate cancer and second-generation hormonal agents (≤ 2) were permitted. Pts in cohort F received pembro 200 mg IV Q3W + lenva 20 mg PO QD. Pts in cohort H received pembro/vibo 200 mg/200 mg IV Q3W. Pembro or pembro/vibo were given for ≤ 35 cycles; lenva was given until discontinuation criteria were met. Primary end points were safety, ORR per RECIST v1.1 by blinded independent central review (BICR), and confirmed prostate-specific antigen (PSA) response rate ($\geq 50\%$ decrease from baseline measured twice ≥ 3 weeks apart). Secondary end points included ORR, time to PSA progression, radiographic PFS (rPFS) per Prostate Cancer Working Group 3 (PCWG3)-modified RECIST (mRECIST) v1.1 by BICR, DOR and DCR per RECIST v1.1 by BICR, and OS. **Results:** As of August 25, 2025, 14 and 20 pts received ≥ 1 dose of study treatment in cohort F or cohort H, respectively. Median follow-up was 25.6 mo (range, 22.9–35.1) and 31.4 mo (range, 23.2–45.9), respectively. Among pts with RECIST-measurable disease, confirmed ORR was 23.1% (3/13; 95% CI, 5.0–53.8) in cohort F and 12.5% (2/16; 95% CI, 1.6–38.3) in cohort H. Additional efficacy results are shown in the table. Treatment-related adverse events (TRAEs) occurred in 85.7% of pts in cohort F (64.3% grade 3 or 4) and 55.0% of pts in cohort H (25.0% grade 3 or 4). No grade 5 TRAEs occurred in either cohort. In cohorts F and H, TRAEs resulted in treatment discontinuation in 21.4% and 10.0% of pts, respectively, and immune-mediated AEs occurred in 35.7% and 15.0%. **Conclusions:** Pembro + lenva or pembro/vibo had a manageable safety profile and only modest antitumor activity in pts with NEPC. Clinical trial information: NCT02861573. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	Cohort F n = 14	Cohort H n = 20
PSA response rate (95% CI), %	14.3 (1.8–42.8)	10.0 (1.2–31.7)
Median time to PSA progression (95% CI), mo	NR (NR–NR)	NR (2.9–NR)
ORR per mRECIST v1.1 (95% CI), %	15.4 (1.9–45.4)	12.5 (1.6–38.3)
DCR per RECIST v1.1 (95% CI), %	23.1 (5.0–53.8)	12.5 (1.6–38.3)
Median DOR per RECIST 1.1 (95% CI), mo	NR (1.1–NR)	NR (8.3–NR)
Median rPFS per mRECIST v1.1 (95% CI), mo	3.9 (2.1–NR)	2.0 (1.6–4.3)
Median OS (95% CI), mo	4.3 (2.8–NR)	7.0 (2.5–12.9)

Can TGF- β inhibition (galunisertib) enhance response to enzalutamide in metastatic castration-resistant prostate cancer (mCRPC)? Results from a randomized phase II trial.

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Background: Resistance to androgen receptor (AR)-directed therapies is a major challenge in advanced prostate cancer, and enzalutamide shows limited activity after progression on abiraterone. Aberrant transforming growth factor- β (TGF- β) signaling promotes prostate cancer progression and contributes to resistance to AR-directed therapies. Preclinical studies suggest TGF- β inhibition may overcome resistance to enzalutamide. We hypothesized that combining TGF- β receptor I kinase inhibitor, galunisertib, with enzalutamide may delay enzalutamide resistance in patients with mCRPC who have progressed on abiraterone. **Methods:** This multicenter, randomized phase II trial enrolled chemotherapy-naïve mCRPC patients with disease progression on abiraterone. There was a cycle 1 safety run-in for the first 6 patients, followed by a randomized phase with patients assigned 3:2 to receive galunisertib plus enzalutamide or enzalutamide alone. The primary endpoint was radiographic progression-free survival (rPFS). Secondary endpoints included PSA response, overall survival (OS), safety, and tolerability. rPFS and OS were compared between arms using Cox regression, with medians estimated by Kaplan-Meier method. **Results:** Of 61 patients randomized, 60 received treatment: 23 with enzalutamide and 37 with galunisertib plus enzalutamide. There was no significant difference in rPFS between the combination and enzalutamide arms (HR 1.23; 95% CI: 0.72, 2.11; $p=0.44$), with a median rPFS of 5.6 and 7.3 months, respectively. The OS was also similar between the two groups (HR 1.00; 95% CI: 0.55, 1.83, $p=1.00$), with a median OS of 21.6 months in the combination arm and 24 months in the enzalutamide arm. PSA30 response was seen in 22% of patients in the combination arm vs. 35% in the enzalutamide arm ($p=0.30$), and PSA50 response in 19% vs. 26%, respectively ($p=0.50$). The most common treatment-related adverse events (AEs) were fatigue, anorexia, and nausea. Grade 3-4 treatment-related AEs occurred in 11% of patients in the combination arm vs. 13% in the enzalutamide arm. **Conclusions:** The addition of galunisertib to enzalutamide did not improve the rPFS, OS, or PSA response compared to enzalutamide alone in patients with chemotherapy-naïve mCRPC with disease progression on abiraterone. These findings do not support further development of galunisertib plus enzalutamide in patients with mCRPC. Clinical trial information: NCT02452008. Research Sponsor: Department of Defense/CDMRP; W81XWH-22-2-0024; Eli Lilly and Company; National Cancer Institute; P30CA006973; National Cancer Institute; K23CA197526.

Baseline characteristics of randomized patients.

	N (n=61)	Enzalutamide (n=24)	Galunisertib + Enzalutamide (n=37)	P
Age, median (range)	51	72 (57, 84)	68 (53, 85)	0.06
Race, n (%)	58			1.00
White		17 (81.0)	30 (81.1)	
Other		4 (19.0)	7 (18.9)	
Ethnicity, n (%)	60			0.66
Hispanic		0 (0.0)	2 (5.4)	
Non-Hispanic		21 (91.3)	33 (89.2)	
Unknown		2 (8.7)	2 (5.4)	
ECOG, n (%)	55			0.16
0		12 (54.5)	24 (72.7)	
1		10 (45.5)	9 (27.3)	
Baseline PSA, median (range)	60	11.1 (1.0, 2151.3)	18.2 (0.2, 522.4)	0.51

A randomized phase Ib/II study of enzalutamide (Enza) with and without ribociclib (Rib) in patients with metastatic castrate-resistant prostate cancer (mCRPC) that retains RB expression: RiboX study.

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Background: RB function is often attenuated in tumors through hyperphosphorylation; thus, RB activity can be “re-awakened” in RB+ tumors by suppressing key kinases that phosphorylate RB (CDK4/6). We report a phase Ib/II trial to determine the safety, tolerability and antitumor activity rib with enza in patients (pts) with mCRPC (NCT02555189). **Methods:** RiboX was a multicenter, phase Ib/II, open label trial which enrolled taxane-naïve pts with progression to mCRPC and retained RB expression. For phase Ib, a traditional 3x3 dose-escalation was used to establish the RP2D for the phase II portion. Pts received rib at 200, 400 or 600mg once daily (QD) Days (D) 1-21 in combination with fixed dose enza (160mg QD D1-28). In phase II, pts were randomized 1:1 to enza monotherapy (Arm A) or enza + rib (Arm B). The study was later modified to a single arm Simon two-stage design using the RP2D of 600mg rib with 160mg enza. The primary phase II endpoint was the proportion of pts a PSA50 response at 12 weeks. The null hypothesis was that the PSA50 response was $\leq 78\%$ and 31 responses were required to reject the null hypothesis. Secondary endpoints were rPFS, PSA PFS, OS and safety. **Results:** 12 pts were enrolled in the phase Ib portion across three dose levels upon confirmation of RB expression on tumor biopsy. No DLTs were observed in dose-escalation and the RP2D was established at rib 600mg QD D1-21 + enza 160mg QD D1-28. The phase II portion included 12 pts treated with enza mono; 28 phase II pts and 6 phase Ib pts yielded 34 pts treated with combination at RP2D. The PSA50 response at 12 weeks was 75% (95% CI, 43-95) for enza mono and 82% (95% CI, 65-93) for the combination, failing to reject the null hypothesis. Median rPFS for evaluable pts was 10.9 mo (95% CI, 2.5-45.9) for enza mono (n = 12) and 27.0 mo (95% CI, 11.3-37.0) for combination (n = 30). PSA PFS was 10.1 months (95% CI, 1.8-33.1) for enza mono (n = 12) and 14.8 mo (95% CI, 6.7-35.9) for combination (n = 34). OS was 31.2 mo (95% CI, 15.0-NA) for enza mono (n = 12) and 58.1 mo (95% CI, 33.4-NA) for combination (n = 34). Four pts treated with combination were included for PSA PFS but did not have data for rPFS. Among pts treated at RP2D in the combination arm, the most common TEAE's included fatigue 59%, nausea 26.9%, neutropenia 26.7% (grade 3, 12%), diarrhea 20.9%, dizziness 14.7%, arrhythmia 2.9%, seizure 2.9%. **Conclusions:** The combination of enza + rib was well tolerated; however, no significant difference in PSA50 response was observed, and the primary endpoint was not met. A disease-stabilizing effect was observed in a subset of patients treated with the enza + rib combination, with evidence of prolonged survival. Further investigation into this disease-stabilizing effect and refinement of patient selection criteria beyond RB expression may be warranted. Funding: Novartis Pharmaceuticals and DOD (W81XWH-22-2-0020). Clinical trial information: NCT02555189. Research Sponsor: Novartis.

Belzutifan in docetaxel-pretreated metastatic castration-resistant prostate cancer (mCRPC): Phase 1b/2 KEYNOTE-365 cohort J.

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Background: Hypoxia-inducible factor 2α (HIF- 2α) is an established oncogenic driver, and HIF- 2α expression in prostate cancer is positively correlated with aggressive disease. Belzutifan is a selective HIF- 2α inhibitor approved for use in clear cell renal cell carcinoma. Cohort J of the multicohort, phase 1b/2 KEYNOTE-365 study (NCT02861573) evaluated the safety and efficacy of belzutifan in participants (pts) with mCRPC. **Methods:** Eligible adults had histologically or cytologically confirmed adenocarcinoma of the prostate without small cell histology, had an Eastern Cooperative Oncology Group performance status score of 0 or 1, and had received prior docetaxel for mCRPC. Prior treatment with 1 other chemotherapy and ≤ 2 second-generation hormonal agents were allowed. Pts received oral belzutifan 120 mg daily. Primary end points were safety and tolerability, prostate-specific antigen (PSA) response rate (PSA decline $\geq 50\%$), and objective response rate (ORR) per RECIST v1.1 by blinded independent central review (BICR). Secondary end points included time to PSA progression, ORR, and radiographic progression-free survival (rPFS) per PCWG3-modified RECIST v1.1, duration of response and disease control rate (DCR; complete response + partial response + stable disease ≥ 6 mo) per RECIST v1.1 and PCWG3-modified RECIST v1.1 by BICR, and overall survival (OS). **Results:** A total of 21 pts were allocated to receive belzutifan. Median age was 69.0 y (range, 56–84). Median study follow-up was 17.6 mo (range, 15.9–21.8). All pts discontinued treatment as of the data cutoff (August 25, 2025), most commonly due to progressive disease ($n = 12$; 57%). Median duration of belzutifan therapy was 2.8 mo (range, 0.7–8.7). Treatment-related adverse events (AEs) occurred in 20 pts (95%); grade 3 or 4 treatment-related AEs occurred in 11 pts (52%), most commonly anemia ($n = 8$; 38%). A total of 2 pts (10%) discontinued treatment, and no pts died due to treatment-related AEs. Among pts with a baseline PSA measurement ($n = 20$), PSA response rate was 0% (95% CI, 0–17) and median time to PSA progression was 3.0 mo (95% CI, 2.8–not reached [NR]). Among 12 pts with RECIST-measurable disease, ORR and DCR per RECIST v1.1 were both 0%; ORR and DCR per PCWG3-modified RECIST v1.1 were 0% and 8%, respectively. In all pts, median rPFS was 3.7 mo (95% CI, 1.9–NR) and median OS was 16.9 mo (95% CI, 10.8–NR). **Conclusions:** In cohort J of the KEYNOTE-365 trial, belzutifan monotherapy had a manageable safety profile but did not show meaningful antitumor activity in mCRPC. Future research is needed to determine effective treatments for pts with mCRPC. Clinical trial information: NCT02861573. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Utidelone in heavily pretreated metastatic castration-resistant prostate cancer progressing after docetaxel and novel hormonal agents: Results of a completed phase II trial.

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Background: Patients with metastatic castration-resistant prostate cancer (mCRPC) who have progressed after both docetaxel and novel hormonal agents (including abiraterone and/or androgen receptor pathway inhibitors [ARPIs]) have a poor prognosis with limited treatment options. This study aimed to evaluate the efficacy and safety of utidelone, a genetically engineered epothilone analogue with antitumor activity in taxane-resistant cancers, in these patients. **Methods:** In this prospective, single-arm, phase II clinical trial, eligible male patients were aged 18 to 75 years with mCRPC who had progressed on docetaxel and at least one prior ARPI or abiraterone. Patients received utidelone monotherapy (30 mg/m²/day intravenously for 5 days, every 3 weeks) until progression, intolerable toxicity, or death. Recruitment has been completed with 43 patients enrolled at Sun Yat-sen University Cancer Center from March 23, 2022, to December 10, 2025. The primary endpoint was prostate specific antigen (PSA) response rate, defined as a 50% or greater reduction in serum PSA. Secondary endpoints included radiographic progression-free survival (rPFS) according to PCWG3 criteria, OS, and safety. **Results:** Analysis was performed on the full cohort. The median age was 66 years, and patients had received a median of 4.0 (range, 2–8) prior lines of treatment. All patients were pre-treated with docetaxel and 97.7% with abiraterone; 90.7% patients had progressed after ARPI, and 14.0% after radionuclide therapy. Visceral metastases were present in 32.6% patients, and 67.4% had de novo metastatic disease. Among 28 patients with available genetic data, BRCA1/2 mutations were identified in 3 (10.7%). By the data cut-off (January 4, 2026), the PSA50 response rate ($\geq 50\%$ decline) was 23.3%, and 32.6% of patients achieved a PSA30 response ($\geq 30\%$ decline). The median rPFS was 6.7 months, and median OS was 11.4 months. Most of the treatment-related adverse events (TRAEs) were grade 1 or 2 and were considered manageable. Grade 3/4 TRAEs consisted of anemia (14.0%), peripheral sensory neuropathy (2.3%), vomiting (2.3%), and diarrhea (2.3%). No treatment-related deaths occurred. **Conclusions:** Utidelone monotherapy exhibits promising antitumor activity and manageable safety profile in heavily pretreated mCRPC patients, including those who have progressed on ARPIs, abiraterone, and docetaxel. The study results support further investigation of this regimen. Clinical trial information: ChiCTR2200061635. Research Sponsor: Beijing Biostar Pharmaceuticals Co., Ltd.

Rad2Nivo: Phase IB study of radium-223 (Rad) with nivolumab (Nivo) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).

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Background: Rad is an α -emitting calcium-mimetic radiopharmaceutical that is FDA approved for pts with mCRPC with symptomatic bone metastasis (mets) and no visceral mets. Preclinical data suggest that radiation might enhance the anticancer effect from PD-1 therapy [PMID 25274032, 29137877]. Nivo is a PD-1 immune checkpoint antagonist. Few pts experience PSA reduction with Rad, and objective responses in bone mets cannot be assessed. We hypothesized that Rad+Nivo would be safe and result in decreased ctDNA variant allele frequency (VAF) as a marker of clinical efficacy. **Methods:** In this phase IB, prospective, open-label, single-center, single-arm study (NCT04109729), pts with symptomatic bone-metastatic mCRPC without visceral mets were eligible. Participants received intravenous Rad (55 kBq/kg IV) monotherapy for 6 cycles. Nivo (480mg IV) was introduced starting with cycle 3 and continued for up to 2 years. ctDNA collected at baseline, cycle 3 and 6 weeks after. Primary endpoints: (1) frequency of grade ≥ 3 non-hematologic treatment-emergent adverse events (TEAEs) and (2) change in ctDNA VAF from baseline compared to after 6 weeks of nivolumab therapy. Mean VAF was defined as average VAF of all somatic mutations present at baseline at a VAF 1%. Null hypothesis: proportion of pts with a non-zero ctDNA reduction is $\leq 20\%$. A one-sided exact binomial test was used to evaluate whether the proportion of pts demonstrating a decrease in mean VAF on-treatment exceeded 20%. With 36 pts, there will be 83% power at one-sided $\alpha = 0.05$ to detect an alternative proportion of subjects with ctDNA reduction = 40%. **Results:** Overall, 39 pts were enrolled trial between 9/2020 and 1/2025, and 35 pts were treated with both Rad+Nivo. Median age was 71 years (54–84), median PSA at study entry was 13.9 ng/dL (0–3245). 22 pts (56.4%) had Gleason score ≥ 8 (unavailable for 3 pts). Median number of prior lines of therapy was 3 (1–7). 53.9% (n = 21) of pts had received prior chemotherapy. 61% (n = 24) of pts completed 6 doses of Rad (range 2–6). The median number of Nivo cycles was 4 (0–25). Dose holds or delays occurred in 26% (n = 10) and 31% (n = 12) of pts receiving Rad and Nivo, respectively. 38% (n = 15) of pts experienced at least one grade 3–5 TEAE regardless of attribution. Grade 3–4 TEAE related to Rad and Nivo occurred in 15% (n = 6) and 18% (n = 7) of pts, respectively. No dose-limiting toxicities were observed. Serious adverse events related to Rad and Nivo occurred in 5% (n = 2) and 2.6% (n = 1) of pts, respectively. Paired molecular data was available for 25 pts. VAF was measurable in all patients who had samples collected and reduction was observed in 15 of 25 pts (60%, one-sided 95% CI, 41.7%–100%; $p < 0.01$). **Conclusions:** The study met its primary endpoints. Rad+Nivo appears to be safe and VAF was decreased in 60% of patients tested. Survival outcomes and clinical correlation data with VAF will be presented at the meeting. Clinical trial information: NCT04109729. Research Sponsor: Bristol Myers Squibb.

Mortality trends and disparities in prostate cancer with co-occurring cardiometabolic disorders among U.S. men aged ≥ 55 years, 1999–2024.

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Background: Prostate cancer (PCa) survivors are at significant risk for cardiometabolic disorders (CMD) including hypertension, diabetes, and cerebrovascular diseases which often act as competing causes of death. While PCa survival with CMD has improved but trends in deaths remain poorly characterized across demographic and geographic strata. This study evaluates longitudinal trends to identify success in management and remaining inequities in men aged ≥ 55 . **Methods:** We analyzed U.S. mortality data (1999–2024) from the CDC WONDER database for men aged ≥ 55 years with PCa as the underlying cause of death (UCOD) and CMD as the multiple cause of death (MCOD). Age-adjusted mortality rates (AAMR) per 100,000 and joinpoint regression were used to estimate Annual Percent Change (APC) and Average Annual Percent Change (AAPC). Stratified analyses were performed by race, census region, and urbanization. **Results:** A total of 151,108 deaths were identified (cumulative AAMR: 18.78). Overall mortality demonstrated a significant declining trend (1999–2024; AAPC: -2.48% , $p < 0.001$). Significant declines were observed across all racial groups. Black or African American men experienced the highest mortality burden but also the most rapid decline (AAPC: -6.01% , $p < 0.001$), narrowing the gap with White men (AAPC: -4.33% , $p < 0.001$). While all regions showed improvement, the Southern U.S. demonstrated the slowest rate of decline (AAPC: -4.13% , $p < 0.001$) compared to the Northeast, which saw the most substantial reduction (AAPC: -5.76% , $p < 0.001$). Recent trends (2019–2024) showed sharp decreases across regions, including the South (APC: -11.28% , $p = 0.002$). Declines were consistent across the rural–urban continuum. Micropolitan (non-metropolitan) areas showed a significant overall decline (AAPC: -1.72% , $p < 0.001$). However, segments of transient increase were noted between 2015–2020 in Medium Metro (APC: $+3.77\%$, $p = 0.004$) and Large Fringe Metro (APC: $+3.55\%$, $p = 0.005$) areas before resuming a downward trend. **Conclusions:** Mortality for prostate cancer with contributing cardiometabolic causes is significantly decreasing among U.S. men aged ≥ 55 . The accelerated decline among Black men and in the Northeast reflects improvements in integrated oncological and cardiovascular care. However, the slower decline in the South and transient increases in specific metropolitan areas underscore the necessity for targeted cardio-oncology interventions. Continued focus on equitable access to cardiometabolic risk management is vital to sustaining these positive trends and eliminating geographic and racial disparities in PCa survivorship. Research Sponsor: None.

Efficacy, safety, and quality of life outcomes of 177Lu-PSMA-617 in metastatic castration-resistant prostate cancer: A GRADE-assessed systematic review, meta-analysis, and trial sequential analysis of randomized controlled trials.

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Background: 177Lu-PSMA-617 radioligand therapy (RLT) offers a targeted approach for metastatic castration-resistant prostate cancer (mCRPC). However, its consolidated impact on survival, patient-reported outcomes, and safety requires rigorous validation. We conducted a systematic review, meta-analysis, and trial sequential analysis (TSA) to evaluate the robustness of evidence regarding efficacy, toxicity, and quality of life (QoL). **Methods:** We systematically searched PubMed, Cochrane, and Embase for prospective randomized controlled trials (RCTs) comparing 177Lu-PSMA-617 versus standard-of-care (SOC) in mCRPC. Primary outcomes included overall survival (OS), radiographic progression-free survival (rPFS), and PSA response. Secondary outcomes included QoL (FACT-P scores, pain intensity) and adverse events (AEs). TSA was performed to assess the conclusiveness of the cumulative evidence. Data were pooled using a random-effects model. **Results:** Six prospective RCTs comprising 2,113 patients (1,263 Lu-PSMA; 850 SOC) were included. Lu-PSMA significantly improved overall survival (HR 0.76; $P = 0.02$) and radiographic progression-free survival (HR 0.55; $P < 0.00001$) compared to SOC. QoL metrics significantly favored Lu-PSMA, including mean difference in QoL scores (MD 2.93; $P < 0.00001$), time to deterioration of FACT-P (RR 0.58; $P < 0.00001$), and worsening of pain intensity (OR 0.61; $P = 0.002$). TSA demonstrated conclusive evidence for PSA response (RR 2.33; $P = 0.001$), as the Z-curve crossed the monitoring boundary. However, TSA for ORR and PFS remained inconclusive despite favorable point estimates. Regarding safety, Lu-PSMA was associated with higher risks of Grade 1-2 dry mouth (RR 9.75), Grade ≥ 3 thrombocytopenia (RR 6.20), and Grade 1-2 dry eyes (RR 6.66). **Conclusions:** 177Lu-PSMA-617 demonstrates a significant survival benefit and conclusively improves PSA response rates in mCRPC. Crucially, it preserves quality of life by delaying the deterioration of physical function and pain. While effective, the therapy carries specific toxicity risks, notably xerostomia and high-grade thrombocytopenia, necessitating careful patient monitoring. Research Sponsor: None.

Outcome	Effect Estimate (95% CI)	P-Value	I ²	TSA Status
Overall Survival	HR 0.76 (0.59–0.96)	0.02	68%	-
Radiographic PFS	HR 0.55 (0.43–0.71)	<0.00001	67%	Inconclusive
PSA Response Rate	RR 2.33 (1.38–3.93)	0.001	93%	Conclusive
Objective Response Rate	RR 2.94 (1.55–5.55)	0.0009	72%	Inconclusive
Quality of Life (MD)	MD 2.93 (1.80–4.07)	<0.00001	20%	-
Time to Det. FACT-P	RR 0.58 (0.51–0.66)	<0.00001	0%	-
Worsening Pain Score	OR 0.61 (0.44–0.84)	0.002	81%	-
Dry Mouth (Grade 1-2)	RR 9.75 (6.85–13.88)	<0.00001	91%	-
Thrombocytopenia (G ≥ 3)	RR 6.20 (2.18–17.65)	0.0006	0%	-
Dry Eyes (Grade 1-2)	RR 6.66 (2.79–15.91)	<0.0001	0%	-

A phase I study of [225Ac]Ac-PSMA-XT, a novel alpha-particle-emitting radioligand therapy, in patients with metastatic castration-resistant prostate cancer.

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Background: Targeted alpha therapy (TAT) is an emerging modality for metastatic castration-resistant prostate cancer (mCRPC), offering the potential for precise tumor cell eradication with limited off-target exposure. [225Ac]Ac-PSMA-XT (XT381) is a PSMA-targeted alpha-emitting radiopharmaceutical designed to deliver high linear energy transfer radiation. This single-center, open-label Phase I study (NCT07135102) in China aims to assess the safety, tolerability, and preliminary efficacy of [225Ac]Ac-PSMA-XT in heavily pretreated mCRPC. **Methods:** Patients with PSMA-positive mCRPC (confirmed by THERP trial criteria, ≥ 1 lesion with $SUV_{max} > 20$ on PSMA PET/CT imaging, and all measurable lesions with $SUV_{max} > \text{liver } SUV_{mean}$) who progressed after ≥ 1 line of androgen receptor pathway inhibitor were enrolled. A standard "3 + 3" design was used across five dose levels (25, 50, 75, 100 and 125 kBq/kg), with up to 6 cycles administered every 6 weeks. Primary endpoints were safety/tolerability (CTCAE v5.0). Key secondary endpoints included PSA50 response ($\geq 50\%$ decline), radiographic progression-free survival (rPFS), objective response rate (ORR) by RECIST 1.1, and disease control rate (DCR). Enrollment has completed through the 75 kBq/kg cohort, the 100 kBq/kg cohort is ongoing. **Results:** As of December 12, 2025, 12 patients were dosed (cohorts 25-100 kBq/kg, $n = 3$ each). All patients received at least one dose of [225Ac]Ac-PSMA-XT. No dose-limiting toxicities have been observed. Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 2 patients. The most common TRAEs were xerostomia and grade 1-2 hematologic toxicities, including anemia (55.6%, 5/9), leukopenia (44.4%, 4/9), lymphopenia (22.2%, 2/9), neutropenia (11.1%, 1/9), and thrombocytopenia (11.1%, 1/9). Among 9 evaluable patients (≥ 6 weeks follow-up), 7 (77.8%) achieved a PSA50 response, and 4 (44.4%) achieved a PSA90 response. The 6-month progression-free survival (PFS) rate was 71.4 (5/7). In 5 patients with RECIST-measurable disease, ORR was 60% (3 partial responses). Overall DCR was 67%. **Conclusions:** [225Ac]Ac-PSMA-XT shows a favorable and manageable safety profile with no DLTs observed up to 100 kBq/kg. Early efficacy signals are highly encouraging, with deep PSA declines and durable disease control observed in this heavily pretreated mCRPC population. These data support continued dose escalation and further development of this alpha-emitting PSMA-targeted therapy. Clinical trial information: NCT07135102. Research Sponsor: Beijing Sinotau International Pharmaceutical Technology Co. Ltd.

Genomic biomarkers of sensitivity to bipolar androgen therapy (BAT) in metastatic castration-resistant prostate cancer (mCRPC).

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Background: In most cases, mCRPC remains driven by persistent androgen receptor (AR)-signaling. BAT has shown benefit in a subset of patients (pts) with mCRPC through multiple mechanisms of action, including modulation of AR activity, induction of DNA double-strand breaks and cell cycle arrest. There is a need for predictive biomarkers to identify patients most likely to benefit from BAT. **Methods:** This retrospective multicenter study included pts with mCRPC treated with BAT who had undergone tumor genomic profiling up to one month prior to BAT initiation. Somatic alterations were correlated with PSA50 response rates ($\geq 50\%$ decline in PSA from baseline), time to treatment failure (TTF) and overall survival (OS). PSA50 associations were assessed using Fisher's exact test and logistic regression. Time-to-event outcomes were analyzed using Kaplan-Meier and Cox models. Independent predictors were evaluated using multivariable logistic regression and Cox models. **Results:** We identified 104 pts for inclusion. The median age was 72 years and 49.4% of pts presented with metastases at diagnosis. PSA50 was achieved in 39.4% overall. Median TTF and OS were 3.7 (95% CI: 3.0–4.9) and 28.5 (95% CI: 23.5–35.1) months, respectively. AR amplification, *TP53* alterations and double-hit tumor suppressor alterations involving *TP53/RB1/PTEN* were all strongly associated with better PSA50 (Table). In multivariable analysis (MVA), AR amplification (OR 4.00, 95% CI 1.23–13.01; $p = 0.021$) and *TP53* alterations (OR 5.18, 95% CI 1.71–15.71; $p = 0.0037$) remained independently associated with PSA50. In survival analyses, AR ligand-binding domain mutations that reduce testosterone binding affinity (low-affinity AR-LBD mutations: L702H, W742C, T878A/S) were linked to shorter TTF and remained independently associated in MVA (HR 2.19, 95% CI 1.15–4.18; $p = 0.017$), together with metastatic disease at diagnosis (HR 1.82, 95% CI 1.17–2.84; $p = 0.008$). **Conclusions:** Distinct genomic alterations are associated with sensitivity to BAT in mCRPC patients. AR amplification, *TP53* alterations and *TP53/RB1/PTEN* double-hit status were all associated with increased likelihood of PSA response, while low-affinity AR-LBD mutations identify patients at risk for early treatment failure. These findings are in line with prior studies and support genomic profiling to refine patient selection for BAT. Research Sponsor: None.

	PSA50		TTF		OS	
	OR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
TP53 alterations	5.3 (1.9–15.4)	0.002	0.7 (0.4–1.1)	0.100	1.8 (1.0–3.3)	0.067
Double hit (TP53, RB1, PTEN)	4.4 (1.4–13.6)	0.013	0.8 (0.5–1.3)	0.313	1.7 (0.9–3.2)	0.115
AR amplification	4.6 (1.7–13.0)	0.003	0.7 (0.4–1.1)	0.110	0.9 (0.5–1.7)	0.809
Low affinity AR-LBD mutations	0.4 (0.1–1.5)	0.231	2.6 (1.4–4.6)	0.002	1.9 (0.9–3.89)	0.076
DDR alterations	0.6 (0.2–1.3)	0.210	1.3 (0.8–2.0)	0.223	1.6 (1.0–2.6)	0.057

Early chemo-induced TME alterations as a predictor of response to PD-1 blockade in AVPC: Single-cell data from C3NIRA.

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Background: Aggressive variant prostate cancer (AVPC) criteria enrich for androgen-indifferent disease that is highly aggressive and has limited therapeutic options. Single-agent immune checkpoint inhibitors have not demonstrated activity in prostate cancer patients. The C-COLA study (NCT03263650) showed that Cabazitaxel/Carboplatin (CabCarb) elicited inflammatory signaling in responsive patients with AVPC. Based on these findings, we hypothesized that chemotherapy-induced inflammation in the tumor microenvironment (TME) may prime tumors for immunotherapeutic approaches. **Methods:** The C3NIRA trial (NCT04592237) employed one cycle of CabCarb, followed by the addition of the PD-1 blocker Cetrelimab, from cycle 2 for up to 6 cycles of induction treatment in patients with AVPC. Among 120 enrolled men, 20 discontinued due to toxicities and 40 due to progression during induction. Sixty patients completed induction and were subsequently randomized to Niraparib maintenance with or without Cetrelimab. The 30 randomized to Niraparib with Cetrelimab had significantly longer progression free (PFS) and overall survivals than the 30 randomized to Niraparib alone. To investigate whether treatment-induced alterations in the TME could predict immunotherapy response, biopsies were obtained at baseline, and after cycles 1, 3 and 9 for single-cell RNA sequencing (scRNAseq). **Results:** scRNAseq analysis of tumor biopsies showed a high proportion of GZMK⁺ CD8⁺ T cells and CD8⁺ T effector memory clusters, and a low proportion in FOXP3⁺ CD4⁺ T regulatory cells, in the TME of responders (PFS ≥ 10 months) after cycle 1 of CabCarb, which was not seen in progressors. Similarly, SPP1⁺ macrophages scoring high immunosuppressive signatures were reduced in responders after CabCarb but not in progressors. Consistent with these suppressive and effector cell changes, LAG3⁺ TIGIT⁺ CD8⁺ T exhausted cells gradually accumulated in progressors from baseline through CabCarb and Cetrelimab treatment, while remaining unchanged in responders over the same interval. **Conclusions:** One cycle of CabCarb induction altered the TME in a subset of AVPC tumors, with reduction of suppressive myeloid and T cell populations and expansion of anti-tumor effector cells associated with clinical responses. These early TME changes may predict benefit from the addition of PD-1 blockade and help refine patient selection for immune checkpoint inhibition. Ongoing analyses are identifying additional therapeutic vulnerabilities in the TME that can be targeted to further improve outcomes in men with AVPC. Clinical trial information: NCT04592237. Research Sponsor: U.S. Department of Defence; W81XWH-20-1-0257; Janssen Scientific Affairs, LLC.

Genomic predictors of response to cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC): A real-world analysis from the PROMISE registry.

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Background: Cabazitaxel (Cabazi) is an important treatment for refractory mCRPC, but responses are heterogeneous. Homologous recombination repair (HRR) and tumor suppressor gene (TSG) alterations (alt) can predict aggressive behavior in patients (pts) with mCRPC. We hypothesize that Cabazi has enhanced efficacy in pts with these aggressive alt. **Methods:** The multi-institutional PROMISE clinical-genomic database was queried for patients who had undergone tumor next-generation sequencing prior to initiating Cabazi monotherapy for mCRPC. We evaluated the association of select gene alt HRR (*BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *CDK12*, *CHEK2*, *PALB2*, *RAD51*, *RAD51B/CD*), TSG (*RB1*, *PTEN* loss, *TP53*) and other common alt in mCRPC with PSA response and clinical Progression to Cabazi. Comparisons of PSA50 responses were made using Fisher's exact tests, and associations between genetic alterations and both OS and PFS were conducted using log-rank tests. **Results:** Among 383 pts who met inclusion criteria median age was 61 years, with 283 (74%) Caucasian pts, 71 (19%) African-American/Black pts, 9 (2%) Asian pts, and 20 (5%) Hispanic pts. 302 (79%) had prior docetaxel, 23 (6%) had received PARP inhibitor, and 16 (4%) had received Lu-177 PSMA. The most frequent alt noted were: TSG in 204 (53%) pts, TP53 in 164 (43%), AR alt in 130 (34%) pts, and HRR alt in 91 (24%) pts. No significant difference was noted in PSA50 responses in pts with TSG or HRR alt relative to wild-type, though there was a difference noted in pts with PIK3CA alt (Table). Progression-free survival (PFS) on Cabazi was shorter in pts with TP53 alt [HR 1.55 (1.19 – 2.04), $p=0.001$], any TSG alt [HR 1.51 (1.15 – 1.98) $p=0.003$], RB1 [HR 2.34 (1.38 – 3.99), $p=0.005$], and AR alt [HR 1.37 (1.04 – 1.79) $p=0.03$]. There was no difference in pts with HRR alt [HR 0.83 (0.60 – 1.15), $p=0.26$]. Overall survival (OS) was prolonged in pts with HRR alt [HR 0.69 (0.59 – 0.92), $p=0.009$] and worse in pts with TP53 alt [HR 1.54 (1.20 – 1.98) $p<0.001$], any TSG alt [HR 1.36 (1.07 – 1.74), $p=0.01$], or RB1 alt [HR 1.94 (1.18 – 3.18) $p=0.02$]. **Conclusions:** Common genomic alt including TSG, HRR, and PI3KA were not predictive of Cabazi response in mCRPC. TSG alt were associated with worse outcomes, consistent with aggressive disease biology. Improved OS in pts with HRR alt likely reflects PARP inhibitor or platinum use rather than Cabazi efficacy. Research Sponsor: None.

Association between genomic alterations and cabazitaxel response in mCRPC.

Genetic Alteration	PSA50 Response	PFS (HR)	OS (HR)
Any TSG	26.8% vs 25.4% ($p=0.80$)	1.51 ($p=0.003$)	1.36 ($p=0.01$)
AR	20.8% vs. 28.6% ($p=0.16$)	1.37 ($p=0.03$)	1.19 ($p=0.19$)
Any HRR	31.8% vs. 24.6% ($p=0.27$)	0.83($p=0.26$)	0.69 ($p=0.009$)
PTEN	35.7% vs. 24.0% ($p=0.09$)	1.12 ($p=0.50$)	0.98 ($p=0.92$)
PIK3CA	5.6% vs. 27.4% ($p=0.05$)	1.53 ($p=0.22$)	1.27 ($p=0.36$)

Correlation between dual FDG/PSMA PET mismatch and ctDNA genomic profiling in metastatic castration-resistant prostate cancer (mCRPC) patients screened for ¹⁷⁷Lu-PSMA.

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Background: ¹⁷⁷Lu-PSMA radioligand therapy is now a standard treatment for patients (pts) with mCRPC. Dual-tracer FDG/PSMA PET imaging mismatch (i.e. FDG+ and PSMA- lesions) is currently the main selection criterion used to predict ¹⁷⁷Lu-PSMA response. However, this approach is time-consuming, resource-intensive and may not fully capture tumor biological aggressiveness. More accessible and biologically informative biomarkers are therefore needed.

Methods: This retrospective, single-center study included pts diagnosed with mCRPC who underwent FDG and PSMA PET for ¹⁷⁷Lu-PSMA screening and circulating tumor DNA next-generation sequencing (ctDNA) as part of the STING program (NCT04932525) at Gustave Roussy. A tumor suppressor gene alterations (TSalt) signature was defined by ≥ 2 alterations among *TP53*, *PTEN* and/or *RB1*. Univariate logistic and linear regression models were used along with area under the curve (AUC) to assess associations between genomic and mismatch as well as PET-derived parameter. Progression-free survival (PFS, PCWG3 criteria) and overall survival (OS) were analyzed using univariate Cox models. **Results:** Among the 110 pts with available ctDNA and dual-tracer imaging, 18 (16.4%) exhibited mismatch. TSalt+ tumors were identified in 24 pts (21.8%) and were enriched in the mismatch group (50.0 vs 16.3%, $p = 0.004$) and in case of liver metastases (33.3% vs 10.5%, $p = 0.011$). TSalt was associated with mismatch ($p = 0.003$, AUC = 0.625). TSalt predicted higher total lesion glycolysis (TLG; $p < 0.001$, AUC = 0.720), increased ratio TLG/total lesion activity (TLA; $p = 0.008$, AUC = 0.657), larger FDG+ tumor volume ($p = 0.008$, AUC = 0.720), and lower PSMA+ tumor volume ($p < 0.001$, AUC = 0.725). TSalt+ pts had significantly shorter OS compared with TSalt- pts (median 5.7 vs 16.5 months; HR 3.31, 95% CI [1.93–5.69], $p < 0.001$). Similarly, pts with mismatch had inferior OS (median 4.7 vs 16.3 months; HR 3.17, 95% CI [1.69–5.95], $p < 0.001$). Among the 79 pts treated with ¹⁷⁷Lu-PSMA, TSalt+ status ($n = 14$, 17.7%) was associated with shorter median PFS (3.5 vs 5.1 months; HR 2.37, 95% CI [1.29–4.34], $p = 0.004$) and OS (5.5 vs 15.3 months; HR 4.19, 95% CI [2.17–8.10], $p < 0.001$). Patients with mismatch ($n = 3$, 3.8%) also experienced inferior outcomes, with shorter PFS (2.5 vs 4.9 months; HR 3.80, 95% CI [1.14–12.7], $p = 0.02$) and OS (5.6 vs 15.1 months; HR 4.97, 95% CI [1.48–16.7], $p = 0.004$). **Conclusions:** The TSalt genomic signature was associated with FDG/PSMA PET mismatch, adverse metabolic imaging features, and poorer survival in patients with mCRPC, including those treated with ¹⁷⁷Lu-PSMA. These findings suggest that ctDNA genomic profiling may help identify molecular imaging mismatch, associated with biologically aggressive disease, such as lineage plasticity phenotypes. Prospective studies are warranted to validate its clinical utility. Research Sponsor: None.

Predicting response to ^{177}Lu -PSMA-617 in metastatic prostate cancer (mPC) using plasma-derived extracellular vesicles (EVs).

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Background: ^{177}Lu -PSMA-617 (LuPSMA) is a groundbreaking therapy for mPC, but biomarkers are urgently needed to improve patient selection. Plasma-derived EVs are emerging blood-based markers of tumor burden. Here, we analyzed levels of EVs of 123 patients (pts) from 4 cohorts: a pre- and during LuPSMA treatment for a contemporary prospective Mayo Clinic cohort, pre-treatment plasma levels of EVs for a historical Tulane cohort, localized prostate cancer (LPC) after radical prostatectomy (RP), and male healthy donors (HD). **Methods:** Blood samples were collected from 51 pts pre-cycles (pre-C) 1-3 of LuPSMA at Mayo Clinic from 12/2024-12/2025 and 26 pts pre-C1 at Tulane Cancer Center between 12/2018-1/2025. Small and large EVs were incubated with fluorescently conjugated antibodies (PSMA, STEAP1, CEACAM5, and TROP2) and enumerated using nanoscale flow cytometry. EVs from blood samples of 10 HD and 36 LPC post-RP from 6/2020-8/2024 at Mayo Clinic as controls. AUC-ROC and logistic regression analyses were performed to identify marker signatures associated with PSA50 response. **Results:** Baseline demographics are shown in the table. Median levels of PSMA, STEAP1, CEACAM5, and TROP2 EV/milliliter (mL) were all significantly higher for pts with mPC (pooled Tulane and Mayo cohorts) compared to LPC post-RP ($p < 0.001$) and HD ($p < 0.001$). In the Mayo cohort, 10 of 51 pts (20%) had undetectable PSA pre-C1. There were no significant differences in median pre-C1 plasma EV levels for these 4 different types of EVs comparing pts with undetectable vs detectable PSA. For 41 Mayo pts with detectable PSA pre-C1, 20 achieved PSA50 response at time of data cutoff (49%), while 7 pts (17%) had persistent PSA rise on LuPSMA. For pts who achieved PSA50, there was a significant decline in both CEACAM5 and TROP2 EVs/mL pre-C1 compared to pre-C3 (19×10^6 vs 5.8×10^6 , $p = 0.003$ and 16×10^6 vs 5.5×10^6 , $p < 0.001$, respectively), while no significant changes occurred for the 7 pts with no PSA response. A composite score of pre-C1 CEACAM5 and TROP2 EVs (large- and small-sized EVs) demonstrated the strongest association with PSA50 response (OR=2.96, 95% CI: 1.27-6.44, $p = 0.038$), achieving AUC of 0.73. PSMA and STEAP1 EVs did not show any significant changes from pre-C1 to pre-C3. **Conclusions:** Plasma-derived EVs are a promising biomarker to identify patients who will benefit from LuPSMA. Longer follow-up and enrolling a larger cohort are underway. Clinical trial information: NCT06200103. Research Sponsor: Mayo Clinic Comprehensive Cancer Center Vranos Family Career Development Award.

Median values for pre-LuPSMA (Mayo and Tulane), post-RP for LPC, and HD.

	Mayo mPC (n=51)	Tulane mPC (n=26)	LPC (n=36)	HD (n=10)
Age (range)	73 (57-87)	71 (54-83)	66 (56-77)	55 (50-57)
Prior lines (range)	1 (1-3)	4 (1-11)	-	-
Gleason score	9	8	7	-
PSA (range)	1.0 (0-182)	75 (0.8-503)	-	-
PSMA EV/mL	3.7×10^6	14×10^6	2.0×10^6	1.4×10^6
STEAP1 EV/mL	30×10^6	45×10^6	12×10^6	12×10^6
CEACAM5 EV/mL	17×10^6	5.1×10^6	3.7×10^6	3.9×10^6
TROP2 EV/mL	13×10^6	5.2×10^6	4.5×10^6	3.6×10^6

Final results of Alliance A031902: A phase III trial of enzalutamide plus rucaparib as first-line therapy in metastatic castration-resistant prostate cancer (CASPAR).

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Background: Inhibition of androgen receptor (AR)-signaling results in increases in double-strand DNA breaks and genomic instability. PARP inhibitors (PARPi) are a standard treatment option for patients (pts) with homologous recombination repair mutations (HRRm). Combinations of PARPi and AR pathway inhibitors (ARPI) are associated with synthetic lethality in multiple pre-clinical studies. Clinical trials have suggested potential benefits with co-targeting PARPi and ARPI in pts with and without HRRm. **Methods:** Alliance A031902 compared radio-graphic progression-free survival (rPFS) and overall survival (OS) as co-primary endpoints with enzalutamide and rucaparib (Enz/Ruca) versus enzalutamide plus placebo (Enz/Plac) for pts with metastatic castration resistant prostate cancer (mCRPC) regardless of BRCA/HRRm status. This trial was conducted by the Alliance for Clinical Trials in Oncology in 36 centers in the US. Target sample size was 1,002 patients. Eligibility required mCRPC with or without measurable metastatic disease and was agnostic regarding HRRm status. The trial was discontinued in 10/2023 due to changes in the treatment landscape for this pt population. **Results:** Between 10/21 and 4/23, 61 pts were randomized to Enz/Ruca (n=30) or Enz/Plac (n=31). Known BRCA1/2 or PALB2 mutations were present in 1 pt (3.3%) in the Enz/Ruca arm and 1 pt (3.2%) in the Enz/Plac arm; wildtype in 14 (46.7%) vs 15 (48.4%), and unknown in 15 (50%) vs 15 (48.4%), respectively. Three patients (11.5%) in the Enz/Ruca arm discontinued due to an adverse event (AE) vs 0 in the Enz/Plac arm. Among response-evaluable pts, 7/26 (27%) in the Enz/Ruca arm discontinued due to disease progression vs 10/31 (33%) in the Enz/Plac arm. Most common grade 3+ AEs were anemia (33% vs 3%) and hypertension (17% vs 10%) in the Enz/Ruca arm and Enz/Plac arm, respectively. All 61 pts were evaluable for response assessment. PSA declines $\geq 50\%$ and $\geq 90\%$ were observed in 79% vs 45% and 60% vs 43% of pts receiving Enz/Ruca versus Enz/Plac, respectively. Median PFS in the Enz/Ruca vs Enz/Plac arms was 17.1 vs 14.2 mos, respectively (HR 1.13 [95% CI: 0.42-3.01], $p=0.81$), median rPFS (inclusive of unequivocal clinical progression) was 17.1 vs 11.7 mos (HR 0.72; 95% CI: 0.31-1.67, $p=0.44$), and median OS was not reached vs 27.0 mos (HR 0.65; 95% CI: 0.29-1.45, $p=0.29$). **Conclusions:** In this prematurely terminated phase III study, Enz/Ruca was generally well tolerated, with the safety profile consistent with prior PARPi/ARPI combinations. Efficacy outcomes for rPFS and OS are inconclusive due to limited sample size. Definitive conclusions regarding the clinical benefit of this combination cannot be determined from this study. Clinical trial information: NCT04455750. Research Sponsor: Alliance for Clinical Trials In Oncology.

Initial results of a phase 1 dose exploration and expansion study of xaluritamig plus abiraterone acetate (AA) in patients (pts) with mCRPC.

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Background: Xaluritamig (xalu) is a STEAP1 x CD3 T-cell engager, that has shown potent, durable monotherapy activity in pts with mCRPC progressing on taxane chemotherapy. This activity may be further enhanced when given in combination with an androgen receptor pathway inhibitor (ARPI) prior to chemotherapy or radioligand therapy. We therefore evaluated xalu + AA in chemotherapy-naïve pts with mCRPC as a potential chemo-sparing strategy. Here, we report initial safety and efficacy findings. **Methods:** This open-label, multicenter phase (ph) 1 dose exploration and expansion study (NCT04221542) enrolled pts who were taxane-naïve in mCRPC and had received ≤ 2 prior ARPIs (no prior AA permitted). In dose exploration, xalu was administered at a target dose of 0.3, 0.75 or 1.5 mg weekly (QW) via 1-, 2- or 3-step up regimen with 1000 mg AA and prednisolone daily. Expansion cohort was 3-step up dosing to target dose of 1.5 mg QW then 1.5 mg Q2W. Primary endpoints were safety and tolerability; secondary endpoints were pharmacokinetics and antitumor activity. **Results:** As of data cutoff (15 Oct 2025), 39 pts were enrolled with a median age of 68 years (range: 43–81). Patients received a median of 2 prior therapies, including 56% with prior taxane for mHSPC. Most common treatment-emergent adverse events (all grade [G]/ $\geq$ G3) were myalgia (92.3%/41%), cytokine release syndrome (CRS; 64.1%/7.7%), and anemia (46.2%/12.8%); there were 2 G4 (decrease in lymphocyte count and blood calcium) and no G5 treatment-related AEs reported. Dose-limiting toxicities (n=4) were reported across all dose levels (soft tissue swelling and CRS, 0.3 mg; myalgia n=2, 0.75 and 1.5 mg). Escalation completed at the planned 1.5 mg QW target dose and 1.5 mg Q2W was selected for dose expansion to align with RP3D monotherapy regimen. In the expansion cohort (n=20), confirmed PSA50, PSA90, and objective response rates (RECIST v1.1) were 58%, 47%, and 43%, respectively (Table). Median PSA response duration and radiographic progression free survival were 6.7 (95% CI: 3.8–not estimable [NE]) and 10.5 (95% CI: 8.1–NE) months, respectively. Median OS was not yet reached with 12 months median follow up (95% CI: 11.8–12.3). Seven pts across escalation and expansion remained on treatment. **Conclusions:** Xalu + AA demonstrated manageable safety and promising antitumor activity in taxane-naïve mCRPC and is now being evaluated in the randomized ph3 XALience study (NCT07213674). Clinical trial information: NCT04221542. Research Sponsor: Amgen Inc.

	Dose Escalation 0.3–0.75 mg QW N=11	Dose Escalation 1.5 mg QW N=8	Dose Expansion 1.5 mg Q2W N=20	Total N=39
PSA evaluable	11	7	19	37
PSA50 response, n (%)	6 (54.5)	7 (100)	11 (57.9)	24 (64.9)
PSA90 response, n (%)	5 (45.5)	7 (100)	9 (47.4)	21 (56.8)
Best Overall Response RECIST evaluable	6	1	7	14
Complete response, n (%)	1 (16.7)	0	0	1 (7.1)
Partial response, n (%)	3 (50)	1 (100)	3 (42.9)	7 (50)
Stable disease, n (%)	1 (16.7)	0	4 (57.1)	5 (35.7)
Not evaluable, n (%)	1 (16.7)	0	0	1 (7.1)

Real-world use of olaparib in US veterans with metastatic castration-resistant prostate cancer: Treatment patterns and outcomes.

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Background: Olaparib, a targeted therapy for metastatic castration-resistant prostate cancer (mCRPC), has demonstrated clinical benefits in patients with homologous recombination repair (HRR) gene alterations, as shown in the PROfound trial. As the largest integrated healthcare system in the US, the Veteran’s Health Administration (VHA) offers insights into olaparib use among a diverse population. We characterized the treatment patterns and outcomes of patients with mCRPC treated with olaparib. **Methods:** We identified all VHA patients with mCRPC who received olaparib between May 2020 and December 2023. We then performed a retrospective chart review of data from May 2018 to June 2025 to capture pre- and post-treatment data. Demographics, baseline characteristics, biomarker testing and treatment sequencing were summarized. We analyzed time to event outcomes: time to next therapy (TTNT), and overall survival (OS) via Kaplan-Meier methods, both starting from olaparib initiation. **Results:** We identified 477 mCRPC patients receiving olaparib. Median age at initiation was 75, older than subjects in PROfound (median age 69). Most patients were non-Hispanic White (69%), followed by Black/African American (20%) and Hispanic/Latino (6%). Between 2020 and 2023, olaparib was most commonly initiated in ≥5th line after prostate cancer diagnosis (46%), followed by 4th (25%), 3rd (22%), and 2nd line (6.5%). All patients had received an androgen receptor pathway inhibitor prior to olaparib. Median time from HRR testing to olaparib initiation was 5 months. Median TTNT was 7 months; OS was 12 months. Use of olaparib in an earlier line post first NHA was associated with numerically longer OS (17 months for 1st line vs. 8 months for 4th or later). **Conclusions:** Within the VHA, olaparib showed favorable outcomes despite older age and late-line use, supporting effectiveness in routine practice and in a more diverse population with substantially higher representation of Black/African American and Hispanic/Latino individuals than in clinical trials. Understanding these treatment patterns provides insight into clinical practice and helps guide towards optimal integration of olaparib into management of mCRPC. Research Sponsor: AstraZeneca; Merck.

Kaplan-Meier estimates for time to event outcomes.		
	#Events/Total	Median Time (95% CI) (months)
Time to Next Treatment		
- All Patients	449/477	7 (6-8)
- Olaparib Line of Treatment Post NHA		
1st line	100/111	9 (7-10)
2nd line	151/162	8 (7-10)
3rd line	92/96	6 (5-8)
4th line or later	91/92	5 (4-6)
Overall Survival		
- All Patients	395/477	12 (11-13)
- Olaparib Line of Treatment Post NHA		
1st line	79/111	17 (12-22)
2nd line	133/162	15 (12-17)
3rd line	85/96	10 (8-12)
4th line or later	88/92	8 (6-9)

Sequencing of PARP inhibitors and taxane chemotherapy in HRR-altered metastatic castration-resistant prostate cancer: A real-world VA analysis.

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Background: Taxane-based chemotherapy (taxane) and poly(ADP-ribose) polymerase inhibitors (PARPi) are established life-prolonging therapies for patients with homologous recombination repair (HRR)-altered metastatic castration-resistant prostate cancer (mCRPC), particularly tumors with BRCA1/2 alterations. However, data informing the optimal sequencing of PARPi and taxane chemotherapy in this patient population is limited, especially because subsequent treatments may not be captured in reports of clinical trials. Real-world evidence may help describe treatment sequencing patterns and outcomes. **Methods:** We conducted a retrospective cohort study using the nationwide Veterans Affairs (VA) healthcare system. Patients with mCRPC and HRR alterations treated with either PARPi or taxanes for mCRPC were included. HRR mutation status was ascertained from genomic results captured within the VA database and included different platform/assays. Baseline characteristics were assessed at mCRPC treatment initiation. The primary endpoint was overall survival (OS) from the initiation of PARPi or taxane. Secondary analyses included OS comparisons by initial treatment class and OS from initiation of second-line therapy among patients who received both PARPi and taxane chemotherapy. Survival was estimated using Kaplan-Meier methods and compared using Cox proportional hazards models with inverse probability of treatment weighting (IPTW) to adjust for baseline differences. **Results:** Between Jan 2014 - May 2025, a total of 418 patients (26.8% non-Hispanic Black, median age 74.5 years), with HRR-altered mCRPC (31.3% BRCA2, 26.8% ATM, 21.1% CDK12, 13.4% CHEK2) were included in the final analysis. Metastatic involvement included bone metastases in 80.9% of patients, and visceral metastases in 11.2%. Median PSA was 30.2 ng/mL. Prior to mCRPC, 58.6% of patients had received ARPIs and 14.1% had received taxane chemotherapy. With a median follow-up of 14.1 months, patients received PARPi (N=211) or taxane (N=207), and 30.1% received both treatments for mCRPC. OS was similar between patients initially treated with PARPi versus taxane for mCRPC (HR 1.09, 95% CI 0.84-1.41). Among patients who received both therapies, OS did not differ based on treatment sequence (PARPi→taxane vs taxane→PARPi; HR 0.90, 95% CI 0.41-1.85). **Conclusions:** In this real-world VA cohort of HRR-altered mCRPC, overall survival was similar whether PARP inhibitors or taxanes were used as initial therapy and did not differ by subsequent treatment sequence. Treatment crossover was observed in routine clinical practice. Research Sponsor: VA Office of Research and Development.

Dissecting metastatic castration-resistant prostate cancer using regulatory network analysis of tumor transcriptomes.

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Background: Metastatic castration-resistant prostate cancer (mCRPC) is characterized by profound clinical and biological heterogeneity, including variable dependence on androgen receptor signaling, frequent genomic instability, lineage plasticity, and highly divergent clinical outcomes. Despite the widespread use of genomic profiling and expression-based signatures, robust patient-level risk stratification and biologically grounded disease subtyping remain limited. We hypothesized that inference of transcriptional regulatory programs underlying tumor state, integrated with genomic and clinical features, would improve prognostication in mCRPC. **Methods:** We analyzed genomic, transcriptomic, and clinical data from mCRPC tumors in the Stand Up To Cancer (SU2C) cohort. A transcriptional regulatory network was reverse-engineered using the latest version of the Algorithm for the Reconstruction of Accurate Cellular Networks (ARACNe3) and transcriptional regulator activity was inferred using Nonparametric analytical Rank-based Enrichment Analysis (NaRnEA). We constructed a novel prognostic machine learning model using a random survival forest integrating regulatory activity features, canonical genomic alterations, and clinical variables. **Results:** Samples were stratified by RNA-sequencing library preparation method into polyA-purified (training, n=150) and exon-capture (testing, n=100). Our model demonstrated strong and statistically significant performance in both the training cohort (out-of-bag Cox PH $p=4.63 \times 10^{-8}$, AUROC = 0.7711) and the independent test cohort (Cox PH $p=2.92 \times 10^{-5}$, AUROC = 0.7413). The most informative features included inferred activities of key transcriptional regulators implicated in proliferation, lineage programs, and neuroendocrine differentiation (E2F1, MYC, SOX2, AR, REST), canonical genomic alterations relevant to mCRPC biology (AR, TP53, RB1, FOXA1, APC, PI3K pathway), and select clinical variables (prior therapy, Gleason score, age, metastatic site). Our model also outperformed several widely used gene expression signatures (AR, NEPC, Cell Cycle Progression, RB1 Loss). Regulatory activity-based analyses also revealed substantially greater biological structure and cluster coherence than gene expression-based analyses in subsequent analyses, highlighting distinct and clinically aggressive regulatory states in this dataset. **Conclusions:** Integrating regulatory network-inferred transcriptional programs with genomic and clinical features enables robust, independently validated prognostication in mCRPC that outperforms widely used expression-based signatures. This approach exposes clinically relevant biological heterogeneity underlying aggressive and treatment-resistant disease states and provides a framework for improved risk stratification in advanced prostate cancer. Research Sponsor: National Cancer Institute; R01CA276438.

Clinical outcomes of sequential androgen receptor pathway inhibitors (ARPIs) versus novel therapies in metastatic castration-resistant prostate cancer after progression on second-generation ARPIs: A systematic review and meta-analysis.

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Background: Most recent pivotal, randomized controlled trials (RCTs) testing novel therapies in ARPI pretreated mCRPC patients have incorporated sequential ARPI as the comparator. Given that sequential ARPI could be an inferior control arm based on CARD data, we conducted a meta-analysis to quantify the treatment effect of novel agents vs sequential ARPI and to evaluate whether sequential ARPI constitutes an appropriate control arm for future trials. **Methods:** A systematic search of PubMed, Europe PMC, and ClinicalTrials.gov up to August 14, 2025, identified 2,904 records. After removal of duplicates and exclusions, 17 RCTs met the inclusion criteria. Eligible studies enrolled patients with mCRPC who had progressed after prior exposure to second-generation ARPIs, comparing a novel agent (chemotherapy, targeted therapy, Immunotherapy and radioligands) with sequential ARPI treatment. Three independent reviewers screened the studies and extracted data in accordance with PRISMA guidelines. The primary endpoints were overall survival (OS) and progression-free survival (PFS), and the hazard ratios (HRs) were pooled using a random-effects model. **Results:** We included a total of 6,725 patients in this meta-analysis, with 3,579 (53.2%) receiving novel agents and 3,146 (46.8%) receiving ARPIs. Analysis revealed the pooled HR for OS was 0.86 (95% CI: 0.76–0.96; $p < 0.01$). Substantial heterogeneity was observed ($I^2 = 64.05\%$). This heterogeneity reflects the inclusion of trials with different novel agents and molecular selection criteria, with some highly selective trials (e.g., PROfound HR 0.58) showing greater benefit than others (e.g., ERA 223 HR 1.22). In addition, the pooled PFS analysis demonstrated a highly significant clinical advantage for novel therapies, resulting in a pooled HR of 0.72 (95% CI: 0.61–0.86; $p < 0.01$). This PFS analysis exhibited very high heterogeneity ($I^2 = 84.44\%$), driven by exceptional outcomes observed in trials targeting specific biomarkers. **Conclusions:** Across RCTs, novel therapies consistently outperform sequential ARPI for both OS and PFS in post-ARPI mCRPC. These pooled effects, and their amplification in biomarker-selected populations, suggest that sequential ARPI is a suboptimal control arm in this setting. Future trials should consider more appropriate, biomarker-driven or guideline-concordant active comparators, enabling fairer tests of clinical benefit and more generalizable results. Research Sponsor: None.

Androgen receptor (AR) gene dynamics in ctDNA post-abiraterone/enzalutamide: Longitudinal study in mCRPC with germline results.

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Background: Approximately 10–15% of men with metastatic prostate cancer harbor germline mutations. Circulating tumor DNA (ctDNA) provides a non-invasive approach to identifying AR mutations as resistance mechanism after abiraterone and enzalutamide initiation. In this study, we report longitudinal ctDNA profiling in patients with metastatic castration-resistant prostate cancer (mCRPC) who had germline testing. **Methods:** A retrospective review was conducted at Tulane Cancer Center to identify mCRPC patients with serial ctDNA after starting abiraterone and/or enzalutamide and germline test results. Germline testing was performed using a multi-gene cancer panel from Invitae, covering 50–86 genes, while somatic alterations in ctDNA were assessed through Guardant360, which included 70–83 genes. Linear mixed-effects models (LMMs) with random intercepts were used to model AR gene allele fraction and AR amplification copy number as continuous outcomes. Fixed effects included serial ctDNA timepoints and germline gene pathogenicity, and random effects accounted for repeated measure using patient-specific intercepts. Cox Proportional Model was used to analyze the time from initiation of ARPi to AR amp and/or AR mutation in ctDNA. Analyses were performed using the R version 4.4.2. **Results:** From 2015–2025, 341 mCRPC patients with germline test results received an average of 2.96 ctDNA tests post abiraterone or enzalutamide. In this cohort, 47 patients had germline pathogenic mutations (14%) and 294 patients had germline non-pathogenic mutations (86%). Among those with pathogenic germline findings, there were 29 patients with mutation in homologous recombination repair genes (62%) and 18 patients with mutation in other genes. Overall, 55.7% patient in this cohort developed either AR amplification or AR pathogenic mutation in ctDNA. In linear mixed models, germline pathogenicity and pathogenic HRR mutations were not associated with AR copy number, AR allele frequency, or occurrence of somatic AR alterations. Serial ctDNA timepoints following baseline assessment are associated with a significant increase in AR amplifications copy numbers in ctDNA ($p=0.003$). AR amplification copy number increases by 0.12 for each subsequent time-point from baseline. Only 318 patients were included in survival analysis due to missing ARPi start date. Time to ctDNA AR amplification or mutation after 1st ARPi initiation was shorter in mCRPC patients without pathogenic HRR germline mutations compared to those with pathogenic HRR mutations (median: 38 vs 58 months, $p = 0.049$). **Conclusions:** Later serial timepoints correlated with a significant increase in AR amplifications copy numbers but not correlated with highest AR mutant allele frequency. mCRPC patients without germline HRR mutations will find ctDNA AR amplification or mutation sooner than those with germline HRR mutations. Research Sponsor: None.

Effect of frailty measures on overall survival in prostate cancer: A systematic review and meta-analysis.

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Background: Prostate cancer at all stages is associated with a favorable prognosis and treatment is generally well tolerated, including in the elderly. Frailty screening tools such as the Geriatric 8 (G8) have been associated with decreased survival across different cancers. However, the effect of frailty on overall survival (OS) in prostate cancer is poorly understood. **Methods:** A comprehensive search of PubMed, Embase, and Scopus was performed through December 2025 for studies evaluating the impact of frailty on OS in patients with prostate cancer. Data were analyzed in two distinct cohorts: patients with metastatic castration-resistant prostate cancer (mCRPC) and those with unspecified prostate cancer (PC) (at any stage). Meta-analysis was performed using a random-effects model to calculate pooled hazard ratios (HR) and 95% confidence intervals (CI). Statistical heterogeneity was assessed using the I² statistic and Chi² test. **Results:** Of the twelve studies that met the inclusion criteria, two were excluded due to non-availability of survival statistics for analysis. Four studies could not be included in the meta-analysis as hazard ratios were not reported. A total of 7120 patients across seven studies were included in the meta-analysis. In the mCRPC cohort (n=4 studies), frailty was a significant predictor of mortality, associated with a pooled HR of 2.16 (95% CI: 1.34–3.49; P = 0.002). Moderate-to-high heterogeneity was observed in this group (I² = 65%). In the unspecified PC cohort (n=2 studies), the association between frailty and OS did not reach statistical significance, yielding a pooled HR of 1.74 (95% CI: 0.69–4.40; P = 0.24). Heterogeneity for the unspecified PC group was I² = 61%. **Conclusions:** Frailty is associated with increased mortality in elderly patients with metastatic castration-resistant prostate cancer. This effect of frailty was not statistically significant when the population was expanded to include early-stage prostate cancer. These results highlight the importance of geriatric screening for prognostic assessment in elderly patients with prostate cancer, especially in those with metastatic castration-resistant disease. Research Sponsor: None.

Study characteristics and hazard ratios for overall survival.							
Study	Cancer type	Design	N	Age	Assessment tool	Frailty %	OS
Beardo (2019)	mCRPC	RS	70	≥75	G8	NR	3.13 (1.13–8.66)
Banna (2022)	mCRPC	PS	234	78	G8	38%	3.58 (1.72–7.49)
Wilk (2022)	mCRPC	PS	49	71	G8	47%	2.24 (1.15–4.36)
Deol (2023)	mCRPC	RS	5822	75.4	VA-FI	39.70%	1.44 (1.35–1.52)
Royset (2023)	PC	PS	73	73.6	EFS	24.60%	1.27 (1.20–1.35)
Siwakoti (2024)	PC	PS	70	70	CARE-FI	21%	3.55 (1.01–12.47)

Abbreviations: Retrospective study (RS); Prospective study (PS); Sample size (N); Geriatric 8 (G8); Veterans Affairs Frailty Index (VA-FI); Edmonton Frail Scale (EFS); Cancer and Aging Resilience Evaluation Frailty Index (CARE-FI); Not reported (NR).

Transient prostate-specific antigen flare induced by lutetium Lu 177 vipivotide tetraxetan in patients with metastatic castration resistant prostate cancer.

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Background: Prostate-specific antigen (PSA) flare, an initial rise in PSA that subsequently falls, is a well-known phenomenon in prostate cancer patients treated with hormone therapy and chemotherapy. However, its incidence, chronology, and clinical significance for treatment outcome of patients undergoing lutetium Lu 177 vipivotide tetraxetan (Lu-177), a newly FDA-approved radiopharmaceutical agent for metastatic castration-resistant prostate cancer (mCRPC), is uncertain. Our retrospective study, included mCRPC patients treated with Lu-177 between June 2022 and March 2025 at University of Kansas Cancer Center, aims to evaluate the association of PSA flare with clinical outcomes in patients with mCRPC undergoing Lu-177. **Methods:** PSA flare was defined as any initial increase in PSA level from baseline before start of 3rd cycle followed by a decrease in PSA level of any degree or a decrease to less than baseline PSA level. The primary endpoint was progression-free survival (PFS). The secondary endpoints were overall survival (OS), PSA50 response, and disease control rate (DCR). The log-rank test was applied to compare PFS and OS between patient group with PSA flare and patient group without PSA flare. **Results:** The data from 158 patients were analyzed. The median age was 73.5 years old (range: 52-100). The median number of Lu-177 cycles received was 4 (range: 1-6). Forty five patients (28.5%) experienced PSA flare. The median time from treatment initiation to onset of PSA flare was 3 weeks (range: 1-9); whereas the median interval between PSA flare and PSA nadir was 14 weeks (range: 2-72). The median increase in PSA from baseline to flare was 39.1% (range: 3.3-1,133%); whereas the median decrease in PSA from flare to nadir was 70.1% (range: 8.4-98.4%). There was no statistically significant difference in PFS and OS between patient group with PSA flare and patient group without (median PFS: 8.2 vs. 5.6 months, $p=0.20$; median OS: 14.3 vs. 12.5 months, $p=0.29$). PSA50 response was observed in total of 76 patients (48.1%). In patient group with PSA flare, 48.9% of the patients achieved PSA50 response. Similarly, 48.7% of the patients achieved PSA50 response in patient group without PSA flare. Majority of patients were also assessed for radiographic response ($n=139$). Between patient group with PSA flare and group without PSA flare, DCR was achieved in 60% and 49.5% of the patients respectively (RR = 1.21, 95% CI: 0.88 to 1.67, $p=0.26$). **Conclusions:** The PSA flare phenomenon is not rare in mCRPC patients treated with Lu-177. Our study suggests the clinical outcome appears consistent regardless of the PSA flare. Therefore, Lu-177 should not be withdrawn early and prematurely in mCRPC patients who have an initial but isolated PSA rise following the therapy. Further studies are warranted to validate our findings. Research Sponsor: None.

Post-ARPI sequencing in mCRPC: A propensity-matched real-world comparison of ¹⁷⁷Lu-PSMA-617 versus docetaxel for early clinical outcomes.

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Background: Treatment sequencing in metastatic castration-resistant prostate cancer (mCRPC) after ADT and ARPI exposure varies in practice. While ¹⁷⁷Lu-PSMA use is expanding in routine practice, real world head to head comparisons with docetaxel in ARPI-exposed mCRPC are limited, particularly for short-term outcomes and treatment related acute care utilization. **Methods:** Using TriNetX, adults > 18 years of age with metastatic prostate cancer and prior ARPI exposure who initiated ¹⁷⁷Lu-PSMA or docetaxel were identified (index = first administration). Cohorts were balanced with 1:1 propensity score matching (PSM) on demographics and baseline comorbidities. Outcomes from day 1–180 post-index included all-cause mortality (primary), hospitalization, acute kidney injury (AKI; ICD-10 N17), and thromboembolic/ischemic events (ICD-10 I21/I26/I63/I82). For each outcome, patients with prior documentation of that outcome were excluded. Outcomes are reported as risks and risk ratios (RR) with 95% confidence intervals. **Results:** Before matching, 563 patients initiated ¹⁷⁷Lu-PSMA-617 and 8,749 initiated docetaxel; after 1:1 PSM, 497 patients per cohort were analyzed. At 180 days, all-cause mortality was 7.3% (36/494) with ¹⁷⁷Lu-PSMA-617 versus 12.2% (60/491) with docetaxel (RR 0.60, 95% CI 0.40–0.88). Hospitalization occurred in 7.2% (21/290) versus 21.1% (52/247) (RR 0.34, 95% CI 0.21–0.55). In a separate matched renal-safety analysis (480 per cohort), AKI occurred in 2.8% (11/390) versus 9.0% (36/399) (RR 0.31, 95% CI 0.16–0.60). Thromboembolic/ischemic events were 3.8% (15/394) versus 6.4% (26/404) (RR 0.59, 95% CI 0.32–1.10). **Conclusions:** In ARPI-exposed mCRPC, ¹⁷⁷Lu-PSMA was associated with lower 180-day mortality risk and substantially fewer hospitalizations than docetaxel, with a lower risk of AKI. These findings highlight a potential short-term effectiveness and acute-care utilization advantage of ¹⁷⁷Lu-PSMA in routine practice and support further prospective evaluation. Research Sponsor: None.

Key 180-day outcomes after matching.

Outcome	¹⁷⁷ Lu-PSMA	Docetaxel	Effect estimate (180 days)
All-cause mortality	36/494 (7.3%)	60/491 (12.2%)	RR 0.596 (0.402-0.884)
Hospitalization	21/290 (7.2%)	52/247 (21.1%)	RR 0.344 (0.213-0.554)
Acute kidney injury (AKI)*	11/390 (2.8%)	36/399 (9.0%)	RR 0.312 (0.163-0.595)
Thromboembolic/ischemic†	15/394 (3.8%)	26/404 (6.4%)	RR 0.592 (0.318-1.100)

*AKI analysis used a separate matched run (480 per cohort).

†Composite of I21, I26, I63, I82.

Real-world characteristics, homologous recombination repair mutation (HRRm) testing, treatment patterns, and outcomes of patients with metastatic castration-sensitive prostate cancer (mCSPC) in the US community oncology setting.

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Background: Homologous recombination repair mutation (HRRm) testing is recommended by NCCN guidelines for metastatic castration-sensitive prostate cancer (mCSPC). The real-world CAPTURE study is one of the first to associate HRRm carriers with worse outcomes. However, real-world data to quantify prognostic and predictive value of HRRm in mCSPC are limited and heterogeneous, especially for patients treated within US community oncology settings.

Methods: This was a retrospective observational cohort study of patients with documentation of HRRm testing who initiated systemic therapy for mCSPC (index) between 1/1/2019–3/31/2024 in The US Oncology Network or non-Network practices. Stratified random samples of 150 patients with HRRm and 150 patients without HRRm were selected for chart abstraction to collect patient characteristics within 60 days prior to index and prostate cancer treatments (androgen deprivation therapy, ADT; androgen receptor pathway inhibitors, ARPi; docetaxel, DOC) through the end of follow-up (3/31/2025). Somatic and/or germline testing results for a 12-gene HRRm panel (ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C) were recorded from all available records. Descriptive Kaplan–Meier analyses of overall survival (OS) and real-world progression-free survival (rwPFS) were assessed per HRRm, de novo metastatic and high-volume disease (HVD) status. **Results:** Overall, 300 patients were selected with median (IQR) age of 69 (63–77) years and median (IQR) follow-up of 25 (15–36) months. Among patients with available data at baseline, most were Gleason ≥ 8 (79% of 181) and PSA >4 ng/mL (85% of 274). In the HRRm cohort (N=150), 70 (47%) patients were BRCAm and 80 (53%) patients had non-BRCAm HRRm mutations. De novo mCSPC was identified in 97 (65%) patients with HRRm and 100 (67%) patients without HRRm. HVD was observed in 85 (57%) patients with HRRm and 96 (64%) without HRRm. Frontline (index) systemic therapies for mCSPC in the HRRm/non-HRRm subgroups included ADT (28%/22%), ADT+ARPi (39%/47%), ADT+DOC (15%/15%) and ADT+ARPi+DOC (15%/15%). Outcomes are summarized below. **Conclusions:** Patients with HRRm mCSPC experienced numerically shorter OS and rwPFS than non-HRRm patients. This highlights an important need for early HRRm testing and targeted treatment strategies within earlier disease settings. Research Sponsor: None.

Outcome, median (95% CI), months	HRRm (N=150)	No HRRm (N=150)
OS, overall	44.0 (36.8–55.2)	48.5 (40.2–NR)
rwPFS, overall	17.5 (14.4–22.1)	22.6 (17.9–33.4)
N (%), de novo	97 (65)	100 (67)
OS, de novo	41.7 (30.6–44.9)	48.5 (33.4–69.4)
rwPFS, de novo	15.4 (13.0–23.1)	22.0 (17.2–32.3)
N (%), HVD	85 (57)	96 (64)
OS, HVD	44.4 (36.8–55.2)	42.5 (33.4–69.4)
rwPFS, HVD	17.7 (12.0–27.3)	19.2 (16.3–30.3)

Comparative efficacy and safety of systemic therapies in high-risk hormone-sensitive prostate cancer: A network meta-analysis of 13 phase III randomized trials.

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Background: Treatment intensification improves survival in hormone-sensitive prostate cancer (HSPC). However, direct comparisons between triplet therapies consisting of androgen-deprivation therapy, docetaxel, and an androgen receptor pathway inhibitor (ADT+Docetaxel+ARPI) and ARPI doublets are limited. In addition, available evidence remains fragmented between high-risk non-metastatic (nmHSPC) and metastatic (mHSPC) disease states. We conducted a network meta-analysis (NMA) to rank treatment regimens and inform clinical decision-making. **Methods:** We analyzed 13 phase III RCTs including approximately 13,000 patients with high-risk HSPC, encompassing metastatic and high-risk non-metastatic disease. Treatment strategies included ADT alone, docetaxel (DOC), abiraterone (ABI), enzalutamide (ENZ), apalutamide (APA), darolutamide (DARO), and triplet combinations. A frequentist random-effects NMA was performed with overall survival (OS) as the primary endpoint. Secondary efficacy endpoints included progression-free survival (PFS) and time to castration resistance (TTCR). Safety was assessed using treatment-emergent grade ≥ 3 AEs, assuming network transitivity. **Results:** For the primary endpoint (OS), triplet therapies ranked highest, including ADT+DOC+DARO (HR 0.55 [95% CI 0.43–0.69]) and ADT+DOC+ABI (HR 0.60 [95% CI 0.45–0.81]) compared with ADT alone. ARPI doublets also demonstrated robust OS benefits, including ABI (HR 0.63 [0.58–0.69]), APA (HR 0.67 [0.51–0.89]) and ENZ (HR 0.69 [0.51–0.94]). No statistically significant OS difference was observed between triplets and ARPI doublets, although triplets numerically favored higher efficacy. For PFS ($I^2 = 86.5\%$), triplet therapies remained superior, with ADT+DOC+DARO showing the greatest benefit (HR 0.24 [0.13–0.45]), followed by the ENZ doublet (HR 0.40 [0.27–0.60]). Secondary endpoints (TTCR, PSA-PFS) consistently favored ARPI-based regimens. Regarding safety, triplet therapies significantly increased the odds of Grade ≥ 3 AEs versus ADT (OR ~2.6–3.7), driven primarily by docetaxel-associated fatigue and ABI-related hypertension. Conversely, APA, ENZ, and DARO doublets demonstrated favorable safety profiles, with no significant increase in overall Grade ≥ 3 AEs compared with ADT alone (ORs 1.02–1.06). Benefits were consistent across nmHSPC and mHSPC subgroups (p for interaction = 0.66). **Conclusions:** Triplet therapy represents the efficacy standard for fit patients with high-volume mHSPC. However, ARPI doublets offer a compelling alternative with comparable survival benefits and a superior safety profile, making them the preferred choice for high-risk nmHSPC and patients prioritizing tolerability. Clinical selection should stratify based on disease volume and fitness for docetaxel-associated toxicity. Research Sponsor: None.

Independent validation of a model to predict early favorable PSA response (NADIR model) in enzalutamide-treated patients of the ARCHES trial.

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Background: Our group recently trained and independently validated a multivariable logistic regression model (NADIR model) to predict early favorable PSA response (≤ 0.2 ng/mL) in metastatic hormone sensitive prostate cancer (mHSPC) patients (pts) within 6 months of treatment initiation with androgen receptor pathway inhibitor (ARPI). In this work, we independently validated the NADIR model in the enzalutamide (enza) treated patients from the ARCHES trial. **Methods:** ARCHES is a phase III randomized controlled trial where patients with mHSPC were randomly assigned to ADT versus ADT plus enzalutamide. The locked model was applied to patients in the enza arm and model discrimination was assessed using area under the receiver operating curve (AUC) with 95% confidence intervals (CI) from 5000 bootstrap iterations. Additional performance metrics included Index of prediction accuracy (IPA) relative to null model, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive likelihood ratio (PLR) and negative likelihood ratio (NLR). A Cox proportional hazard model was applied in a 6-month landmark population to determine the hazard of death in middle and lower tertile relative to upper tertile when stratified by tertiles of predicted probability from the NADIR model. **Results:** 1125 patients with non-missing data were included in this independent validation cohort of whom 559 patients were treated with enza. Approximately 64% (n=360) achieved PSA ≤ 0.2 ng/mL within 6 months of treatment initiation. The AUC was 0.80 [95% CI 0.76–0.83] and IPA was 23%. The sensitivity, specificity, PPV, NPV, PLR, and NLR were 0.82 [0.77–0.86], 0.56 [0.49–0.63], 0.77 [0.72–0.81], 0.63 [0.55–0.70], 1.85 [1.57–2.17], and 0.33 [0.26–0.42], respectively. The early favorable PSA response rates in patients stratified by decreasing order of tertiles of predicted probability of PSA response from the NADIR model were 92% [88–96], 64% [57–71], and 37% [30–45], respectively. Compared to those in the upper tertile, patients in the middle tertile (HR 1.97 [1.33–2.91]) and lower tertile (HR 2.18 [1.48–3.21]) had significantly worse OS. Among patients with < 3 months of ADT before ARPI initiation, the AUC was 0.79 [0.75–0.83] with IPA of 22%. **Conclusions:** In this independent validation using the ARCHES trial, the NADIR model showed strong discriminatory performance and effectively stratified enzalutamide-treated patients by early favorable PSA response and overall survival. With prospective validation, this model may provide a useful tool for early prognostication in patients with mHSPC receiving ARPI therapy. Research Sponsor: None.

Comeback from long-course ADT with relugolix (rel) and darolutamide (daro) in hormone-sensitive prostate cancer (PC) (CLEARED).

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Background: The oral luteinizing hormone releasing hormone antagonist rel and androgen receptor pathway inhibitor (ARPI) daro are approved for treatment of advanced PC but the combination has not been prospectively investigated, and kinetics of testosterone (T) recovery after 2 years of rel have not been reported. Here we report pharmacokinetics (PK) as well as initial safety and reduction in T and PSA from a phase 2 trial of rel plus daro in high risk localized (HRL), lymph node-positive (N+) or low volume metastatic (LV) PC. **Methods:** Eligible patients (pts) had PSA > 0.02 ng/ml, T $\geq$ lower limit of normal (LLN) and were planned for 2 years of ADT+ARPI for HRL, N+ or LV PC. Prior ADT $\pm$ ARPI was permitted if T recovered to $\geq$ LLN, but pts with high volume metastatic PC, prior PSA rise with castrate T, or on medications with significant predicted drug-drug interactions with rel or daro were excluded. Pts received rel 360 mg $\times$ 1 on day 1 (D1) followed by 120 mg QD and daro 600 mg BID starting on D1, and elected for PK sampling at 0h, 2h, 4h, 8h on D1 (cohort 1) or pre-dose on D1, 2, 8 and 29 (cohort 2). Radiation therapy to local and/or metastatic sites was delivered per standard of care. Pts receive up to 26 28-day treatment cycles with PSA/T monitoring every 3 months (mo) until 18 mo after end-of-treatment (EOT). The primary endpoints are rate of T recovery to > LLN by 18 mo after EOT and safety/adverse events (AEs). Secondary endpoints include PK, rate of treatment discontinuation, and pt-reported outcomes. **Results:** 33 pts enrolled: 8 with HRL, 11 with N+ and 14 with LV PC. 21 chose cohort 1 and 12 chose cohort 2. Single dose maximum concentrations (C_{max}) on D1 for rel and daro, and D29 pre-dose trough level (C_{trough}) for rel were similar to historical monotherapy comparators (comp) with geometric mean ratios (GMR) between 0.80–1.25 (Table), while D8 C_{trough} for daro was slightly outside this range. By cycle 7 (C7) D1, 15 pts experienced Grade $\geq$ 3 AEs: 12 lymphopenia (3 possibly related to daro), with the remainder not treatment-related. 0 pts discontinued rel or daro; 3 dose-reduced daro. 33/33 (100%) pts achieved castrate T < 50 ng/dl and 32/33 (97%) achieved profound castrate T < 20 ng/dl (1 with T 24 ng/dl on C7 D1). PSA decline of $\geq$ 50% was achieved in 33/33 (100%) and decline $\geq$ 90% in 32/33 (97%) by C7 D1. **Conclusions:** The combination of rel and daro was safe and well-tolerated during the 1st 6 treatment cycles, with PK parameters similar to historical monotherapy comparators. Appropriate initial T and PSA reduction were observed, and pts will be followed after EOT for the primary endpoint of T recovery (NCT06463457). Clinical trial information: NCT06463457. Research Sponsor: NCCN; Sumitomo Pharma America; Pfizer; Bayer.

PK for rel and daro.

	Geometric Mean	Coefficient of variation (%)	GMR
rel D1 C_{max} (N=19) [comp]	141.5 ng/ml [1.25]	145.2% [220%]	1.13
rel D29 C_{trough} (N=11) [comp]	6.34 ng/ml [7.54]	62.6% [91.9%]	0.84
daro D1 C_{max} (N=18) [comp]	2.10 μ g/ml [1.77]	29.0% [26.4%]	1.19
daro D8 C_{trough} (N=11) [comp]	2.52 μ g/ml [1.82]	24.7% [32.8%]	1.38

Remote activity monitoring to detect physical function decline and unexpected medical events in patients with prostate cancer undergoing androgen deprivation therapy.

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Background: Among patients with prostate cancer (PC), treatment with androgen deprivation therapy (ADT) is associated with reduced physical function, which can result in diminished quality of life and the occurrence of adverse medical events. The use of wearable activity monitors allows for remote monitoring of daily activity to potentially detect early functional decline and predict significant medical events such as hospitalization, serious adverse events, and premature death. This study evaluated whether wearable activity monitoring could serve as an early indicator of functional decline and impending adverse events in patients with PC undergoing ADT. **Methods:** PC patients receiving ADT at Cedars-Sinai and Durham VA who enrolled in the DigiPRO trial (NCT04575402) wore a Fitbit Charge over 12 weeks to track quantitative physical activity and sleep data for prediction of the occurrence of unexpected medical events (composite of hospitalization, premature death, or fall) and significant patient-reported physical function decline (> 5 NIH PROMIS T score points) within 6-months follow-up. **Results:** 40 patients were included in the analysis (median age 70, range 51–87, 37% Black and 63% White; 10% identified as Hispanic). On average, PC patients walked 5,189 steps/day, were sedentary 16 hours/day, and slept 5.8 hours/night. A clinically meaningful decline in daily steps (> 500 steps) within the first 3 months of initiating ADT was associated with higher odds of experiencing an unexpected medical event (hospitalization, death, fall) (OR = 3.03; 95% CI 1.6–5.9, $p = 0.001$) and clinically meaningful decline in patient-reported physical function (> 5 PROMIS T score points) occurring within 6 months from study completion (OR = 5.2, 95% CI 1.3–11.7, $p = 0.02$). **Conclusions:** These findings suggest remote activity monitoring may serve as a novel early warning system to identify patients who are at increased risk of unexpected medical events and clinically meaningful physical function decline in PC patients undergoing ADT. Use of this early warning system could lead to targeted interventions in high-risk patients to reduce morbidity and perhaps even prolong survival in patients undergoing ADT. Clinical trial information: NCT04575402. Research Sponsor: U.S. Department of Defense.

Cognition of apalutamide + ADT treatment responders versus non-responders.

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Background: LIBERTAS (NCT05884398) evaluates intermittent androgen deprivation therapy (ADT) with apalutamide monotherapy in metastatic castration-sensitive prostate cancer (mCSPC). ADT is known to affect cognitive domains such as visuospatial ability and executive function. However, links between cognition and treatment responses remain unclear. LIBERTAS offers an opportunity to examine this relationship in participants with mCSPC. **Methods:** All 410 participants received apalutamide and continuous ADT during the initial treatment phase, 144 without prior ADT exposure (ADT naïve). Participants with PSA <0.2 ng/mL at 6 months were considered responders, otherwise they were non-responders. Cognition was assessed by two tasks from Cambridge Cognition's CANTAB battery: Paired Associates Learning (PAL; visual memory) and Spatial Working Memory (SWM; executive function) at baseline (C1), 2 months (C3), and 4 months (C5). Outcomes included PAL First Attempt Memory Score (PALFAMS28, higher=better), PAL Total Errors Adjusted (PALTEA28, lower=better), and SWM Between Errors (SWMBE468, lower=better). At each visit, group differences were evaluated using the Mann-Whitney U test. Longitudinal change within and between groups were assessed using linear mixed effect models adjusted for age and testosterone. **Results:** At all visits, responders had higher PALFAMS28, lower PALTEA28, and lower SWMBE468 than non-responders in the entire sample (Table 1). In ADT-naïve participants, responders (N=100) had higher PALFAMS28 than non-responders (N=44) at C3 (10.48 ± 4.74 vs. 8.59 ± 5.00 , $p=0.01$). SWMBE468 was lower in ADT-naïve responders than ADT-naïve non-responders at C1 (14.25 ± 9.12 vs. 19.30 ± 8.37 , $p=0.001$) and C5 (15.42 ± 8.58 vs. 19.77 ± 11.06 , $p=0.01$). Among all participants and within the ADT-naïve group, only the responders' performance changed over time: PALFAMS28 increased and PALTEA28 decreased from C1 to C5 and SWMBE468 increased from C1 to C3 ($p < 0.01$). No significant time-by-group interaction emerged. **Conclusions:** Analyzed in retrospect, responders outperformed non-responders in visual memory and executive function at baseline and throughout initial treatment, maintaining a cognitive advantage. Though not tested, we hypothesize early cognitive performance could be considered among a constellation of clinical factors to prognosticate treatment response, support patient stratification and personalize treatment strategies. Clinical trial information: NCT05884398. Research Sponsor: Johnson & Johnson.

Significant differences between responders and non-responders.

Measure	Visit	Responders (N=266): Mean $\pm$ SD	Non-Responders (N=144): Mean $\pm$ SD	P value
PALFAMS28	C1	9.43 $\pm$ 4.53	8.18 $\pm$ 4.08	0.005
	C3	9.78 $\pm$ 4.65	8.07 $\pm$ 4.30	<0.001
	C5	10.16 $\pm$ 4.85	8.47 $\pm$ 4.80	0.003
PALTEA28	C1	28.52 $\pm$ 17.94	32.92 $\pm$ 17.83	0.02
	C3	26.74 $\pm$ 17.90	31.90 $\pm$ 18.83	0.007
	C5	25.74 $\pm$ 18.40	31.80 $\pm$ 20.00	0.004
SWMBE468	C1	15.26 $\pm$ 9.00	18.03 $\pm$ 7.95	0.008
	C3	16.44 $\pm$ 9.08	18.73 $\pm$ 9.07	0.03
	C5	14.79 $\pm$ 9.30	17.89 $\pm$ 9.83	0.004

Evaluation of concomitant medications in advanced prostate cancer patients receiving apalutamide: TITAN and SPARTAN post-hoc analysis.

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Background: Apalutamide (APA) is an androgen receptor pathway inhibitor (ARPI) approved for use with androgen-deprivation therapy (ADT) in patients with metastatic castration-sensitive prostate cancer and nonmetastatic castration-resistant prostate cancer based on data from the phase 3 TITAN and SPARTAN trials. APA induces cytochrome (CYP) 3A4/2C19 and P-glycoprotein, which may alter the pharmacokinetics of commonly used medications, raising the possibility for adverse events (AEs) or serious adverse events (SAEs) due to drug-drug interactions (DDIs). **Methods:** A post-hoc analysis was conducted to evaluate the incidence of AEs associated with select concomitant medication classes—antihypertensives, antidiabetics, statins, proton pump inhibitors (PPIs), and corticosteroids, among patients treated with APA + ADT or placebo + ADT in the TITAN and SPARTAN trials. The selected drug classes include some of the most frequently prescribed agents with significant CYP 3A4/2C19 activities. This analysis was also done in comparison to non-recipients of concomitant medications. **Results:** See Table. **Conclusions:** In this exploratory post-hoc analysis of >2,200 patients from TITAN and SPARTAN, concomitant use of commonly prescribed medications (antihypertensives, antidiabetics, statins, PPIs, and corticosteroids) was frequent and reflected routine real-world practice. Across medication classes, we observed no clinically meaningful increase in serious or loss-of-efficacy adverse events among apalutamide-treated recipients compared with placebo or with non-recipients of the class. These findings suggest that co-administration of apalutamide with routine concomitant therapies is safe and feasible under standard clinical monitoring. Clinical trial information: NCT02489318 and NCT01946204. Research Sponsor: Johnson & Johnson.

Medication Class	Treatment	TITAN Recipients (%)	TITAN TEAs (%)	TITAN TE SAEs (%)	SPARTAN Recipients (%)	SPARTAN TEAs (%)	SPARTAN TE SAEs (%)
Antihypertensives	APA+ADT (PBO+ADT)	41 (34.3)	41.9 (39.2)	1.9 (1.7)	42.8 (41)	49.4 (36.8)	0.9 (0.6)
Antidiabetics	APA+ADT (PBO+ADT)	12.2 (10.8)	34.4 (33.3)	1.6 (1.8)	12.2 (9.3)	42.9 (27)	3.1 (0)
Statins	APA+ADT (PBO+ADT)	23.9 (15.6)	12 (11)	0 (0)	33.9 (31.7)	10.7 (6.3)	0 (0)
PPIs	APA+ADT (PBO+ADT)	17.6 (14.6)	6.5 (1.3)	0 (0)	26 (21.6)	8.6 (9.3)	0 (1.2)
Corticosteroids	APA+ADT (PBO+ADT)	14.9 (11.2)	12.8 (18.6)	1.3 (0)	10.7 (8.3)	18.6 (15.2)	1.2 (0)

Treatment-emergent AEs (TEAEs) and SAEs deemed attributable to the pharmacologic class of the concomitant medication are classified as class-related side effects and included in the analysis. Percentages of TEAEs and SAEs are calculated based on recipients of a given class of concomitant medication.

EMBARC: Testosterone recovery to >250 ng/dL following treatment suspension.

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Background: The phase 3 EMBARK trial demonstrated significantly longer metastasis-free survival and overall survival for enzalutamide plus leuprolide (enzalutamide combination) vs leuprolide alone in patients with prostate cancer and high-risk biochemical recurrence (hrBCR). In EMBARK, patients with prostate-specific antigen (PSA) < 0.2 ng/mL at week 36 suspended treatment at week 37. Androgen deprivation-related testosterone suppression has been linked to adverse health outcomes, whereas testosterone recovery while off treatment has been associated with improved quality of life. The objective of this post hoc analysis was to assess testosterone recovery to > 250 ng/dL during treatment suspension in patients treated with enzalutamide combination. **Methods:** Eligible patients had hrBCR, with a PSA doubling time of ≤9 months. Patients were randomized 1:1:1 to enzalutamide + leuprolide, leuprolide alone, or enzalutamide monotherapy. Patients who suspended treatment at week 37 reinitiated treatment upon PSA increase to protocol-defined levels. Testosterone levels were assessed every 12 weeks. **Results:** In the enzalutamide combination group, 320 patients suspended treatment. During treatment suspension, testosterone recovery to > 250 ng/dL occurred in 108 patients (33.8%) (Table). Among those who recovered their testosterone, median and mean time to recovery was 5.6 months and 6.8 months, respectively, although some patients had delayed recovery (Table). **Conclusions:** Testosterone recovery to > 250 ng/dL during treatment suspension was observed in approximately one-third of patients treated with enzalutamide combination. While average time to testosterone recovery among those who recovered was ~6 months, recovery was delayed in some patients. Disclosure: Pfizer’s generative AI tool MAIA was used in developing this abstract; the authors reviewed, edited, and take full responsibility for the content. Clinical trial information: NCT02319837. Research Sponsor: The study was sponsored by Pfizer Inc. and Astellas Pharma Inc., the co-developers of enzalutamide. Medical writing support was provided by Kathleen Richter and Rosie Henderson of the Prime Group of Companies (Knutsford, UK), funded by the sponsors.

	Enza combination(N=320)
Patients who reached testosterone recovery, n (%)	108 (33.8)
Time to testosterone recovery >250 ng/dL, months [†]	
Median (range)	5.6 (0.0–22.1)
Mean (SD)	6.8 (2.87)

The data cutoff date was January 31, 2023.
[†]Time to testosterone recovery during treatment suspension is based on the number of patients who reached testosterone recovery, and was defined as the time from the date of the start of treatment suspension to the date of the first occurrence of testosterone >250 ng/dL. The summary is based on testosterone records during treatment suspension from patients who had treatment suspension and non-missing testosterone records after treatment suspension. For patients who reinitiated treatment, testosterone records after reinitiation were not considered.

Genomic and transcriptomic correlates of deep PSA response in patients with metastatic hormone-sensitive prostate cancer (mHSPC).

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Background: Despite advances in mHSPC treatment with combination therapies, patient outcomes remain heterogeneous. Achieving an undetectable PSA level is a strong prognostic marker for improved overall survival (OS). Baseline molecular predictors of deep PSA response are lacking. We aimed to identify genomic and transcriptomic determinants associated with undetectable PSA using a large clinical-genomic cohort. **Methods:** The Tempus Lens Platform was used to query the de-identified Tempus multimodal database and analyze a cohort of patients with mHSPC who underwent DNA (Tempus xT) and RNA (Tempus xR) clinical sequencing. Patients were restricted to those with stage IV disease within 90 days of sample collection. Samples collected within 12 months prior to or within 3 months of androgen deprivation therapy (ADT)-based therapy initiation were considered hormone-sensitive ($n = 525$). Patients were classified as PSA-low (< 0.1 ng/mL, $n = 285$) or PSA-high (≥ 0.1 ng/mL, $n = 240$) based on the PSA level at 6 months (± 45 days) post-treatment initiation. Genomic alterations, gene expression, and transcriptomic signatures were compared between PSA groups. Real-world OS was defined as the time from ADT start to death or loss to follow-up. Hazard ratios (HR) were estimated using Cox regression and adjusted for age. Significance was calculated using a Wald test at $p < 0.05$. **Results:** Median age at diagnosis was 67.5 years; 69.7% were White and 18.5% were Black/African American. The majority (91%) had de novo metastatic disease. First-line treatments included ADT+androgen receptor pathway inhibitor (ARPI) (65% vs 64%), ADT alone (15% vs 18%), ADT+ARPI+docetaxel (19% vs 15%), and ADT+docetaxel (1.3% vs. 3.5%) for PSA-low vs PSA-high, respectively. Baseline PSA was lower in patients with PSA-low vs PSA-high status (median 24 vs 36 ng/mL, $p = 0.01$). Somatic alterations in *SPOP* (17% vs 11%, $p = 0.04$) and *ZFHX3* (2.5% vs 6%, $p = 0.05$) differed between patients with PSA-low and PSA-high, respectively. No significant differences in expression of actionable novel targets including PSMA, TROP2, B7-H3, or STEAP1 were observed between cohorts. Median OS was not reached for patients with PSA-low and was 47 months for patients with PSA-high, with 36-month landmark OS of 83% vs 66%, respectively. On multivariable analysis, PSA-low was independently associated with improved OS (HR 0.51, 95% CI 0.31-0.85, $p = 0.01$). **Conclusions:** In a real-world cohort, deep PSA response at 6 months portends significantly improved OS in patients with mHSPC and is associated with more *SPOP* and fewer *ZFHX3* alterations. No transcriptomic differences in emerging therapeutic targets were identified. Validation in independent cohorts is warranted. Research Sponsor: None.

Rezvilutamide (Rez) versus bicalutamide (Bic) plus androgen-deprivation therapy (ADT) in high-volume, metastatic, hormone-sensitive prostate cancer (mHSPC): 5-year outcomes of the phase 3 CHART trial.

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Background: In the CHART trial, Rez plus ADT significantly improved radiographic progression-free survival (rPFS) and overall survival (OS) compared with Bic plus ADT in patients (pts) with high-volume mHSPC (Gu et al., Lancet Oncol 2022). Here, we present updated outcomes ~5 years after the enrollment of the last pt. **Methods:** Pts with high-volume mHSPC and without previous chemotherapy or other localized treatment for PC were eligible to be enrolled. Pts were randomized 1:1 to receive ADT plus either Rez (240 mg) or Bic (50 mg) orally once daily. Final analysis for OS was planned after 325 deaths were reported. **Results:** Between Jun 28, 2018, and Aug 6, 2020, 654 pts were randomized to receive Rez plus ADT (n=326) or Bic plus ADT (n=328). As of data cutoff (Jun 6, 2025), with a median follow-up of 72.8 months (IQR 69.1-77.4), there were 141 (43.3%) deaths in Rez plus ADT group and 194 (59.1%) in Bic plus ADT group. OS was improved with Rez plus ADT versus Bic plus ADT (median 78.8 months [95% CI 68.3-not reached (NR)] vs 44.8 months [95% CI 37.1-57.4]; HR 0.59 [95% CI 0.47-0.73]; 2-sided p<0.0001). Risk of progression or death in Rez plus ADT group was reduced by 62% compared with Bic plus ADT group (HR 0.38 [95% CI 0.30-0.48]). Other efficacy outcomes also favored Rez plus ADT (Table). Rez plus ADT improved patient-reported quality of life. No new safety signals were observed. **Conclusions:** Rez plus ADT continued to show meaningful survival benefits with manageable toxicities after long-term follow-up, further supporting Rez plus ADT as frontline treatment for pts with high-volume mHSPC. Clinical trial information: NCT03520478. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy endpoints.				
	Rez plus ADT (n=326)	Bic plus ADT (n=328)	HR (95% CI)	2-sided p-value
OS, months	78.8 (68.3-NR)	44.8 (37.1-57.4)	0.59 (0.47-0.73)	<0.0001
rPFS per investigator, months	81.0 (62.6-NR)	18.5 (14.8-25.7)	0.38 (0.30-0.48)	<0.0001
rPFS per investigator (sensitivity analysis ^a), months	58.9 (50.10-NE)	18.6 (16.30-22.90)	0.38 (0.31-0.47)	<0.0001
Time to PSA progression, months	NR (NR-NR)	11.0 (9.2-12.9)	0.21 (0.17-0.27)	<0.0001
Time to next skeletal-related event, months	78.8 (58.9-NR)	37.7 (34.3-48.2)	0.63 (0.51-0.78)	<0.0001
Time to initiation of new anti-prostate cancer therapy, months	62.4 (46.4-75.6)	15.1 (13.6-18.1)	0.32 (0.26-0.39)	<0.0001

Data are median (95% CI) unless otherwise indicated.

^aNew anti-cancer therapy and missing tumor assessments were not considered. PSA, prostate specific antigen.

Does a statin a day keep prostate cancer (PC) away?: Statin use and disease progression in patients receiving androgen deprivation therapy (ADT) after radical prostatectomy (RP) in SEARCH.

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Background: Prior studies suggest statin use may improve PC outcomes, including PC specific mortality (PCSM) and disease progression in patients receiving ADT. However, prior studies compared patients taking vs not taking statins at the time of ADT, ignoring that many statin non-users initiate statins later on. We evaluated the association between statin use and PC outcomes using both baseline (yes/no) and time-dependent exposure definitions in patients initiating ADT after RP. **Methods:** We conducted a retrospective cohort study of 9,931 patients with PC treated with RP between 1988 and 2020 at 9 VA hospitals from SEARCH Database. Patients who received ADT for biochemical recurrence after 2000 were included. Those with known metastasis prior to ADT or missing covariates of interest were excluded. Characteristics at ADT were stratified by statin use at time of ADT and compared with rank-sum for continuous variables and chi-square for categorical. Univariable and multivariable Cox models tested associations between statin use at ADT and time to metastasis, castration-resistant PC (CRPC), PCSM and all-cause mortality (ACM), adjusted for clinicopathological variables. As ~50% of non-statin users initiated statins after ADT, additional models treated statin use as time-dependent covariate. **Results:** Among 1,274 patients treated with ADT, 784 (62%) used statins at time of ADT. Users were older (median 67 vs 65), initiated ADT in more recent years (median 2013 vs 2010), had longer time from RP to ADT (median 39 vs 21 months), and had higher obesity rates (38% vs 25%). PC characteristics were similar between groups, except users had lower rates of positive nodes (11% vs 17%) and seminal vesicle invasion (28% vs 33%). Statin use at ADT was not significantly associated with time to metastasis, CRPC, PCSM or ACM, though HRs indicated lower risk for statin users (all HRs 0.89–0.98, all $p>0.2$; see table). On time-dependent multivariable analysis, statin use was significantly associated with lower risk of CRPC ($p=0.019$), PCSM ($p=0.020$) and ACM ($p<0.001$). Similar results were seen for metastases, though this did not reach significance ($p=0.058$) (see table). **Conclusions:** Statin use at ADT was not associated with PC outcomes after RP. However, accounting for statin initiation during ADT, statin use was associated with notably lower rates of CRPC, PCSM and ACM, with a trend towards reduced metastasis. These findings support the potential role of statins in slowing PC progression and highlight the need for prospective randomized trials of statins in patients initiating ADT. Research Sponsor: None.

Outcome	Statin at ADT, HR (95% CI)	p	Time-varying statin, HR (95% CI)	p
Metastasis	0.92 (0.71, 1.20)	0.541	0.74 (0.55, 1.01)	0.058
CRPC	0.95 (0.73, 1.24)	0.702	0.69 (0.51, 0.94)	0.019
PCSM	0.98 (0.70, 1.39)	0.920	0.62 (0.42, 0.93)	0.020
ACM	0.89 (0.73, 1.08)	0.229	0.51 (0.40, 0.64)	<0.001

Efficacy and safety of enzalutamide (ENZA) in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC) and cardiometabolic comorbidities (CMDs) and/or related concomitant medications (meds): ARCHES post hoc.

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Background: In ARCHES, ENZA improved radiographic progression-free survival (rPFS; primary: data cutoff, Oct 14, 2018) and overall survival (OS; prespecified secondary: data cutoff, May 28, 2021; 5-yr follow-up; data cutoff: Jul 31, 2024) vs placebo (PBO) in mHSPC. Our objective was to evaluate efficacy/safety of ENZA in pts with CMDs on related concomitant meds. **Methods:** We examined two groups: 1) full CMD (fCMD): pts with CMDs or on concomitant CMD meds; 2) confirmed CMD (cCMD): pts on CMD-related meds + confirmed CMD diagnosis, validated by medical history captured in concomitant med domain. CMDs included hypertension, cardiac disorders, dyslipidemia, diabetes mellitus. Related concomitant meds were diabetes meds, vasoprotectives, cardiac meds, lipid-modifying agents, antithrombotics, antihypertensives. Primary endpoint: rPFS (fCMD population; data cutoff: Oct 14, 2018). Other endpoints: OS, safety (fCMD population; data cutoff: May 28, 2021). Kaplan–Meier used for time-to-event analysis, with treatment (tx)-group comparisons assessed by stratified log-rank test and hazard ratios (HRs) relative to PBO using Cox proportional hazard models. Sensitivity analysis with cCMD population evaluated rPFS and OS, with OS adjusted for cross-over with rank-preserved structure failure time model. **Results:** Of 1150 pts, 938 (82%) were categorized as fCMD and 756 (66%) as cCMD. In the fCMD group, ENZA showed an association with improved rPFS and OS, with similar results for all sensitivity analyses (Table). Similar results also seen in all concomitant med subgroups. At 2021 data cutoff, median tx duration was 41 mo in the ENZA arm, 14 mo in the PBO arm. Tx-emergent adverse event (TEAE) rates (per 100 pt-yr) were similar with ENZA (313.8) and PBO (468.0). TEAEs of special interest rates (per 100 pt-yr) with ENZA vs PBO: fatigue (14.4 vs 18.0); falls (6.2 vs 2.6); fractures (7.3 vs 5.4); select cardiovascular events (2.5 vs 1.6); convulsions (0.2 vs 0.5). No new safety signals were identified. **Conclusions:** Similar to the overall mHSPC study population, ENZA was efficacious and tolerable in pts with CMD. Optimizing CMD may further enhance outcomes for pts with mHSPC, but ENZA remains a front-line option for all mHSPC pt subgroups. Clinical trial information: NCT02677896. Research Sponsor: Astellas Pharma Inc.; Pfizer Inc.

	ENZA, n (%)	ENZA, median (mo) (95% CI)	PBO ^a , n (%)	PBO ^a , median (mo) (95% CI)	HR (95% CI) ^a	Nominal P value
fCMD	n = 468		n = 470			
rPFS	73 (16)	NE (NE–NE)	159 (34)	19.5 (16.6–NE)	0.39 (0.29–0.51)	<0.0001
OS	123 (26)	NE (NE–NE)	169 (36)	NE (49.7–NE)	0.62 (0.49–0.78)	<0.001
Crossover adjusted OS ^b	123 (26)	NE (NE–NE)	169 (36)	49.7 (44.5–NE)	0.56 (0.43–0.69)	<0.001
cCMD	n = 377		n = 379			
rPFS ^b	59 (16)	NE (NE–NE)	126 (33%)	19.5 (16.6–NE)	0.41 (0.30–0.56)	<0.0001
OS ^b	98 (26)	NE (NE–NE)	137 (36)	NE (49.7–NE)	0.62 (0.48–0.80)	0.0002

^aComparator; ^bSensitivity analysis.
NE, not evaluable.

Predictors of treatment (tx) duration in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC) treated with enzalutamide (ENZA): A post hoc analysis of ARCHES.

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Background: In ARCHES (NCT02677896), ENZA + androgen-deprivation therapy (ADT) significantly improved radiographic progression-free survival (primary: data cutoff, Oct 14, 2018) and overall survival (prespecified secondary: data cutoff, May 28, 2021; 5-year follow-up: data cutoff, Jul 31, 2024) vs placebo + ADT in mHSPC. This post hoc analysis explored factors associated with different ENZA tx durations (5-year follow-up). **Methods:** Reasons for tx discontinuation (DC) including toxicity and progression, and baseline and on-treatment factors underlying tx persistence, were compared descriptively among pts with short (0–2 years [y]; STx), medium (2–5 y; MTx), and long Tx duration (> 5 y; LTx) (STx pts represent non-responders; MTx/LTx pts represent tx responders). **Results:** Of 572 ENZA-treated pts, 204 (36%) were STx; 140 (24%) MTx; 228 (40%) LTx. STx pts were more likely to be older vs MTx and LTx, with high-volume disease (HVD) and Eastern Cooperative Oncology Group performance status (ECOG PS) 1, although 55.3% of LTx had HVD and 73.2% had synchronous metastases. Progressive disease and tx-emergent adverse events (TEAEs) were the most common reasons for tx DC. Drug-related TEAEs (per 100 pt-y) were more common in STx (156.0) vs MTx (89.5) and LTx (47.1), as were those leading to tx DC (STx: 12.4; MTx: 1.5; LTx: 0.1). Rates (per 100 pt-y) of TEAEs leading to ENZA dose reduction were higher in STx (6.2) vs MTx (5.8) and LTx (2.0). The rate (per 100 pt-y) of drug-related TEAEs of special interest were generally higher in STx vs MTx and LTx: convulsions (1.0 vs 0.0 vs 0.0); fatigue (19.0 vs 10.7 vs 4.8), select cardiovascular events (1.0 vs 0.6 vs 0.1); falls (2.4 vs 3.2 vs 1.1); fractures (0.5 vs 1.5 vs 0.5). **Conclusions:** Our findings demonstrate that LTx and MTx tended to have more favorable pt and disease characteristics vs STx, although majority of LTx had adverse prognostic features. While progressive disease was the most common reason for DC, AEs/withdrawals were the second most common. Most TEAEs of special interest were more frequent in STx. Reasons for AE-related tx changes are multifactorial, and optimal management of AEs and comorbidities, as well as dose modifications, can optimize ENZA tx. Clinical trial information: NCT02677896. Research Sponsor: Astellas Pharma Inc.; Pfizer Inc.

Pt characteristics	STx (n = 204) n (%)	MTx (n = 140) n (%)	LTx (n = 228) n (%)
Age: ≥ 18 to 64/≥ 65 to ≤ 84/≥ 85 y	45 (22.1)/150 (73.5)/9 (4.4)	38 (27.1)/100 (71.4)/2 (1.4)	65 (28.5)/159 (69.7)/4 (1.8)
Prostate-specific antigen nadir < 0.2 ng/mL post-baseline	84/189 (44.4)	97/123 (78.9)	181/198 (91.4)
ECOG PS 0/1	147 (72.1)/57 (27.9)	110 (78.6)/30 (21.4)	190 (83.3)/37 (16.2)
HVD	148 (72.5)	80 (57.1)	126 (55.3)
Synchronous disease	162 (79.4)	108 (77.1)	167 (73.2)
Reasons for tx DC			
Progressive disease	106 (52.0)	63 (45.0)	19 (8.3)
AE + withdrawal	74 (36.3)	40 (28.6)	7 (3.1)
AE	40 (19.6)	25 (17.9)	2 (0.9)
Withdrawal	34 (16.7)	15 (10.7)	5 (2.2)
Death	10 (4.9)	10 (7.1)	10 (4.4)

Outcomes with androgen-deprivation therapy (ADT) plus androgen receptor pathway inhibitors (ARPIs) in veterans with de novo metastatic castration-sensitive prostate cancer (mCSPC) who were elderly, frail, or had high comorbidity: A subgroup analysis of enzalutamide and high-volume disease.

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Background: Clinical trials show significant overall survival (OS) benefits of combining ADT with ARPIs (abiraterone, apalutamide, darolutamide, or enzalutamide [ENZA]) vs ADT in mCSPC. The effects of ADT + ARPI in patients (pts) who are elderly, frail, or have high comorbidity burden remain unclear due to underrepresentation in clinical trials. This observational cohort study examined OS in two subgroups of this population: pts who received ENZA and those with high-volume disease (HVD). **Methods:** Veterans Health Administration records were used to assess OS in pts with de novo mCSPC treated with ADT + ARPI ± nonsteroidal antiandrogen (NSAA; ADT + ARPI group) or ADT ± NSAA (ADT group). Pts were aged ≥75 years (y) or had Veterans Affairs Frailty Index (VA-FI) > 0.2 or Charlson Comorbidity Index (CCI) ≥3. Subgroups comprised pts who: 1) initiated ADT + ENZA (HVD or low-volume disease); or 2) had HVD with any ARPI. Pts were indexed on first ADT date (Jun 1, 2017–Dec 31, 2022) and followed until censoring (Jun 1, 2025) or death. Mortality risk was estimated using a multivariable, time-varying Cox model to account for time between ADT + ARPI initiation adjusted for volume of disease, age, body mass index, CCI, and prostate-specific antigen level. **Results:** Of 1,629 pts, 272 (16.7%) received ADT + ENZA and 1,357 (83.3%) received ADT; median follow-up was 34.1 and 23.4 months (mo), respectively. Compared with ADT, the ADT + ENZA subgroup was younger (median age 77.5 vs 81.2 y, standardized mean difference [SMD]: −0.34) with similar frailty (VA-FI > 0.2: 67.3% vs 71.5%, SMD: 0.09) and more HVD (71.7% vs 61.5%, SMD: 0.22). ADT + ENZA was associated with significantly lower risk of death vs ADT (adjusted hazard ratio [aHR] 0.70; 95% CI: 0.60–0.83; $P < 0.001$; Table). Among 1,541 pts with HVD, 706 (45.8%) received ADT + ARPI and 835 (54.2%) received ADT; median follow-up was 29.1 and 18.8 mo, respectively. Pts who received ADT + ARPI were younger (median age 77.1 vs 81.9 y, SMD: −0.44) and had less frailty (VA-FI > 0.2: 66.2% vs 72.9%, SMD: 0.15). ADT + ARPI was associated with significantly lower risk of death vs ADT (aHR: 0.73; 95% CI: 0.65–0.83; $P < 0.001$). **Conclusions:** In this real-world cohort analysis of pts with de novo mCSPC who were elderly, frail, or had high comorbidity, ADT + ENZA was associated with prolonged survival compared with ADT. In pts with HVD, ADT + ARPI was associated with longer survival vs ADT. Research Sponsor: Astellas Pharma Inc.; Pfizer Inc.

Subgroup	ADT Median survival, mo (95% CI), n	ADT + ARPI ^a Median survival, mo (95% CI), n	aHR (95% CI) ^b ; P value
ENZA	23.4 (21.9–25.2), n = 1,357	36.1 (32.9–40.1), n = 272	0.70 (0.60–0.83); $P < 0.001$
HVD	18.8 (17.5–20.5), n = 835	29.1 (26.0–32.3), n = 706	0.73 (0.65–0.83); $P < 0.001$

^aENZA subgroup treatment arm: ADT + ENZA.

^bADT = reference.

Classification tree phenotypes for early treatment-limiting toxicity after androgen receptor pathway inhibitor initiation in metastatic hormone-sensitive prostate cancer from the IRONMAN registry.

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Background: Androgen receptor pathway inhibitors (ARPIs) improve survival in metastatic hormone-sensitive prostate cancer (mHSPC), but early treatment-limiting toxicity remains common. Using the IRONMAN (International Registry for Men with Advanced Prostate Cancer; NCT03151629) registry, we developed an interpretable classification tree that yields simple rule-based 1-year risk strata for a composite adverse outcome (AO) after ARPI initiation. **Methods:** Men with mHSPC initiating first-line ARPI with at least 12 months follow-up or AO within 365 days were included (n=583). AO was the first serious adverse event (SAE) or ARPI discontinuation for toxicity or other non-progression reasons; progression-attributed events were not counted. Candidate peri-ARPI initiation predictors (demographics, labs, treatments/medications, patient-reported outcomes) were screened for missingness, imbalance, and collinearity, reduced by stepwise logistic regression, and entered a recursive-partitioning classification tree with restricted depth and node size. Discrimination was summarized by area under the receiver operating characteristic curve (AUC) and repeated 3-fold cross-validation. Terminal nodes were collapsed into low, intermediate, and high-risk strata by predicted 1-year AO. **Results:** Overall, 122/583 men (20.9%) had AO within 1 year (85 SAEs; 37 discontinuations [28 toxicity, 9 other non-progression]). AO-free survival did not differ by ARPI agent (log-rank p=0.40); ARPIs were pooled. Peri-ARPI docetaxel exposure (triplet therapy) was uncommon (2.4%). The final tree retained nine predictors, including European Organization for Research and Treatment of Cancer global health rating (1-7), hemoglobin, worst pain (0-10), lactate dehydrogenase (LDH), age, docetaxel, and opioid agonist and systemic steroid use. In-sample AUC was 0.76 (95% CI 0.71-0.81); cross-validated AUC was 0.60 (95% CI 0.55-0.65). Collapsed strata showed distinct 1-year AO risk (Table 1). High-risk phenotypes reflected poor health/symptoms with anemia and/or elevated LDH, and a treatment-intensity phenotype with triplet therapy plus opioids and steroids. **Conclusions:** A small classification tree identified three clinically transparent phenotypes of early AO after ARPI initiation in mHSPC and can be applied as simple decision rules to support monitoring and shared decision-making. External validation is needed. Research Sponsor: Movember Foundation; Sanofi; Prostate Cancer Clinical Trials Consortium (PCCTC); Amgen; Astellas; Astra-Zeneca; Bayer; Janssen; Merck; Novartis.

Tree risk strata and 1-year AO risk.

Risk stratum	n (%)	1-year AO %, (95% CI)
Low	422 (72)	10.7 (7.7-13.6)
Intermediate	80 (14)	26.3 (16.6-35.9)
High	81 (14)	69.1 (59.1-79.2)

Correlation of baseline testosterone (T) level 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: Retrospective data suggest that low baseline serum T may be associated with inferior survival outcomes in mHSPC [PMID: 38444678]. Whether this relationship persists in rigorously controlled, randomized clinical trial populations remains unclear. We examined the prognostic impact of baseline T using patient-level data from the phase 3 SWOG 1216 trial which randomized pts with mHSPC in 1:1 to ADT + bicalutamide (standard arm) or ADT + orteronel (experimental arm). **Methods:** Patients treated on SWOG 1216 trial with available baseline T levels were eligible and included in this secondary analysis. Baseline T was summarized by median (IQR) and dichotomized at the median as $\leq$ median vs $>$ median. Overall survival was the primary endpoint; progression-free survival (PFS) and prostate-specific antigen (PSA) response were secondary endpoints. PSA response rates were divided into complete response (CR; PSA <0.2 ng/mL), partial response (PR; PSA between 0.2 and 4.0 ng/mL), and no response (NR; PSA >4.0 ng/mL) at a 7-month landmark following randomization. OS and PFS were estimated by Kaplan-Meier within each arm, with median survival (95% CI) and number of events reported. Comparisons were performed using the log-rank test. PSA response was summarized as n (%), and groups were compared using Pearson's chi-squared test. All tests were two-sided with $\alpha = 0.05$. **Results:** Of 1279 pts, 218 pts had baseline T levels. Median T level was 312.5 ng/ml (IQR 89.25 - 462 ng/ml). In both experimental and standard arms, there was no significant difference in OS, PFS, or PSA response between patients with baseline T levels above vs below the median (Table). Similarly, in both arm, there was no difference in outcomes based on baseline T levels grouped by quartiles, as well as baseline T levels as a continuous variable (data will be presented at the conference). **Conclusions:** In this patient-level analysis of a phase 3 trial, there was no statistically significant association between baseline T and outcomes in mHSPC. Based on these data, baseline T may not be used for prognostication or treatment selection in patients receiving systemic therapy in mHSPC. Limitations include a small sample size. These hypothesis-generating data require external validation before clinical application. Research Sponsor: Supported by NIH/NCI/NCTN under grant No. U10CA180888, U10CA180819, U10CA180820, and U10CA180821; Millennium Pharmaceuticals, Inc (Takeda Pharmaceutical Company LTD).

Treatment Arm	T Level	OS Median (95% CI), months	N (events)	P-value	PFS Median (95% CI), months	N (events)	P-value	PSA complete response n (%)	PSA partial response n (%)	No PSA Response (%)	P-value
Experimental	$\leq$ Median	63 (47, NR)	71 (37)	0.11	30 (20, 64)	71 (49)	0.11	37 (50%)	18 (60%)	16 (62%)	0.5
	$>$ Median	NR (68, NR)	59 (22)		57 (26, NR)	59 (30)		37 (50%)	12 (40%)	10 (38%)	
Standard	$\leq$ Median	72 (45, NR)	38 (20)	0.7	19 (12, 34)	38 (29)	0.9	14 (42%)	9 (45%)	15 (43%)	>0.9
	$>$ Median	57 (43, NR)	50 (22)		19 (13, 35)	50 (39)		19 (58%)	11 (55%)	20 (57%)	

Outcomes of radical radiotherapy in de novo low-burden metastatic hormone-sensitive prostate cancer vs prostate radiotherapy alone.

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Background: The current standard of care (SoC) for metastatic hormone-sensitive prostate cancer (mHSPC) is androgen deprivation + systemic therapy. Oligometastatic HSPC, however, represents a unique disease entity following the STAMPEDE trial, where de novo mHSPC patients with a CHAARTED-defined low disease burden (DN-mHSPC-LV) had a hazard ratio of death of 0.68 after prostate radiotherapy (PRT). Despite the SABR-COMET results of a survival benefit with stereotactic RT on metachronous oligometastatic sites of predominantly prostate patients, radical RT (RRT) in the DN-mHSPC-LV setting has not been studied. This study analysed the outcomes of such patients receiving RRT to all disease sites vs PRT alone. **Methods:** DN-mHSPC-LV patients receiving RRT to the prostate and all oligometastatic sites (Arm A) vs PRT alone (Arm B) in a Hong Kong tertiary hospital between 1st January 2012 and 1st January 2023 were reviewed. Outcomes of progression-free survival (PFS), overall survival (OS) and treatment-related toxicity (TrT) were analysed using the Kaplan-Meier and multivariable Cox-proportional hazards models. **Results:** 127 eligible patients (60 in Arm A & 67 in Arm B) were identified. The median numbers of oligometastatic sites of 1-3 and ≥ 4 were balanced between the two arms. The median Gleason score was 8 in both arms. Median T/N/M staging was mostly balanced but more patients in Arm B had N1 disease. Presenting PSA (ng/mL) was higher in Arm A (38.5) than Arm B (27.9). Arm A received up to 76Gy/38# to the prostate + a boost of up to 67.5Gy or stereotactic RT to the oligometastatic sites. Arm B received 55-60Gy/20# to the prostate alone. Patients were started on long-term androgen deprivation therapy. Median follow-up was 40.2 months and 30.3 months in Arms A and B, respectively. Median PFS was not reached (NR) in either of the treatment arms. On multivariate analysis, 5-year PFS was 86.1% vs 50.3% in Arms A and B, respectively ($P = 0.0173$; HR 0.213; 95% CI 0.059-0.761). OS data were not yet mature and there was no difference in TrT between the arms. **Conclusions:** To our knowledge, this is the first study comparing radical RT against the SoC of prostate RT alone in DN-mHSPC-LV. Radical RT was well tolerated and is significantly cheaper than next-generation hormone agents in prostate cancer. 5-year PFS was significantly better with radical RT vs prostate RT alone. PFS is an established surrogate for OS in prostate cancer. This study therefore justifies prospective studies on RRT for DN-mHSPC-LV. More importantly, as prospective trials with an OS endpoint in prostate cancer will take close to a decade to mature, this study provides interim evidence to support radical treatment in this group of patients, in whom cure or long-term control may be achieved, where prospective trials are anticipated to take much longer to complete. Research Sponsor: None.

Impact of a whole-food plant-based diet (WFPBD) on weight and metabo-inflammation in men with prostate cancer (PC) receiving androgen deprivation therapy (ADT): A multi-center randomized control trial.

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Background: Obesity promotes a chronic inflammatory state associated with PC progression. ADT can cause weight gain, accumulation of body fat, insulin resistance and increased risk of diabetes and cardiovascular disease. A WFPBD promotes weight loss, decreases inflammation, and shifts the gut microbiome to promote insulin sensitivity. We hypothesized that a WFPBD and behavioral intervention will promote weight loss and a reduction in adiposity in overweight/obese patients with PC on ADT. **Methods:** Pts with PC with BMI ≥ 27 receiving ADT with an LHRH/GnRH analogue for >24 wks pre-study (+ AR pathway inhibitor allowed if stable dose for >3 mos) with plan >26 more wks were eligible. 60 patients were randomized 1:1. WFPBD group: 12 prepared and home delivered WFPBD meals per wks 1-4, 6 meals wks 5-8 and coaching to assist in self-prepping plant-based meals (wks 9-26); Control group: counseling on a general healthful diet from a Registered Dietician weekly for 8 wks, then monthly (wks 9-26). Baseline and serial measurements (pre-intervention, wks 4, 8 and 26): weight, body composition assessment via dual energy x-ray absorptiometry (DXA), and biomarkers of inflammation and metabolism were collected. Primary endpoint was weight loss at 4 weeks (with an 80% power to detect an effect size 0.74 standard deviations with a 2-sided significance level of 0.05 using a two-sample t-test). Secondary objectives were change in body composition, biomarkers of metabolic disorders and cardiovascular risk and quality of life measurements. **Results:** 60 pts were randomized (31 control, 29 WFPBD). Median age was 73; Race: 65% white, 28% Black, 2% Asian, 5% other/unknown; Median baseline weight 98 kg; No difference in baseline HbA1c or lipid profile between groups. Mean weight loss (kg) at 4, 8 and 26 wks: WFPBD: 3.9, 5.3 and 6.1 kg; Control 1.3, 1.6, 2.1 kg, respectively (each timepoint pair $p<0.001$). DXA measured BMI change at 4 and 26 wks: WFPBD: -1.1 and -1.93 kg/m², Control: 0.35 and 0.25 kg/m² (each timepoint pair $p<0.001$). DXA measured mean lean (LM), fat (FM) and total mass (TM) showed declines at 4 wks in WFPBD versus Control (LM -2.4 vs -0.64 ($p<0.001$); FM -1.3 vs -0.35 ($p=0.023$); TM -3.61 vs -0.88 ($p<0.001$), whereas at 26 weeks only FM and TM remained significantly less (LM -2.2 vs -1.4 ($p=0.143$); FM -5.3 vs -0.8 ($p=0.001$); TM -6.7 vs -2.2 ($p<0.001$). No significant differences were seen in HbA1c or lipid profiles at 6 mos. **Conclusions:** Compared with nutritional counseling, obese men with PC on ADT subjected to a home-delivered WFPBD for 2 mos and behavioral coaching experienced significantly greater weight loss, BMI reduction and decreases in total and fat mass that persisted for 6 months. Biomarkers of metabo-inflammation, insulin levels, fecal microbiota and metabolites, and serum for metabolomics collected are undergoing analyses. Clinical trial information: NCT05471414. Research Sponsor: Prostate Cancer Foundation; U.S. Department of Defense; U.S. National Institutes of Health.

Germline genetic correlates in metastatic hormone-sensitive prostate cancer (mHSPC) treated with androgen deprivation therapy (ADT) plus non-steroidal anti-androgen (NSAA) or enzalutamide (ENZA): Correlative study of ENZAMET (ANZUP 1304).

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Background: The international, randomized, phase III ENZAMET trial (n=1125) showed improved overall survival (OS) with ADT plus ENZA vs ADT plus NSAA for mHSPC. Observational studies showed that the mHSPC genetic landscape is comparable to castration resistant prostate cancer (CRPC). Prognostic and predictive impact of inherited pathogenic variants (PVs), including those affecting *BRCA1*, *BRCA2* and other DNA damage and repair (DDR) genes, on androgen receptor pathway inhibitor (ARPI)-treated mHSPC is under investigation. **Methods:** Whole exome sequencing of germline DNA prospectively obtained from ENZAMET pts. Variant annotation and effect prediction identified PVs (altered "+" vs wild-type "-"). Prognostic effect of PVs was assessed within arms. Endpoints: clinical progression-free survival (PFS) and OS by Kaplan-Meier method. Hazard ratios (HRs) were estimated using Cox models. Multi-variable analyses (MVA) adjusted for Gleason score (GS), volume (vol), metachronous vs synchronous and docetaxel (D) use. **Results:** All 847 available samples were successfully sequenced. 123 PVs were identified in 117 (13.8%) pts, of which 46 (5.43%) pts harbored a PV in ≥ 1 DDR gene. The rate of pathogenic germline *BRCA1/BRCA2* (BRCA) PVs was 2.13% (39.1% of DDR PVs). Proportions of arm, D use, vol and visceral disease were similar between DDR+ vs DDR- and BRCA+ vs BRCA-. Synchronous mHSPC in DDR+ vs DDR- and BRCA+ vs BRCA- was 41.3% vs 63.0% and 44.4% vs 62.2%, respectively. PFS and OS estimates were similar between BRCA+ and BRCA- groups in the overall cohort (5-yr OS: 55.6% vs 61%; 3-yr PFS: 50% vs 53.5%, respectively) and in the ENZA arm, but differed in the NSAA arm (Table). BRCA+ treated with ADT+NSAA (67% D use) had shortest PFS (median PFS: 11.3m vs 24.9m [BRCA-], HR 1.85, 95% CI: 0.95-3.6). D use associated with poorer outcomes. In MVA, the HR(PFS) for BRCA+ in NSAA arm was 1.47 (95% CI 0.71-3.04, p=0.3) vs ENZA arm: HR 0.98, (95% CI 0.31-3.08, p=0.97). Vol and GS were independently significant in both arms. **Conclusions:** In one of the largest germline genetic studies from a phase III mHSPC trial, we observed recurrent DDR and BRCA PVs at a lower rate than institutional cohorts. Germline BRCA PVs are associated with a shorter PFS on ADT+NSAA – an effect which may be mitigated by ENZA. Validation in independent trial cohorts is ongoing. Research Sponsor: National Cancer Institute; Movember Foundation; Australian Department of Health; Astellas and Pfizer; US Department of Defense.

Outcomes by arm/docetaxel and BRCA status.

	n	5y-OS % (95% CI)	3y-PFS % (95% CI)
NSAA only BRCA-	238	56.6 (50.0-62.7)	42.9 (36.5-49.1)
NSAA only BRCA+	3	66.7 (5.4-94.5)	66.7 (5.4-94.5)
NSAA+D BRCA-	176	54.7 (47.0-61.8)	32.5 (25.7-39.6)
NSAA+D BRCA+	6	33.3 (4.6-67.6)	16.7 (0.8-51.7)
ENZA only BRCA-	228	70.6 (64.2-76.0)	73.3 (67.0-78.5)
ENZA only BRCA+	7	71.4 (25.8-92.0)	71.4 (25.8-92.0)
ENZA+D BRCA-	187	60.7 (53.2-67.3)	62.3 (54.9-58.8)
ENZA+D BRCA+	2	NE	50.0 (0.6-91.0)

Prognostic value of PSA nadir ≤0.2 ng/mL in metastatic castration-sensitive prostate cancer: A systematic review and meta-analysis.

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Background: The treatment landscape for metastatic castration-sensitive prostate cancer (mCSPC) has changed substantially with the adoption of early treatment intensification using androgen-receptor pathway inhibitors (ARPI) and chemotherapy, in addition to traditional androgen deprivation therapy (ADT). PSA nadir has long been used to support prognosis and inform treatment decisions; however, the historical thresholds were established based on patients treated solely with ADT and may not fully reflect outcomes in the modern era of combination therapy. Although emerging evidence suggests that a PSA nadir of < 0.2 ng/dl is associated with improved disease control and survival, a systematic evaluation across available mCSPC trials is needed to clarify the prognostic value of PSA nadir and its potential role in guiding treatment decisions. **Methods:** A systematic search of PubMed, Cochrane Library, and ClinicalTrials.gov was conducted through October 31, 2025, to identify studies reporting outcomes by PSA nadir category in men with mCSPC. Eligible studies included patients initiating systemic therapy with ADT alone or in combination with ARPI and/or chemotherapy. The reported hazard ratios (HR) for time-to-event endpoints stratified by PSA nadir (≤ 0.2 ng/dl) were analyzed to get pooled HR. The primary outcome was overall survival (OS). **Results:** A total of eight trials comprising 6,582 patients were included. The pooled HR for the primary endpoint, overall survival (OS), was 0.27 (95% CI: 0.21–0.36; $I^2 = 88.1\%$), indicating a clinically meaningful survival advantage among patients achieving PSA nadir. Consistent findings were observed for secondary outcomes. Achieving a PSA nadir ≤ 0.2 ng/mL was associated with longer radiographic progression-free survival (HR 0.23; 95% CI: 0.12–0.45; $I^2 = 87.8\%$) and longer PSA progression-free survival (HR 0.19; 95% CI: 0.08–0.45; $I^2 = 92.6\%$). A PSA nadir ≤ 0.2 ng/mL also correlated with a delayed onset of castration resistance (HR 0.31; 95% CI: 0.16–0.61; $I^2 = 93.5\%$). Assessment of publication bias using Begg’s and Egger’s tests revealed no significant evidence of small-study effects for any endpoint. **Conclusions:** Across contemporary mCSPC trials, achieving a PSA nadir of ≤ 0.2 ng/mL consistently predicts improved survival and delayed disease progression. These findings establish PSA nadir as a clinically meaningful and cost-effective biomarker that can help guide treatment-intensification and de-intensification strategies in routine practice. Research Sponsor: None.

Study	Hazard Ratio (HR)	95% Confidence Interval (CI)	Weight (%)
SWOG9346	0.23	[0.19, 0.27]	13.80
SWOG S0925	0.20	[0.14, 0.28]	12.06
ARASENS	0.49	[0.37, 0.65]	12.65
CHAARTED	0.41	[0.32, 0.53]	13.00
ARCHES	0.24	[0.17, 0.34]	11.82
TITAN	0.35	[0.25, 0.48]	12.09
ARANOTE	0.14	[0.09, 0.21]	10.79
SWOG S1216	0.25	[0.21, 0.30]	13.78
Overall (Pooled)	0.27	[0.21, 0.36]	100.00

Clinical impact and molecular profiling of *PTEN* loss and *TMPRSS2:ERG* fusion in metastatic hormone-sensitive prostate cancer.

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Background: *PTEN* loss in prostate cancer (PC) is associated with aggressive disease and resistance to conventional treatments. *TMPRSS2:ERG* fusion (TE+) is one of the most frequent genomic alterations in PC and frequently co-occurs with *PTEN* loss, yet the clinical impact of this association remains unclear. The aim of the present study is to evaluate clinical outcomes in metastatic hormone-sensitive PC (mHSPC) patients (pts) stratified by TE and *PTEN* status and to characterize associated gene expression signatures. **Methods:** We conducted a multicenter ambispective study enrolling mHSPC pts receiving different treatment strategies. The primary objective was to evaluate castration resistant PC-free survival (CRPC-FS) according to *PTEN* and TE. TE fusion and *PTEN* status were assessed in FFPE tumor samples using mRNA expression profiling by nCounter. $PTEN_{low}$ was defined with a previously validated cut-off (Jimenez, *Eur Urol Onc* 2023). RNA-seq analysis was performed to molecularly characterize $PTEN_{low}$ and TE associated transcriptional profiles using gene set variation analysis. **Results:** A total of 295 pts were included; median age was 72.9 years, 46.1% had high-volume disease and 66.8% presented *de novo* stage IV disease. Treatment consisted of androgen deprivation therapy (ADT) plus abiraterone (n=97), apalutamide (n=157), enzalutamide (n=41). Overall, 74 pts were $PTEN_{low}$ and 90 pts were TE+. There were no significant differences in baseline characteristics according to *PTEN* or TE. Among $PTEN_{low}$ pts, 33 (44.6%) were TE+. There was a positive correlation between $PTEN_{low}$ and TE+ ($p=0.01$). With a median follow-up of 31.9 months (range 0.8 – 91.3), 32% of pts progressed to CRPC and 31.2% died. In the overall cohort, $PTEN_{low}/TE-$ tumors (14.1%) were associated with the poorest clinical outcomes, showing significantly inferior CRPC-free survival (HR 2.1, $p=0.0027$) and overall survival (HR 2.1, $p=0.0058$). Within the $PTEN_{low}$ subgroup, TE+ tumors demonstrated significantly improved CRPC-FS compared with TE- negative tumors (HR 0.45, $p=0.04$), with a non-significant trend toward improved overall survival (HR 0.48, $p=0.07$). In the 35 pts with RNA-seq analysis, $PTEN_{low}/TE-$ tumors were characterized by enrichment of DNA repair and neuroendocrine and EZH2 signatures ($p=0.04$ and $p=0.03$ respectively). $PTEN_{low}/TE+$ had enrichment of PI3K signaling ($p=0.01$) and epithelial differentiation ($p=0.05$). Androgen-response hallmark was infraexpressed in $PTEN_{low}$ tumors regardless of TE status. **Conclusions:** $PTEN_{low}/TE-$ tumors exhibited the worst clinical outcomes, while TE+ in $PTEN_{low}$ disease partially rescued the adverse phenotype. Combined *PTEN* and TE stratification may therefore inform risk-adapted treatment escalation and intensification strategies. Research Sponsor: Janssen-Pharmaceuticals [56021927PCR4029]; Instituto de Salud Carlos III [PI18/00714 and PI24/00631], co-funded by the European Union.

Quantitative results from PSMAtrack: A prospective study evaluating changes in PSMA-PET during initial systemic therapy for metastatic hormone-sensitive prostate cancer (mHSPC).

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Background: PSA <0.2 ng/mL after 6 months (m) of therapy with androgen deprivation therapy (ADT) and an androgen receptor pathway inhibitor (ARPI), $\pm$ docetaxel is strongly prognostic in patients (pts) with mHSPC. This prospective, single-institution pilot study aimed to investigate PSMA-PET for assessing early dynamic changes in PSMA expression and tumor volume in response to treatment for mHSPC and to determine if changes in quantitative PSMA-PET parameters are associated with 6m PSA response. **Methods:** Key eligibility was mHSPC by conventional imaging with plan to start ADT and ARPI $\pm$ docetaxel. Primary or metastasis-directed radiotherapy was not permitted during the first 6m. F18-flotufolastat PSMA-PET was performed at baseline within 21 days of ADT start and after 6m of ADT+ARPI $\pm$ docetaxel. PSMA-PET scans were qualitatively reviewed for PSMA-avid prostate cancer, (i.e., PSMA uptake $>$ background blood pool in a pattern consistent with prostate cancer). Quantitative PSMA-PET parameters were collected including PSMA-avid total tumor volume (TTV, voxel SUV >3), TTV SUVmean and TTV SUVmax (aPromise, EXINI Diagnostics; LesionID MIM software, GE Healthcare). PSA values at baseline and after 6m of therapy were collected. Descriptive statistical analyses, Wilcoxon test, and Pearson correlations were used. **Results:** 20/21 enrolled pts (median age 70 years [range 60–95]) had evaluable baseline and 6m PSMA-PET scans. 12 (60%) received ADT+ARPI, 8 (40%) received ADT+ARPI+docetaxel, and median baseline PSA was 55ng/mL (range 2–3,696); 13 (65%) had high-volume mHSPC by CHAARTED criteria. At 6m, median PSA was 0.29 ng/mL (range <0.02 –177), and 9 pts (45%) had a PSA ≤ 0.2 ng/mL. All 20 pts had residual PSMA-avid disease at 6m by qualitative review, with most (n=17, 85%) having residual disease outside the prostate; 2 pts (10%) had new lesions seen on 6m PSMA-PET. At 6m, median TTV and SUVmax, but not SUVmean, were significantly lower for those with PSA ≤ 0.2 than PSA >0.2 ng/mL (Table); baseline TTV was strongly correlated with 6m PSA ($r=0.74$, $p<0.01$). PSA and TTV were well correlated at baseline ($r=0.68$, $p=0.001$) and at 6m ($r=0.81$, $p<0.01$), as were changes in PSA and TTV from baseline to 6 m ($r=0.67$, $p=0.001$). **Conclusions:** Persistent PSMA-avid disease was seen in all pts with mHSPC after 6m of ADT+ARPI $\pm$ docetaxel, regardless of PSA at 6m. Pts with 6m PSA >0.2 ng/mL had significantly higher TTV and SUVmax at 6m PSMA-PET, and TTV best correlated with PSA levels at baseline and 6 m. Using 6m PSMA-PET could identify mHSPC pts with suboptimal initial response to standard therapy for consolidative therapeutic strategies. Clinical trial information: NCT06479187. Research Sponsor: Blue Earth Diagnostics.

	6m PSA ≤ 0.2 ng/mL, median (range)	6m PSA >0.2 ng/mL, median (range)	P
TTV (mL)	7.7 (0.4-79.9)	147 (5.9-3440)	<0.01
SUVmax	8.7 (4.8-39.2)	47.4 (11.7-162)	<0.01
SUVmean	5.3 (4.0-8.8)	6.4 (4.2-16.8)	0.14

Prostate-specific antigen outcomes of darolutamide and androgen deprivation therapy in patient subgroups by age, comorbidities, and concomitant medications: ARANOTE post hoc analyses.

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Background: Darolutamide (DARO) + androgen deprivation therapy (ADT) significantly improved radiological progression-free survival (HR 0.54, 95% CI 0.41–0.71; $P < 0.0001$) vs placebo (PBO) + ADT in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC) in the phase 3 ARANOTE (NCT04736199) trial, with a favorable safety profile. Here, we report the impact of age, comorbidities (comorbid), and use of concomitant medications (conmeds) ongoing at baseline on prostate specific antigen (PSA) outcomes in pts treated with DARO or PBO. **Methods:** Pts were randomized 2:1 to DARO 600 mg orally twice daily or PBO, both with ADT. Pts were grouped by age and number/type of comorbid or conmeds reported at baseline. Descriptive statistics (*post hoc*) summarized baseline demographics, disease characteristics, and PSA outcomes by age, comorbid, and conmed subgroups. **Results:** Baseline demographics and disease characteristics were generally similar between DARO ($n=446$) and PBO ($n=223$) across all subgroups by age (<65 , $65-74$, or ≥ 75 years [yrs]), comorbid (<5 or ≥ 5), and conmeds (<5 or ≥ 5), respectively. Rates of reaching PSA <0.2 ng/mL at any time were consistently higher with DARO vs PBO across all age (<65 yrs, 62% [$n=69/112$] vs 21% [$n=13/63$]; $65-74$ yrs, 62% [$n=116/187$] vs 21% [$n=19/89$]; ≥ 75 yrs, 64% [$n=81/126$] vs 12% [$n=7/59$]), comorbid (<5 , 66% [$n=160/244$] vs 21% [$n=26/122$]; ≥ 5 , 66% [$n=86/130$] vs 14% [$n=10/71$]), and conmed (<5 , 67% [$n=115/173$] vs 22% [$n=21/96$]; ≥ 5 , 62% [$n=93/151$] vs 16% [$n=11/71$]) subgroups. With DARO, rates of reaching PSA <0.2 ng/mL at any time were consistent among pts with metabolic disorders with or without corresponding conmeds (71% [$n=43/61$] vs 69% [$n=29/42$]). The rate of reaching PSA <0.2 ng/mL was slightly lower in patients with cardiovascular disorders who were not receiving corresponding conmeds at baseline (51% [$n=22/43$]) compared with those receiving corresponding conmeds (64% [$n=119/187$]). A substantially lower rate of PSA progression was observed with DARO (8% [$n=22/266$]) vs PBO (33% [$n=13/39$]) among pts that reached PSA <0.2 ng/mL. Median time to PSA progression among patients that reached PSA <0.2 ng/mL was 421 days (range, 85–702) and 256 days (range, 85–514) for DARO and PBO, respectively. **Conclusions:** Overall, an efficacy benefit was observed with DARO, irrespective of age, and number of comorbidities or concomitant medications reported at baseline in pts with mHSPC, including those with cardiovascular or metabolic disorders, with or without corresponding conmeds, respectively. These results support the use of DARO in mHSPC, even in pts with older age, substantial comorbidities, and greater use of concomitant medications. Clinical trial information: NCT04736199. Research Sponsor: Bayer.

Prognostic potential of PROSTest for predicting outcome in ADT-treated Black South African prostate cancer patients.

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Background: Prostate cancer (PCa) is the second most common cancer in men with disproportionately aggressive disease observed in black African and Caribbean men. Androgen deprivation therapy (ADT) is commonly used as treatment but there is no personalized strategy to guide patient selection. We investigated the prognostic value of PROSTest before ADT initiation and after the first ADT cycle. **Methods:** We performed a descriptive study of PROSTest with cross-sectional and longitudinal arms in black PCa patients receiving or intended to receive ADT. An ADT-naïve PCa cohort ($n=50$) intended to start ADT was enrolled as well as an ADT-exposed cohort ($n=80$) 6–12, 12–24 or >24 months after starting ADT. Goserelin acetate alone or in combination with cyproterone acetate was administered. The cohorts were followed up 4-monthly for 36 months with evaluation of survival and treatment response (responding, in remission, recurrence, progression, castration resistance). PSA levels were measured using the Architect Total PSA chemiluminescent immunoassay. Whole blood samples were collected into deproteinizing RNA-buffered tubes for determination of the PROSTest activity score using a multiplexed PCR assay. Statistical analysis used non-parametric statistics and Fisher's exact test in GraphPad Prism v8. **Results:** Untreated metastatic PCa patients had the highest baseline PROSTest scores (71.8–85.3). Untreated patients with organ-confined disease were subdivided into group A (PROSTest scores ≤ 32) and group B (PROSTest scores ≥ 70). ADT-treated patients enrolled after starting ADT were subdivided into group C (PROSTest scores 9.8–58.3) and group D (PROSTest scores 70.0 – 90.2). Groups A and C showed improved survival and lower rates of recurrence, progression and castration resistance at 36 months compared to groups B and D ($p<0.05$). Patients that required treatment re-initiation or escalation due to rising PSA all had high enrolment PROSTest scores ≥ 70 . The groups did not differ significantly in terms of age, CAPRA score, Gleason grade, PSA levels, nadir PSA, time to nadir or SUVMAX ($p>0.05$). **Conclusions:** The PROSTest activity score determined pre- or post-ADT (first cycle) identifies PCa patients at risk for poor treatment outcomes. Research Sponsor: South African Medical Research Council (SAMRC); SHIP-RFA-01-2019.

Overall survival in veterans with metastatic hormone sensitive prostate cancer by initial therapy and STRATOS-P somatic tumor classification.

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Background: The STRATOS-P somatic tumor classification stratifies patients with metastatic hormone-sensitive prostate cancer (mHSPC) into favorable, intermediate, or unfavorable risk groups based on tumor comprehensive genomic profiling (CGP). Currently, no studies have compared the mortality benefits or overall survival (OS) differences between mHSPC treatments in these risk categories. **Methods:** Veterans within the Veterans Health Administration with mHSPC diagnosed between December 2018 and September 2024 were included if tumor CGP was completed within 6 months of diagnosis. Patients were grouped based on STRATOS-P genomic classification (favorable vs. intermediate/unfavorable). With each group, OS was analyzed by initial therapy: androgen deprivation therapy (ADT) alone, ADT+androgen receptor pathway inhibitor (ARPI), ADT+docetaxel, or triple therapy with ADT+ARPI+docetaxel. Survival was analyzed using Kaplan-Meier and Cox proportional hazards models, adjusting for baseline differences in age, PSA, Charlson comorbidity index, race, and metastatic volume. **Results:** Of 2,820 veterans with mHSPC, 1,109 (39.3%) had risk classified as favorable per STRATOS-P and 1,711 (60.7%) as intermediate/unfavorable. Initial therapy distribution differed moderately between groups ($p=0.046$). The favorable group had more patients receiving ADT monotherapy (55.5% vs. 52.0%) and fewer receiving ADT+docetaxel or triple therapy (3.0% vs. 4.7%, 4.4% vs. 5.4%, respectively). The intermediate/unfavorable group had a higher max PSA (median 37.7 vs 23.7, $p<0.001$) lower percentage of African American patients (27.5% vs 36.0%, $p<0.001$), and a higher percentage of patients with high volume of disease (28.9% vs. 19.7% $p=0.002$). In the favorable group, OS did not significantly differ by treatment; however, in a pairwise comparison, ADT+ARPI showed a modest decrease in mortality risk versus ADT alone (aHR [95% CI]: 0.745 [0.561 – 0.989]). In the intermediate/unfavorable group, median OS differed by therapy (ADT monotherapy: 30.7 months, ADT+ARPI: 36.8 months, ADT+docetaxel: 27.9 months, Triple Therapy: 37.6 months; $p<0.001$). Further, ADT+ARPI and triple therapy were associated with a decreased risk of mortality compared to ADT alone (aHR [95% CI]: 0.638 [0.541 – 0.753], 0.542 [0.360 – 0.817], respectively). **Conclusions:** In patients with intermediate/unfavorable STRATOS-P genomic risk, choice of initial therapy can lead to differences in OS, with ADT+ARPI and triple therapy associated with decreased mortality compared to ADT alone. In favorable risk, choice of initial therapy had smaller effect on OS, and only ADT+ARPI was associated with a modest decrease in mortality. These findings highlight the role of early genomic testing in mHSPC and that high risk tumors may benefit more from combination therapy than those with favorable risk. Research Sponsor: U.S. Department of Defense; W81XWH-22-1-0602.

STRATOS-P clinical model for prognosis and selection of patients with metastatic hormone sensitive prostate cancer (mHSPC) for intermittent therapy.

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Background: Current trials use prostate-specific antigen (PSA) response of ≤ 0.2 ng/mL at 6–12 months as a prognostic marker and identify patients for intermittent therapy. Clinico-genomic assessment can increase prognostic accuracy and patient selection for intermittent therapy, which would improve quality of life and decrease adverse events associated with mHSPC combination therapies without impacting survival. **Methods:** Retrospective study of veterans diagnosed with mHSPC between 2018–2024. PSA response at 6–12 months and volume of disease were determined. DNA alterations were classified by Somatic Tumor Risk Assessment for Overall Survival-Prostate (STRATOS-P) genomic system, a validated method of risk stratification. PSA response was grouped into ≤ 0.2 , >0.2 – <2 , 2 – <10 , and ≥ 10 ng/mL. Charlson comorbidity index (CCI) high was defined as ≥ 3 . PSMA-PET based staging was determined if PSMA-PET performed within 100 days of mHSPC diagnosis. Multivariable Cox model-based weights were used to create the STRATOS-P mHSPC clinical risk score to prognosticate overall survival and select patients for intermittent therapy. Kaplan-Meier analysis was used to estimate Overall Survival (OS) and time to death or castration resistance from diagnosis, a real-world progression-free survival (rwPFS) surrogate. **Results:** In 3094 Veterans identified, 937 (30.3%) had DNA-based genomic testing within 6 months of diagnosis. There were 1349 patients (43.6%) with a PSA of ≤ 0.2 who had a median OS of 74.6 months. Of patients with genomic testing, 459 (49.0%) were STRATOS-P Clinical low risk with a median OS that was not reached and rwPFS of 72.1 months, moderate risk with median OS of 37.1 months and rwPFS of 21.6 months, and high risk with median OS of 19.1 months and rwPFS of 12.1 months. There were 66 (13.0%) patients that were STRATOS-P Clinical low risk but did not achieve ≤ 0.2 and 116 (22.8%) patients that achieved PSA ≤ 0.2 but were considered STRATOS-P clinical moderate risk. Approximately 497 patient (53%) could be considered for intermittent therapy and had a median OS of 77.9 months and rwPFS of 56.2 months, similar to patients with PSA ≤ 0.2 . **Conclusions:** STRATOS-P Clinical model in mHSPC is prognostic for OS and rwPFS and can identify patients for intermittent therapy to achieve similar OS and rwPFS compared to selection using PSA ≤ 0.2 at 6–12 months. Future trials should incorporate clinico-genomic assessments to improve risk stratification and selection of therapy. Research Sponsor: Veterans Health Affairs Office of Research and Development; 1I01CX002946–01; Prostate Cancer Foundation; PCFCHAL220.

STRATOS-P clinical model (n=937).

		n	HR	95.0% CI
CCI High		397	1.62	1.34-1.95
High Volume		608	1.53	1.31-1.78
STRATOS-P Genomic risk*	Intermediate	470	1.53	1.23-1.92
	Unfavorable	132	2.39	1.80-3.17
Non-PSMA-PET staging		708	1.62	1.23-2.14
		210	1.60	1.25-2.04
PSA Response#	>0.2 - 2	131	2.98	2.30-3.84
	>2 - <10	87	5.64	4.26-7.47
	$10+$			

*STRATOS-P genomic risk favorable is referent, n=335.

#PSA Response ≤ 0.2 is referent, n=509.

Major adverse cardiovascular events in androgen receptor signaling inhibitor–treated patients with metastatic castration-sensitive prostate cancer.

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Background: Cardiovascular disease is highly prevalent in the predominantly older male population with metastatic castration-sensitive prostate cancer (mCSPC). Androgen receptor pathway inhibitors (ARPIs) form the backbone of contemporary doublet and triplet treatment strategies, but—as with any systemic therapy—may influence patients' underlying cardiovascular risk. This study compares the incidence of major adverse cardiovascular events (MACE) in real-world mCSPC patients treated with darolutamide versus abiraterone. **Methods:** This retrospective cohort study included patients in the nationwide VA healthcare system initiating doublet or triplet abiraterone or darolutamide for newly diagnosed mCSPC. After inverse probability of treatment weighting (IPTW), 1-year cumulative MACE incidence was estimated via Kaplan–Meier analysis. Doubly robust multivariable Cox regression using IPTW and multivariable competing risk regression with death as a competing risk assessed the association between treatment and MACE. All analyses were adjusted for age, race, prior MACE, NCI Charlson Score, smoking status, and prior hypertensive combination treatment. **Results:** Among 11,788 patients initiating darolutamide or abiraterone for mCSPC, 9,952 received abiraterone doublet, 936 received darolutamide doublet, 374 received abiraterone triplet, and 526 received darolutamide triplet therapy. In the weighted cohort, the 1-year cumulative incidence of MACE was lower in patients receiving darolutamide (7.2%, 95% confidence interval [CI] 5.6–9.0%) versus abiraterone (10.7%, CI 10.0–11.4%) doublet therapy. For triplet therapy, 1-year MACE incidence was 5.3% (CI 3.4–7.4%) with darolutamide and 9.6% (CI 5.9–13.6%) with abiraterone. In doubly robust multivariable Cox models, darolutamide doublet was associated with a lower hazard of MACE compared to abiraterone doublet (hazard ratio [HR] 0.78, CI 0.62–0.96, $P=0.03$). For triplet, patients receiving darolutamide had a HR of 0.73 for MACE (CI 0.39–1.31, $p=0.29$) compared to patients receiving abiraterone triplet therapy. Competing risk models showed consistent results. **Conclusions:** Darolutamide, particularly in doublet therapy, was associated with lower MACE risk than abiraterone. A similar point estimate in triplet therapy warrants validation in larger cohorts. These findings may inform treatment selection or prophylactic management to improve cardiovascular outcomes in mCSPC. Research Sponsor: Bayer.

Homologous recombination repair (HRR) genes and overall survival prognosis within the STRATOS-P classification in metastatic hormone-sensitive prostate cancer (mHSPC).

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Background: DNA repair genomic alterations are associated with worse overall survival (OS) in patients with metastatic hormone sensitive prostate cancer (mHSPC). It is less clear whether other genomic alterations may affect prognosis of actionable homologous recombination repair (HRR) and mismatch repair (MMR) genes in mHSPC. **Methods:** Retrospective cross-sectional study of veterans diagnosed with mHSPC (n=4401). Tumors with no alterations in HRR/MMR genes (DDRneg) were classified by the Somatic Tumor Risk Assessment for Overall Survival-Prostate (STRATOS-P) genomic system which stratifies patients into favorable, intermediate and unfavorable survival groups based on oncogenic alterations: Favorable, SPOP or no alterations; Intermediate, alterations in *AR*, *BRCA2*, *CCND1*, *CDK12*, *FGF19*, *FGF3*, *FGF4*, *LYN*, *MYC*, *PTEN*, *RAD21*, or *TP53*; Unfavorable, alterations in *FGFR1*, *PRCK1*, *RB1*, or both *TP53* and *PTEN*. OS from metastatic diagnosis was determined using a multivariate Cox model controlling for age, Charleston comorbidity index (CCI) and PSA at diagnosis. **Results:** Among 4401 mHSPC patients, 1027 (23%) patient tumors had at least one oncogenic alteration in an HRR or MMR gene. Of 3374 DDR-Neg tumors, 1593 were classified as STRATOS-P-Favorable, 1357 as STRATOS-P-Intermediate, and 424 as STRATOS-P-Unfavorable. Comparing patients with tumors with oncogenic alterations in an HRR or MMR gene to patients with DDR-neg tumors showed that prognosis was worse in patients with tumor alterations in *ATM*, *BRCA2*, *CHEK2*, *CDK12*, *ATR*, *PALB2*, *NBN* and MMR genes compared to patients with STRATOS-P-Favorable tumors (Table). Prognosis was better in patients with tumor alterations in *ATM*, *BRCA2*, *CHEK2*, *CDK12*, *BRCA1*, *FANCA* and Lynch genes compared to STRATOS-P-Unfavorable tumors (Table). **Conclusions:** In patients with mHSPC, patients with HRR and MMR altered tumors have a worse prognosis compared to patients with STRATOS-P favorable tumors and better prognosis compared to patients with STRATOS-P unfavorable tumors. Overall, HRR and MMR gene alterations impact prognosis of mHSPC patients within the STRATOS-P classification and should be classified as intermediate risk. Research Sponsor: Veterans Affairs Office of Research and Development; I01CX002946; Prostate Cancer Foundation; 22CHAL02.

Gene ¹	n	STRATOS-P-Favorable, DDRneg, n=1593	STRATOS-P-Unfavorable, DDRneg, n=424
		HR (95% CI)	HR (95% CI)
<i>BRCA2</i>	243	2.00 (1.62, 2.47)	0.69 (0.55, 0.87)
<i>CDK12</i>	116	2.07 (1.66, 2.57)	0.74 (0.58, 0.94)
<i>ATM</i>	259	1.55 (1.24, 1.96)	0.51 (0.39, 0.66)
<i>CHEK2</i>	212	1.75 (1.21, 2.52)	0.50 (0.33, 0.76)
<i>ATR</i>	38	2.05 (1.27, 3.31)	0.71 (0.43, 1.17)
<i>BRCA1</i>	37	1.41 (0.81, 2.46)	0.48 (0.27, 0.84)
<i>FANCA</i>	32	1.53 (0.82, 2.87)	0.51 (0.27, 0.97)
<i>NBN</i>	23	2.59 (1.43, 4.68)	0.93 (0.51, 1.69)
<i>PALB2</i>	21	2.31 (1.23, 4.37)	0.79 (0.40, 1.56)
Lynch	128	1.72 (1.28, 2.33)	0.64 (0.47, 0.88)

¹All tumors with alterations in indicated gene regardless of STRATOS-P subgroup were compared to the indicated DDRneg STRATOS-P subgroup.

Optimal prostate-specific antigen cutoff for prostate cancer detection: A prospective cohort study.

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Background: Serum prostate-specific antigen (PSA) testing is crucial for detecting early stage and low-risk prostate cancer. However, standard and uniform PSA thresholds may underestimate risk in males with smaller prostate volumes and distinct epidemiologic characteristics. We aimed to evaluate data-driven, age-specific PSA thresholds for short-term prostate cancer detection in a large screening cohort. **Methods:** We analyzed 512,992 PSA measurements from 123,607 asymptomatic males undergoing annual or biennial health checkups in Kangbuk Samsung Cohort Study (KSCS) from 2011 to 2020. Incident prostate cancer within 1-year of each PSA measurement was identified through linkage to the Korea National Cancer Incidence Database. The dataset was randomly partitioned into training (70%) and test (30%) subsets. To estimate cancer risk, logistic regression models incorporating synthetic minority oversampling technique were used. Optimal PSA thresholds were determined using the Youden index in test datasets. Performance was evaluated by accuracy, precision, recall, and F1-score with bootstrap validation. Associations between risk factors and prostate-cancer risk were evaluated using Cox regression models. **Results:** During follow-up, 224 men developed prostate cancer. The optimal PSA cutoff in the overall population was 2.96 ng/mL. Age-specific thresholds increased with age, with males in their 40s, 50s, 60s, and age ≥ 70 years demonstrating cutoff values of 1.62, 2.54, 2.76, and 3.79 ng/mL, respectively. These thresholds demonstrated high discriminative performance (accuracy, 0.97; F1-score, 0.92) (Table). PSA values exceeding age-specific thresholds were associated with a 20.7-fold elevated risk of prostate cancer (HR 20.65; 95% CI, 16.33–26.12; $P < 0.001$). Older age, family history of prostate cancer (HR 2.27; 95% CI, 1.58–3.27), and dyslipidemia medication use (HR 2.04; 95% CI, 1.49–2.80) were additional independent predictors. **Conclusions:** In this large prospective Asian cohort, age-specific PSA thresholds between 1.6 and 3.8 ng/mL provided robust short-term risk discrimination and identified male at substantially higher 1-year prostate cancer risk than those below the thresholds. Implementing age-adjusted PSA reference values may improve the precision and efficiency of early detection strategies in Asian male and better inform risk-adapted screening and diagnostic pathways. To determine their effect on long-term clinical outcomes, prospective validation is warranted. Research Sponsor: None.

Age-specific PSA cutoffs and performance metrics.

	Cutoff value	Accuracy	Precision	Recall	F1-score
Overall	2.96	0.97	0.89	0.96	0.92
40 ≤ Age < 50	1.62	0.93	0.70	0.99	0.82
50 ≤ Age < 60	2.54	0.95	0.80	0.95	0.87
60 ≤ Age < 70	2.76	0.91	0.66	0.99	0.80
Age ≥ 70	3.79	0.90	0.65	0.91	0.76

Large language model protein set generation for interpretable serum proteomics in localized prostate cancer.

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Background: High-plex serum proteomics can track prostate cancer biology and treatment response beyond PSA, but interpretation is limited by high dimensionality. Pathway analysis can help, but incomplete overlap between legacy pathway libraries and assay panels can yield hard-to-interpret enrichments dominated by a few measured proteins. We evaluated an automated large language model (LLM) workflow using protein annotations to build protein sets containing only measured proteins. **Methods:** Serum from 88 individuals was profiled with an aptamer-based ~7,000-protein assay (SomaScan 7K; SomaLogic, USA). The cohort included localized prostate cancer treated with radiotherapy (RT) with or without androgen-deprivation therapy (ADT) with serial sampling (pre-RT n = 76, end-RT n = 72, ~1-month follow-up n = 76), plus metastatic (n = 4) and normal controls (n = 8). Assay fidelity was assessed by correlating PSA aptamers with clinical PSA. Protein-level analyses tested ADT effects and paired within-patient changes across RT. For program-level analysis, UniProt annotations for each measured protein were processed with an LLM to generate structured summaries, converted to embeddings, and clustered into protein sets restricted to SomaScan proteins. Set coherence and assay coverage were compared to Gene Ontology (GO) and Reactome mappings. Protein-set enrichment comparing ADT vs no ADT identified candidate programs and were evaluated for association with biochemical recurrence among high-risk ADT-treated patients (n = 50; 20 events) using Cox models adjusted for pre-treatment PSA. **Results:** PSA aptamers correlated with clinical PSA (Spearman $r = 0.66-0.77$). ADT suppressed reproductive-axis proteins (LH, FSH, hCG) and prostate-lineage proteins (PSA, PAP, TGM4); RT contrasts captured acute epithelial injury/lymphoid suppression followed by remodeling and stress responses. LLM protein sets showed higher set name/protein description coherence (median cosine similarity 0.59) than GO (0.30) or Reactome (0.36) and covered all measured proteins; GO/Reactome sets averaged ~50% member coverage. Pre-RT ADT enrichment identified histone programs (NES 2.13–2.18; FDR < 0.01), summarized as a Histone H2 score. Histone H2 score increased across no ADT, ADT, and metastatic samples (Kruskal-Wallis $p = 0.003$; all pairwise FDR < 0.05). In high-risk ADT-treated patients, pre-RT Histone H2 score was associated with recurrence (HR 0.53, FDR = 0.024), and remained significant in a bivariate model with pre-treatment PSA (Histone H2 HR 0.49, FDR = 0.013; PSA HR 2.78, FDR < 0.001). Non-H2 histone score (H1/H3) showed no ADT-associated shift (Wilcoxon $p = 0.70$), supporting specificity of the Histone H2 signal. **Conclusions:** LLM-derived protein sets restricted to measured proteins improved interpretability of serum proteomics and revealed an ADT-associated Histone H2 program complementary to PSA. Research Sponsor: U.S. National Institutes of Health; ZIA BC 011552.

Spatial transcriptomics-guided pathology biomarker as a predictor of benefit of adjuvant docetaxel in high-risk localized prostate cancer: NRG/RTOG 0521 (NCT00288080).

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Background: The NRG/RTOG 0521 trial evaluated adding adjuvant docetaxel (DTX) to standard radiotherapy plus androgen deprivation therapy (ADT) in high-risk localized prostate cancer. Adjuvant DTX modestly improved overall survival (OS) in the trial, but the benefit was limited and not all patients benefited. Thus, biomarkers are needed to identify patients most likely to benefit from chemotherapy intensification. ST-DoxPCa (Spatial Transcriptomics-Guided Docetaxel Therapy Stratification in Prostate Cancer) is a novel artificial intelligence (AI) driven histology biomarker that predicts gene expression from H&E slides (virtual spatial transcriptomics). We assessed whether ST-DoxPCa can stratify patients in RTOG 0521 for differential benefit from adjuvant DTX. **Methods:** A Vision Transformer trained on paired histology-spatial transcriptomics (HEST1K) predicts a 208-gene prostate panel at spot level; predictions are distilled into a biologically informed 26-gene signature and aggregated into patient-level features. A prognostic Cox model and fixed median threshold were developed independently in a Cleveland Clinic radical prostatectomy cohort (CCF, n=352; endpoint: biochemical recurrence-free survival). This locked model and threshold were applied unchanged (no refitting or recalibration) to digitized pretreatment diagnostic biopsies from NRG/RTOG 0521 (n=350; RT+ADT n=169, RT+ADT+DTX n=181) to stratify patients into ST-DoxPCa-positive (high-risk) and ST-DoxPCa-negative (low-risk) groups. Overall survival (OS) was compared between treatment arms within each stratum. **Results:** ST-DoxPCa stratified patients into biomarker-defined risk groups using aggregated spatial-expression features from a biologically informed gene panel; key genes included PTEN, NKX3-1, ACP, FASN and TMPRSS2. ST-DoxPCa-positive (high-risk) patients experienced a significant OS benefit from adding DTX to RT+ADT versus RT+ADT alone (HR=0.38, 95% CI 0.18–0.83; p=0.012), whereas ST-DoxPCa-negative (low-risk) patients derived no OS benefit (HR=1.05, 95% CI 0.67–1.63; p=0.84). **Conclusions:** The ST-DoxPCa model identified a subgroup with substantial OS benefit from adjuvant DTX and a subgroup with no benefit within RTOG 0521, supporting risk-aligned chemotherapy intensification using routine histology. Clinical trial information: NRG/RTOG 0521 (NCT00288080). Research Sponsor: National Cancer Institute (NCI), National Institutes of Health (NIH); R01CA268287A1, U01CA269181, R01CA26820701A1, R01CA249992-01A1, R01CA202752-01A1, R01CA208236-01A1, R01CA216579-01A1, R01CA220581-01A1, R01CA257612-01A1, 1U01CA239055-01, 1U01CA248226-01, 1U54CA254566-01; United States Department of Veterans Affairs; IBX004121A; U.S. Department of Defense (DoD) – Prostate Cancer Research Program; W81XWH-20-1-0851; U.S. National Institutes of Health; U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), U24CA180867 (NCORP), U24CA190607 (NRG Specimen Bank); Sanofi.

External validation of new prostate cancer risk groups by PSMA-PET (PPP3).

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Background: Previously, we proposed novel risk group definitions for prostate cancer patients based on Prostate-Specific Membrane Antigen (PSMA) targeted positron emission tomography (PET). PSMA-PET pan-stage nomograms (PPP3) were developed using the international, multicentre PROMISE registry (NCT06320223) to prognosticate overall survival (OS). Here, we present an external validation of PPP3. **Methods:** Eligible patients enrolled into our PROMISE registry database after the PPP3 data cap were included into this external validation study. Included patients had histologically proven prostate cancer and underwent PSMA-PET at hospitals in Turkey, Cyprus, Italy, China, South Africa or Germany between 2015 and 2022. PSMA-PET was standardized by PROMISE version 2 (V2); total lesion count, total tumor volume, PSMA expression score and OS follow-up were obtained as per local site practice. PPP3 nomograms were applied to calculate risk groups and Harrell's C-indices for the external validation cohort. Calibration curves were measured for 5-year OS. Head-to-head comparison between the visual PPP3 nomogram and the simplified risk stratification table was examined by area under the receiver operating characteristics curve (ROC-AUC). **Results:** 1855 male patients across all disease stages with 179 (9.6%) reported deaths and median OS follow-up of 4.8 years (IQR 3.7–6.1) were analysed. In the external validation cohort C-indices (95% CI) were 0.71 (0.67–0.76) for the visual nomogram and 0.73 (0.69–0.77) for the quantitative nomogram, respectively. By simplified risk stratification table, 77 of 1855 patients (4.2%) were underestimated and 16 (0.9%) were overestimated, when compared with visual nomograms. Prognostic accuracy was comparable using both methods (AUC Nomogram: 0.64 vs. AUC Table: 0.63, $p = 0.02$). **Conclusions:** PPP3 nomograms were validated in an external multi-site patient cohort. Prognostication was accurate (C-indices > 0.70) for both PPP3 nomograms. Clinical trial information: NCT06320223. Research Sponsor: German Research Foundation; RA 3222/5-1 / 714210; Prostate Cancer Foundation; Health Initiative Joint Undertaking; 101172722; Novartis; AstraZeneca; Telix.

Is language barrier a mere proxy?: Psychological distress among non-English-speaking prostate cancer patients receiving radiation therapy—A prospective cohort study.

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Background: Cancer patients experience depression and anxiety at elevated rates, with minority and non-English-speaking populations disproportionately affected. Prior research at our institution demonstrated elevated distress among Spanish-speaking breast cancer patients undergoing radiation therapy. However, limited data exist on language-related disparities in prostate cancer patients undergoing radiation therapy. We investigated this while exploring the mediating role of social determinants of health (SDOH). **Methods:** We enrolled prostate cancer patients initiating radiation therapy at an urban safety-net hospital. We assessed anxiety (GAD-2), depression (PHQ-2), and SDOH including food and housing insecurity, and transportation barriers at baseline and treatment completion. Comparisons used t-tests and Mann-Whitney U tests; correlations used Spearman coefficients with statistical significance $p < 0.05$. **Results:** Of 84 patients enrolled (mean age 70.3 ± 8.0 years), 49 (58.3%) were English-speaking and 35 (41.7%) were non-English-speaking (Spanish $n = 20$, Haitian Creole $n = 13$, Portuguese $n = 2$). The sample was predominantly Black/Caribbean (64.3%). Non-English speakers had fewer years in the US (41.1 vs. 50.3 years, $p = 0.016$) and lower educational attainment (25.7% vs. 0% elementary school only, $p = 0.006$). At baseline, non-English speakers showed numerically higher anxiety (GAD-2: 1.31 ± 2.13 vs. 1.08 ± 1.72) and depression (PHQ-2: 1.09 ± 1.87 vs. 0.84 ± 1.57), though this was not statistically significant ($p > 0.50$). Notably, Spanish-speaking patients demonstrated the highest distress (GAD-2: 2.00 ± 2.45 ; PHQ-2: 1.40 ± 1.98), with 30.0% screening positive for clinical anxiety vs. 16.3% of English speakers. SDOH factors were significantly correlated with distress: housing insecurity ($\rho = 0.42$, $p < 0.001$), food insecurity ($\rho = 0.37$, $p = 0.001$), and transportation worry ($\rho = 0.38$, $p < 0.001$). In multivariable regression adjusting for age, stage, race, ethnicity, and education, language was not independently associated with anxiety ($B = -0.64$, 95% CI: -1.76 to 0.48 , $p = 0.26$). Among 73 patients with paired data, distress remained stable from baseline to treatment completion. **Conclusions:** While non-English-speaking prostate cancer patients reported higher psychological distress during radiation therapy, SDOH factors emerged as the strongest predictors of distress regardless of language. Interventions targeting social vulnerability may be more impactful than language services alone. SDOH screening should be integrated into oncology care at safety-net institutions serving diverse populations. Research Sponsor: None.

Assessing the clinical and biological associations between multimodal artificial intelligence (MMAI) and 22-gene genomic classifier (GC) in localized prostate cancer (PCa).

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Background: MMAI and GC are clinically validated prognostic tools for localized PCa, and are incorporated into NCCN guidelines as treatment-decision aids. However, their clinical and biological relationships remain unclear, especially in Asian populations where comparative study is limited. **Methods:** Patients with newly-diagnosed localized PCa from a single institution in Singapore were enrolled into a prospective protocol (NCT04340024), and underwent image-guided radiotherapy with or without hormonal therapy. All subjects had paired GC and MMAI scores. However, colored marker annotations were present on the H&E slides, which could negatively impact MMAI performance. Associations between GC and MMAI scores with metastasis-free survival (MFS) were evaluated using Cox proportional hazards models. Pearson's correlation was used to assess associations between risk scores and cancer hallmark pathways. **Results:** 144 men were included, comprising 142 (99%) with NCCN intermediate (int) to high-risk, and 2 (1%) with low-risk disease; median follow-up duration was 78.5 (interquartile range: 68.2–95.3) mo. MMAI and GC scores were correlated ($R = 0.55$), but differed in risk stratification; 12/144 (8%), 54/144 (38%), and 78/144 (54%) were MMAI low-, int-, and high-risk, respectively, compared with 51/144 (35%), 32/144 (22%), and 61/144 (43%) by GC in the same order. We observed the largest discordance in the GC low-risk subgroup ($n = 51$), where 29/51 (57%) and 14/51 (28%) were classified as MMAI int- and high-risk, respectively. Of note, 16/32 (50%) of GC int-risk men were classified as MMAI high-risk. Nonetheless, both tests were prognostic for MFS (MMAI: hazard ratio [HR] of 2.6 [95% CI:1.0–6.4], $P = 0.035$; GC: HR of 3.4 [95% CI:1.5–7.6], $P = 0.002$), although the difference in HR should be interpreted with caution, as it is attributable to a limited sample size with longer follow-up. Next, we investigated for molecular pathway enrichment of GC and MMAI high-risk groups. Proportions of known prostate cancer molecular subtypes were comparable between the respective GC and MMAI risk-groups (GC high vs MMAI high: PAM50 Basal 51% vs 58%, $P = 0.419$; Luminal B 46% vs 39%, $P = 0.377$; PTEN loss 25% vs 22%, $P = 0.698$; AR lower activity 49% vs 44%, $P = 0.512$). GC high versus GC low/int tumors however showed positive enrichment in E2F, oxidative phosphorylation, and mTORC1 pathways; negative enrichment in P53 and estrogen pathways. MMAI high was only negatively enriched for fatty acid metabolism. **Conclusions:** While MMAI and GC provide differing risk categorization, both tests were significantly associated with MFS in men with localized prostate cancer who underwent radiotherapy. Known prostate cancer-associated transcriptomic subtypes were comparable between the respective MMAI and GC risk groups. Research Sponsor: None.

A prospective study of mpMRI-guided salvage radiotherapy with lesion-directed dose escalation after radical prostatectomy: 10-year follow-up results (MRI Study: UMIN 000009823).

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Background: Salvage radiotherapy (SRT) after radical prostatectomy (RP) has traditionally been delivered as uniform dose distribution of the prostate bed without lesion visualization. We prospectively implemented an image-guided salvage strategy integrating high-resolution multiparametric MRI (mpMRI) and lesion-directed dose escalation. Here we report long-term oncologic outcomes of this pioneering approach. **Methods:** This prospective, single-arm clinical study was registered in the UMIN database in 2013. Patients with biochemical recurrence (BCR, PSA ≥ 0.2 ng/mL) after RP and no evidence of distant metastasis were enrolled. All patients underwent 3 Tesla mpMRI with an endorectal coil prior to SRT. When a focal recurrent lesion was identified, intensity-modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB) was delivered (70 Gy to the MRI-defined lesion and 66 Gy to the prostate bed in 33 fractions). Patients without visible lesions received prostate-bed irradiation alone. Treatment failure after SRT was defined as PSA > 0.2 ng/mL. Long-term clinical outcomes were analyzed. **Results:** A total of 40 patients completed protocol treatment. mpMRI identified focal recurrence sites in 11 patients (27.5%), all of whom received lesion-directed SIB-IMRT. After a median follow-up of 10.6 years, treatment failure occurred in 13 patients (32.5%). Among patients treated with SIB-IMRT, 4 of 11 developed BCR, whereas among 29 patients without mpMRI-detectable recurrence at the time of SRT, 9 developed BCR. There was no statistically significant difference in BCR rates between the two groups. Importantly, no patient developed radiologically evident local recurrence within the irradiated prostate bed, including those treated with SIB in their disease course. All but one patient with treatment failure received subsequent systemic salvage therapy. Distant metastases developed in 3 patients, and 1 patient died from prostate cancer. One patient without SIB experienced grade 3 perforation of the sigmoid colon. During follow-up after SRT, secondary malignancies were diagnosed in 10 patients. **Conclusions:** In this prospective study with long-term follow-up, mpMRI-guided SRT achieved excellent durable local control. Although second BCR occurred in a subset of patients, the absence of in-field local failures regardless of mpMRI detectability at the time of SRT supports the biological and clinical validity of lesion-directed salvage intensification. Our findings underscore individualized SIB approach and highlight the need for future studies to refine patient selection and treatment intensification strategies in salvage settings, including androgen deprivation therapy and/or elective pelvic nodal irradiation. Clinical trial information: UMIN000009823. Research Sponsor: None.

Survival outcomes and subgroup efficacy analysis of Ga-68-NGUL and Lu-177-DGUL (pocuvotide satetraxetan) in patients with mCRPC: Results from a phase 1/2 study.

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Background: Ga-68-NGUL and Lu-177-DGUL (Pocuvotide Satetraxetan) is a novel PSMA-targeting radiopharmaceutical. This study reports the survival outcomes and identifies clinical factors associated with therapeutic response in patients with metastatic castration-resistant prostate cancer (mCRPC). **Methods:** In this phase 1/2 study (NCT05547061), mCRPC patients progressing after ARPI treatment received Lu-177-DGUL (200 mCi every 6 weeks, up to 6 cycles). Efficacy was evaluated using both RECIST v1.1 and PCWG3-modified RECIST v1.1. Key endpoints included ORR, overall survival (OS), and radiographic progression-free survival (rPFS). **Results:** A total of 91 patients were enrolled. Overall Survival: The median OS was 13.31 months (95% CI: 12.02–17.38). The median rPFS was 11.04 months (95% CI: 8.28–14.29) for the entire cohort. Subgroup Analysis by Metastatic Site: Significant differences in ORR were consistently observed across both criteria. Per RECIST v1.1, the ORR was significantly higher in patients with lung metastases (100% vs. 32.43%, $p = 0.0144$) and lymph node involvement (48.08% vs. 11.54%, $p = 0.0015$) compared to those without. These findings align with PCWG3-modified RECIST v1.1 results (Lung: 100% vs. 37.84%, $p = 0.0252$; LN: 51.92% vs. 19.23%, $p = 0.0057$). Furthermore, the presence of liver metastases was associated with significantly shorter rPFS compared to those without liver involvement, consistently across RECIST v1.1 (median 5.55 vs. 11.04 months; $p = 0.0386$) and PCWG3-modified criteria (median 2.76 vs. 8.38 months). Impact of Treatment Cycle on ORR and rPFS: Treatment intensity significantly influenced clinical outcomes across both evaluation criteria (all $p < 0.0001$). For ORR, under RECIST v1.1 criteria, the ORR was 0% for < 4 cycles, 30% for 4 cycles, and 59.46% for > 4 cycles. Similarly, per PCWG3-modified RECIST v1.1, the ORR improved with the number of cycles (0%, 35%, and 67.57%, respectively). For rPFS, under standard RECIST v1.1, the median rPFS increased with the number of cycles: 2.76 months (95% CI: 2.56–2.86), NE (95% CI: 5.55–NE), and 13.34 months (95% CI: 11.04–NE). Per PCWG3-modified RECIST v1.1, the median rPFS also increased consistently (2.66 months [95% CI: 2.56–2.76], 5.55 months [2.73–NE], and 11.04 months [10.18–14.29], respectively). **Conclusions:** Ga-68-NGUL and Lu-177-DGUL (Pocuvotide Satetraxetan) demonstrates promising survival benefits in mCRPC. The clinical response is particularly robust in patients with lung or lymph node metastases and those completing more treatment cycles. The significant difference in rPFS observed only under PCWG3-modified criteria highlights the importance of using PCWG3-specific assessments in bone-predominant mCRPC. Clinical trial information: NCT05547061. Research Sponsor: Cell-Bion Co., Ltd.; The Korea Drug Development Fund; RS-2025-25454770.

Spatially organized immune niches in high-grade primary prostate cancer.

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Background: Prostate cancer (PC) has historically been considered immunologically “cold” due to low immune infiltration and a predominantly immunosuppressive tumor microenvironment (TME). However, this understanding is largely based on immune profiling studies of metastatic castration-resistant prostate cancer and may not apply in earlier stages of disease. The composition and organization of the immune TME in primary PC remains poorly defined, especially in relation to Gleason score, the gold standard of pathologic PC grading. We hypothesized that the local PC immune TME is more heterogeneous than previously appreciated, with differences in immune composition and spatial organization between High Gleason (HG) and Low Gleason (LG) PC. **Methods:** We analyzed 29 radical prostatectomy samples (15 LG vs. 14 HG) using a 40-marker multiplex immunofluorescence panel to profile the TME at single-cell resolution. Immune cell phenotypes were defined with respect to the marker panel. Using R, cell composition was computed within tumor, stroma, and tertiary lymphoid structures (TLS, organized aggregates of immune cells that resemble secondary lymphoid organs) and within defined boundary regions at interfaces between each compartment. **Results:** We discovered that HG PC exhibited higher total immune infiltration ($p < 0.05$) and specifically TLS ($p < 0.05$) relative to LG PC. Furthermore, advancing Gleason grade was associated with increased T cell infiltration ($p < 0.05$) and M2-like macrophage density ($p < 0.05$). Strikingly, TLS were enriched in exhausted (PD1+) CD4 and CD8 T cells, especially near Tregs ($p < 0.001$) and demonstrated a higher M2-like to M1-like macrophage ratio compared to surrounding tumor ($p < 0.001$) and stroma ($p < 0.05$). We observed paradoxically increased proportions of CD4PD1 cells ($p < 0.05$) and Tregs ($p < 0.05$) in HG vs. LG samples at the tumor-TLS interface. In HG samples, CD8PD1 cells ($p < 0.01$), CD4PD1 cells ($p < 0.05$), and Tregs ($p < 0.05$) were enriched in tumor-TLS interface relative to TLS-stroma interface. HG tumors also demonstrated a higher ratio of M2-like to M1-like macrophages at the tumor-TLS interface compared to intra-tumoral regions ($p < 0.05$). **Conclusions:** Our findings challenge the notion that primary PC is uniformly immunologically inert. We show that HG PC has increased levels of immune infiltration. We describe a paradoxical TLS phenotype in HG PC, where TLS harbor high levels of exhausted T cells near Tregs and have an unfavorable macrophage composition. Critically, the tumor-TLS interface emerged as a unique niche of suppression in HG PC, demonstrating multiple features of lymphocytic and myeloid-driven immunosuppression. These immunosuppressive features were not seen in LG PC. The spatial organization of immunosuppressive cells in HG PC provides a rationale for novel immunotherapeutic targeting of the TLS-rich suppressive landscape of HG PC to improve clinical outcomes in the neoadjuvant setting. Research Sponsor: Prostate Cancer Foundation; V Foundation; National Cancer Institute.

Neoadjuvant androgen receptor pathway inhibition for patients with high-risk localized prostate cancer: 5-year survival update and PSMA PET correlatives of the randomized NeoPRO trial.

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Background: Patients with high-risk prostate cancer remain at elevated risk of recurrence after local therapy. Ongoing trials are investigating neoadjuvant strategies using androgen deprivation therapy (ADT) combined with androgen receptor pathway inhibitors (ARPI). **Methods:** This phase II trial randomized patients with Gleason ≥ 8 and/or cT3N0-1 and/or PSA ≥ 20 ng/mL to receive either goserelin (ADT) plus abiraterone acetate and prednisone (AAP arm) or AAP plus apalutamide (A-APA arm) prior to radical prostatectomy. The primary endpoint was the rate of pathological complete response (pCR) or minimal residual disease (tumor ≤ 0.5 cm). Here we present updated survival data after a median follow-up of 59 months. Biochemical-free survival (BFS) was defined as the time from randomization to PSA > 0.1 ng/mL, metastasis, or death. Metastasis-free survival (MFS) was defined as the time from randomization to metastasis or death. Kaplan-Meier method and log-rank tests were used for time-to-event analyses. **Results:** Sixty-two patients were randomized (AAP = 31; A-APA = 31). Previous results showed no significant difference in the primary endpoint (Bastos D, et al. ASCO 2022). A total of 35 patients experienced biochemical recurrence. No significant difference was observed between the AAP and A-APA arms in 5-year BFS (48% vs 35%, $p = 0.55$) or MFS (83% vs 84%, $p = 0.88$). Achieving complete PSMA response on PSMA PET prior to surgery was a significant prognostic factor for improved 5-year BFS (28% vs 66%, $p = 0.003$) and MFS (74% vs 100%, $p = 0.009$). A trend toward higher 5-year overall survival (OS) was also observed among those with complete PSMA response (87% vs 100%, $p = 0.09$). Residual cancer burden ≤ 0.25 cm³ was associated with better 5-year BFS (32% vs 77%, $p = 0.008$), but not with MFS (79% vs 100%, $p = 0.06$) or OS (89% vs 100%, $p = 0.22$). **Conclusions:** No difference in 5-year BFS or MFS was observed between AAP and A-APA. Complete PSMA response on PSMA PET is a promising prognostic marker and may serve as a surrogate for BFS and MFS after neoadjuvant treatment in high-risk prostate cancer. Clinical trial information: NCT02789878. Research Sponsor: Janssen.

A head-to-head comparison of sextant-systematic biopsy versus extended-systematic biopsy for prostate cancer diagnosis in the era of MRI-targeted biopsy: Non-inferiority randomized clinical trial.

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Background: In recent years, combined targeted biopsy (TB) and 12-core extended systematic biopsy (SB) (TB+12SB) has been recommended for biopsy-naïve patients with prostate MRI-visible lesions. However, increasing SB cores elevates complication risks and healthcare expenditure. Retrospective data indicated noninferior PCa detection with TB + sextant-SB (TB+6SB) vs TB+12SB. This RCT aims to compare the novel TB+6SB scheme and classical TB+12SB for PCa diagnosis. **Methods:** In this non-inferiority RCT (NCT06684652), 506 biopsy-naïve men with solitary mpMRI lesions (PI-RADS ≥3) underwent transperineal cognitive fusion 3-core TB within the predefined mpMRI index lesion (ROI), followed by randomization to 12-core SB or 6-core sextant SB (2 peripheral+1 transitional cores/side). The primary outcome was clinically significant PCa [csPCa, grade group (GG) ≥2] detection rate. Non-inferiority was established if the lower 95% CI bound for the rate difference exceeded -15%. **Results:** Baseline characteristics were similar. TB+6SB demonstrated noninferior csPCa detection versus TB+12SB [54.3% (138/254) vs. 54.8% (138/252); rate difference -0.5%, 95%CI -9.2%-8.3%]. Comparable detection was also observed in PCa, high-grade PCa (GG≥3), and clinically insignificant PCa (GG=1). The concordance in GG between biopsy and radical prostatectomy whole-mount specimens was similar for both TB+12SB [52.3% (34/65), κ=0.55] and TB+6SB [51.7% (30/58), κ=0.50] groups (p=0.25). TB+6SB showed superior safety profiles, significantly relieving the procedural discomfort, reducing the post-biopsy pelvic pain, and improving the quality of life (p<0.05). The biopsy time of TB+6SB was significantly shorter than that of TB+12SB (p<0.001). **Conclusions:** TB+6SB achieves non-inferior diagnostic efficacy to classical TB+12SB with fewer cores and improved safety, positioning it as an effective strategy for PCa diagnosis in biopsy-naïve patients with solitary MRI-suspicious lesions. TB+6SB could improve operational efficiency, providing both clinical safety and cost-effectiveness in histopathological workflows. Clinical trial information: NCT06684652. Research Sponsor: Beijing Research Ward Excellence Program; BRWEP2024W054070105; National High Level Hospital Clinical Research Funding (Interdepartmental Research Project of Peking University First Hospital); 2023IR27; National High Level Hospital Clinical Research Funding (Interdepartmental Research Project of Peking University First Hospital); 2024IR16.

Clinicopathological characteristics after biopsy.			
Characteristics	TB+12SB (n=252)	TB+6SB (n=254)	P value
csPCa (%)	138 (54.8)	138 (54.3)	1
RD (95%CI)	-0.5% (-9.2%, 8.3%)		
High-grade PCa (%)	72 (28.6)	74 (29.1)	1
Number of biopsy cores (per case)	15.0	9.0	
Proportion of positive cores (%) (median [IQR])	20.0 [0, 46.7]	33.3 [0, 55.6]	0.02
Procedural time (second) (median [IQR])	234.0 [220.0, 258.3]	167.5 [154.0, 187.0]	<0.001
Cost of pathological examination (\$) (per case)	75.0	50.0	-
Pain level (VAS) (median [IQR])	3.0 [2.0, 4.0]	2.0 [2.0, 4.0]	0.004
Discomfort level (median [IQR])	3.0 [3.0, 5.0]	3.0 [1.5, 4.0]	0.03
OABSS total score after biopsy (median [IQR])	3.0 [2.0, 7.0]	3.0 [2.0, 5.0]	0.02

Long-term oncologic outcomes of PSMA PET-guided salvage radiotherapy for biochemical recurrence after radical prostatectomy: A systematic review and meta-analysis.

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Background: Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging has demonstrated superior diagnostic accuracy over conventional imaging in localizing recurrent prostate cancer after radical prostatectomy. Previous meta-analyses have established its value in detection and treatment planning; however, whether PSMA-guided salvage radiotherapy (SRT) translates into improved long-term oncologic outcomes remains uncertain. We conducted a systematic review and meta-analysis to assess the impact of PSMA PET-guided SRT on survival outcomes in patients with biochemical recurrence after radical prostatectomy. **Methods:** A comprehensive search of PubMed, Embase, and Cochrane Library was performed on January 16, 2025. Studies comparing PSMA PET-guided SRT with conventional SRT in post-radical prostatectomy patients with biochemical recurrence were included. Long-term oncologic outcomes including failure-free survival (FFS), biochemical progression-free survival (bPFS) and metastasis-free survival (MFS), were pooled using hazard ratios (HRs). **Results:** Nine studies comprising 4,278 patients met the inclusion criteria, including 1,418 patients treated with PSMA PET-guided salvage radiotherapy and 2,860 who received conventional salvage radiotherapy. Compared with conventional SRT, PSMA PET-guided SRT was associated with significantly improved FFS (HR, 0.46; 95% CI, 0.28–0.75). However, the PSMA PET-guided SRT group had a significantly higher risk of biochemical progression; bPFS (HR, 1.40; 95% CI, 1.16–1.69) and metastasis; MFS (HR, 3.16; 95% CI, 2.08–4.80). **Conclusions:** PSMA PET-guided salvage radiotherapy was associated with reduced early treatment failure, as reflected by improved failure-free survival, but a higher risk of biochemical progression and metastatic events. These findings indicate that while PSMA PET-guided intervention may reduce early treatment failure, its impact on long-term disease control remains uncertain and requires further prospective validation. Research Sponsor: None.

Evaluation of treatment outcomes in ductal and intraductal prostate cancer: Insights from the National Cancer Database.

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Background: Ductal and intraductal Prostate carcinoma (DPC) are rare and aggressive histological subtypes of prostate cancer. Based on risk stratification, treatment strategies for localized DPC include radical prostatectomy (RP), radiation with androgen deprivation therapy (RT±ADT), and observation. However, literature on outcomes across various treatment modalities in DPC is limited. Understanding the impact of these approaches on survival is important for strategizing DPC management. We used the national cancer database to evaluate the survival outcomes with various treatment strategies in DPC. **Methods:** Our study focused on patients diagnosed with localized DPC between 2004 and 2020. Patients were stratified into three arms: RP arm included those who underwent RP with or without adjuvant therapy, RT +/- ADT arm included patients who underwent RT with or without ADT, and observation arm included those who had no treatment. We performed Multivariate Cox regression analysis adjusting for age, race, NCCN risk classification, comorbidities, socioeconomic factors, and facility type. We also conducted Kaplan-Meier analysis to evaluate Overall Survival (OS) across the treatment arms. **Results:** We analyzed 2,650 patients with localized DPC. 1586(59.9%) underwent RP, 785(29.6%) underwent RT±ADT, and 279(10.5%) were under observation. 2-year OS for RP, RT±ADT, and observation were 98%, 94% and 78% respectively ($p<0.001$). Similarly, 5-year OS was 92%, 81%, and 54%, respectively ($p<0.001$). Multivariate Cox regression showed that RT+ADT was associated with increased mortality compared to RP (HR: 2.27; $p<0.001$). 2-year OS for patients with PSA ≤ 4 ng/dL and >4 ng/dL was 89.9% and 97.2%, respectively. Similarly, 5-year OS were 75.8% and 88.8%, respectively. Multivariate Cox regression showed that PSA ≤ 4 was associated with an increased risk of mortality compared with PSA >4 (HR: 1.27; $p<0.05$). **Conclusions:** Surgery offers better survival than radiation in localized DPC. The association of low PSA with worse prognosis could be due to dedifferentiation-driven aggressiveness. Therefore, further evaluation of treatment strategies for DPC is warranted. Research Sponsor: None.

Association of cardiovascular outcomes with GnRH agonist and antagonist therapy in non-metastatic prostate cancer.

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Background: Androgen deprivation therapy (ADT) is known to increase cardiometabolic risk. Randomized trials suggest GnRH antagonists may reduce major adverse cardiovascular events (MACE) compared with agonists, though studies were limited by short follow-up and low event rates. We evaluated the association between ADT mechanism and cardiovascular (CV) outcomes using large-scale real-world data. **Methods:** We conducted a retrospective cohort study using TriNetX database. Adult men with non-metastatic prostate cancer initiating ADT within 1 year of diagnosis were categorized by GnRH agonist or antagonist exposure. Cohorts were balanced using propensity score, matching demographics, CV co-morbidities, CV medications, and socioeconomic risk. Analyses were performed in the overall cohort and stratified by baseline CVD status. CV outcomes were assessed in years 1-10 following ADT initiation. The primary endpoint was MACE, defined as myocardial infarction, heart failure exacerbation, stroke or cardiac death. Secondary outcomes included atrial fibrillation/flutter, thromboembolism, mortality, and healthcare utilization. **Results:** After matching, 2,538 patients were included in both the GnRH antagonist and agonist group, including 785 with prior CVD and 1,460 without. In the overall cohort, GnRH antagonist therapy was associated with lower risk of MACE compared with GnRH agonists (OR 0.80, 95% CI 0.70–0.99; $p=0.05$) with an absolute risk of 8.0% vs 9.6%. Among patients with established CVD, antagonist use was associated with reduced MACE risk (OR 0.77, 95% CI 0.64–0.93; $p<0.01$) with an absolute risk of 19.6% vs 25.5%. In patients without prior CVD, antagonist use was associated with markedly lower MACE risk (OR 0.30, 95% CI 0.19–0.52; $p<0.01$) with an absolute risk of 1.3% vs 4.2%. For secondary outcomes, antagonist therapy was associated with lower risk of arterial thromboembolism and Emergency visits in the overall cohort, with no significant differences in all other outcomes. Among patients with baseline CVD, antagonist use was associated with lower risk of atrial fibrillation with no significant differences in all other outcomes. Among patients without baseline CVD, antagonist therapy was associated with lower risk of atrial fibrillation, healthcare utilization, and incident type 2 diabetes with no significant difference in all other outcomes. **Conclusions:** GnRH antagonist therapy was associated with lower rates of major adverse cardiovascular events compared with GnRH agonists, regardless of baseline cardiovascular disease status in years 1 through 10 after ADT initiation. Events occurring after the first year are more likely to reflect cumulative treatment-related cardiovascular toxicity, rather than unmasking baseline disease. These findings support further prospective, randomized trials to define the comparative CV safety of different ADT formulations. Research Sponsor: None.

Temporal evolution of prostate cancer incidence and incidence-based mortality from 2000 to 2022: A retrospective analysis by race and age at diagnosis based on USPSTF screening guidelines.

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Background: Prostate-specific antigen (PSA) screening guidelines have evolved substantially since 2000, influencing detection patterns and outcomes. Despite widespread implementation, significant racial disparities persist in prostate cancer incidence and mortality. Understanding temporal trends across guideline eras, stratified by race and age, is critical for optimizing screening strategies and addressing health equity. **Methods:** Using SEER*Stat, we extracted data from the Surveillance, Epidemiology, and End Results (SEER) database (2000–2022). We employed Jointpoint regression to analyze the secular trend in incidence and incidence-based mortality (IBM), which we classified and arranged by race, age at diagnosis, and year of diagnosis. Annual percentage change (APCs) were calculated using weighted least square method. **Results:** A total of 1,259,662 patients met the inclusion criteria for our study. These included diagnosed cases of prostate cancer from 2000–2022. The total age-adjusted incidence rate was 60.7 per 100,000. The APC from 2000–2007 (before 2008 guidelines) was -0.1 ($p < 0.05$), signifying a cumulative annual decrease. The APC was -2.6 ($p < 0.05$) from 2008–2011, 0.1 ($p < 0.05$) from 2012–2017, and 1.5 ($p < 0.05$) from 2018–2022. Based on race, the APC from 2000–2022 was -2.1 for white, -1.7 for blacks, -2.2 for American Indian/Alaska native (AIAN) and -2.7 for asian and pacific islander (API). Based on age at diagnosis, the APC was -1.9 from 55–64 years, -1.7 from 65–74 years, -2.0 from 75–84 years, and -2.2 at 85 years and above. In terms of incidence based mortality, rate increased from 2.4 (2000) to 37.7 (2022) in white, with APC of 6.3% (95% CI 5.0–7.7), in black, rate increased from 4.8 (2000) to 60.5 (2022), with APC of 5.2% (95% CI 4.0–6.4), in API, rate increased from 1.8 (2000) to 17.7 (2022) while in AIAN, rate increased from 2.4 (2000) to 21.5 (2022), with APC of 5.0% (95% CI 3.4–6.6). **Conclusions:** Between 2000 and 2022, prostate cancer incidence demonstrated distinct temporal patterns aligned with changes in PSA screening recommendations, with a marked decline from 2008 to 2011, minimal change from 2012 to 2017, and an increase from 2018 to 2022. Across the same period, incidence-based mortality (IBM) increased steadily in all racial groups, despite long-term declines in overall incidence. Incidence-based mortality rates were consistently higher in black patients compared with white patients throughout the study period. These findings demonstrate a difference between incidence and incidence-based mortality over time and highlight persistent racial differences in prostate cancer outcomes across multiple screening eras. Research Sponsor: None.

Addition of 18F-DCFPyL PSMA PET to MRI to avoid unnecessary biopsy in men on active surveillance: Final results from a phase II diagnostic trial (PROMPT).

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Background: Multiparametric MRI (mpMRI) is used in active surveillance (AS) for prostate cancer (PC) but has limited specificity. This prospective trial evaluated whether combining 18F-DCFPyL PSMA PET with mpMRI improves the detection of clinically significant PC (csPC) in patients on AS and reduces unnecessary biopsies prompted by false-positive mpMRI. **Methods:** In this IRB-approved, single-arm Phase II study, 91 patients on AS underwent PSMA PET and mpMRI on a dedicated PET/MRI scanner followed by systematic and targeted biopsies. PET and mpMRI were interpreted independently. The primary outcome was the diagnostic accuracy of mpMRI versus the combined PSMA PET/MRI for csPC. **Results:** Among 246 targeted lesions, the area under the curve (AUC) for combined PSMA PET/MRI was (0.77) compared to mpMRI alone (0.70) ($p=0.2$). PSMA PET/MRI showed improved specificity (64.6% vs. 27.5%) with a comparable negative predictive value (89.1% vs. 89.7%). Of 57 csPC lesions, 6 (10.5%) were uniquely identified by the combination. Half of the biopsies for false-positive mpMRI or PET lesions (122/246; 50%) encompassing 17/91 (19%) of patients could have been avoided with combined imaging. Management changed in 9% of patients based on PET/MRI. **Conclusions:** In this first-in-field trial the addition of PSMA PET to mpMRI with dedicated PET/MRI imaging enhances sensitivity in detecting csPC and may reduce the need for unnecessary biopsies in AS patients. Incorporating PSMA PET/MRI into clinical practice could refine surveillance protocols and support biopsy omission in select men with negative imaging. The single health-system nature of the trial may limit the generalizability of our findings. Research Sponsor: the Duane and Dorothy Bluemke Foundation.

Diagnostic accuracy of the mpMRI, PSMA PET/MRI, and for the combination, assessed using the "AND" operator.^a

Parameter	MRI, PIRADS≥3	PSMA-PET, Likert≥3	MRI, PIRADS≥4	PSMA-PET, Likert≥4	MRI PIRADS≥3 AND PET Likert≥3	MRI PIRADS≥3 AND PET Likert≥4	MRI PIRADS≥4 AND PET Likert≥3	MRI PIRADS≥4 AND PET Likert≥4
Accuracy	41.9%	48.0%	63.8%	63.8%	66.7%	72.8%	78.5%	79.3%
Sensitivity	89.5%	84.2%	71.9%	73.7%	73.7%	64.9%	63.2%	57.9%
Specificity	27.5%	37.0%	61.4%	60.8%	64.6%	75.1%	83.1%	85.7%
PPV	27.1%	28.7%	36.0%	36.2%	38.5%	44.0%	52.9%	55.0%
NPV	89.7%	88.6%	87.9%	88.5%	89.1%	87.7%	88.2%	87.1%
Number of lesions (% of 257)	188 (76)	167 (68)	114 (46)	116 (47)	109 (44)	84 (34)	68 (28)	60 (24)

^aThe detection of clinically significant cancer was considered on per-lesion analysis.

MRI = magnetic resonance imaging; PET = positron emission tomography; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen. PPV = positive predictive value, NPV = negative predictive value.

Leveraging spatial proteomics to identify epithelial cell subtypes driving poor prognosis in prostate cancer.

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Background: Epithelial cell features, such as morphology and cellular organization within the tumor architecture (e.g. Gleason Score), have long been known to be prognostic in prostate cancer. However, the specific epithelial cell subtypes driving clinical outcomes in patients remains unclear. Traditional tumor profiling techniques lack the resolution needed to interrogate complex single-cell biomarkers. Imaging Mass Cytometry (IMC) now enables high-dimensional identification and detailing of epithelial, stromal, and immune cell subtypes within patient tumors. Using a custom IMC panel, we profiled tumor biopsies from a large prospective biopsy cohort with long-term (median >12-year) clinical follow-up to identify potentially targetable epithelial cell populations associated with adverse outcomes in localized prostate cancer. **Methods:** Spatially resolved protein expression profiling was performed on primary prostate cancer tumor biopsies using a custom IMC assay enriched for targetable tumor markers. Cell segmentation and single-cell expression measurement were performed using the published 'steinbock' toolkit. Biochemical progression-free survival (bPFS) and cancer-specific survival (CSS) were pre-specified clinical endpoints. Univariate and multivariable survival analyses stratified by cell abundance tertiles were performed using a Cox proportional hazards model. The Mann-Whitney U test was used to assess for pairwise differences in cell abundance between patient groups. All significance testing was performed using a two-tailed significance level of 0.05. **Results:** Protein co-expression patterns in >3.4 million cells comprising 573 biopsy samples obtained from 385 patients were measured. Single-cell analysis revealed 15 cell clusters representing luminal prostate cancer cells (including PSMA-high, PSMA-intermediate, and PSMA-low), basal epithelial cells, and lymphocytes. Patients with tumors enriched for PSMA-high epithelial cells demonstrated impaired bPFS ($P<0.001$) and CSS ($P=0.016$). PSMA-high epithelial cells were enriched in high-grade (Gleason Score 8+) tumors ($P<0.05$). Multivariable analysis revealed PSMA-high epithelial cell enrichment to be prognostic of bPFS independently of Gleason Score and serum PSA at time of diagnosis ($P<0.05$). Co-expression analysis demonstrated that these prognostic PSMA-high cells also expressed high levels of the cell-surface targets KLK2, B7-H3, and protein. **Conclusions:** We identified an epithelial single-cell biomarker associated with adverse clinical outcomes in localized prostate cancer. If validated through ongoing experiments in an independent cohort, our findings support new potential strategies for treatment intensification using targeted therapies in select high-risk patients. Research Sponsor: Conquer Cancer, the ASCO Foundation; Prostate Cancer Foundation; Benioff Initiative for Prostate Cancer Research; U.S. National Institutes of Health.

Clinical implications and diagnostic utility of ^{68}Ga Gallium FAPI PET CT in patients with testicular germ cell tumors: The prospective phase Ib FAPI-TEST study.

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Background: The fibroblast activation protein (FAP) is overexpressed in tumor tissue by cancer associated fibroblasts and radiopharmaceuticals can bind to this target. Recently, the ^{68}Ga -FAPI PET has emerged as a novel imaging modality for optimized differentiation between benign and malignant lesions. However, data on patients with testicular germ cell tumors (TGCT) are rare. This prospective study aims to investigate the expression, uptake and sensitivity of the ^{68}Ga -FAPI PET in TGCT patients. **Methods:** In this prospective observational phase Ib study, patients with TGCT up to clinical stage III and unfavorable TGCT histology in the testis such as teratomas were included. A ^{68}Ga -FAPI PET was performed in all included patients and analyzed with static (SUVmax/mean). Histology from the testis and whenever available from the metastasis were also stained for FAP and manually categorized into negative, medium and high expression. This study was approved by the local ethics committee (no 2024-17844). **Results:** We included 12 patients with a mean age of 34.5 (SD 8.81). Clinical stage at time of inclusion were CS II (n = 9), CS1 (n = 1) and CS III (n = 1) as well as one extragonadal TGCT. In eight and four cases the ^{68}Ga -FAPI PET was performed before and after completion of curative chemotherapy, respectively. Histology was available in six cases (5 = LNs, 1 = mediastinal tumor). FAP expression in the tumor of the testis was high in 50%, and in metastasis 60%. Stratification for high and low FAP lesions was performed according to mean SUVmax of 7.81 (SD 7,9) for all radiographic and histopathologic true positive metastasis. Sensitivity for ^{68}Ga -FAPI PET was 57% with a specificity 100%. **Conclusions:** This is the first prospective study that evaluates ^{68}Ga -FAPI PET in TGCT patients with the largest cohort so far. Stratification for SUVmax lesions above 7.81 showed excellent specificity, and the ^{68}Ga -FAPI PET might potentially serve as a useful novel imaging modality for primary staging in clinical stages IIA and IIB, as well as post-chemotherapy with residual mass. Research Sponsor: None.

First-in-human PET imaging of ^{68}Ga -FC516, a novel ACP3-targeted radiotracer for prostate cancer.

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Background: Prostatic acid phosphatase (ACP3) is overexpressed in more than 85% of prostate cancers, and largely absent in normal tissues, resulting in over 100-fold tumor-to-background specificity. ACP3 represents a differentiated imaging biomarker that may complement prostate-specific membrane antigen (PSMA), particularly in PSMA-low or PSMA-treated patients. We developed ^{68}Ga -FC516, a novel ACP3-targeted radiotracer, and evaluated its preclinical characteristics and first-in-human imaging performance. **Methods:** ^{68}Ga -FC516 was studied preclinically using *in vitro* assays (radiochemical stability, enzyme inhibition, cellular uptake, internalization, and efflux) and *in vivo* PET/CT studies, including blocking and biodistribution experiments. A first-in-human exploratory clinical trial was conducted in healthy volunteers and prostate cancer patients. The primary objective was to assess safety and radiation dosimetry; secondary objectives included biodistribution assessment and lesion detection. PET/CT imaging results were compared with PSMA radiotracers or ^{68}Ga -OncoACP3-DOTA when possible. **Results:** ^{68}Ga -FC516 was labeled efficiently with radiochemical purity exceeding 95%. In *in vitro* studies, ^{68}Ga -FC516 demonstrated potent target binding, long cellular retention and high stability. ACP3-specific tumor uptake of ^{68}Ga -FC516 was confirmed via an *in vivo* blocking experiment. The tracer showed low background uptake in liver, kidneys, and salivary glands, with tumor uptake exceeding 16.4% ID/g in a biodistribution study. Gallbladder uptake was markedly lower than that of ^{68}Ga -OncoACP3-DOTA (2.6% vs. 35.0% ID/g) at 1 hour post-injection. In an ongoing clinical trial in metastatic prostate cancer patients, increased uptake of ^{68}Ga -FC516 (SUV_{max} in PET/CT) was observed at 1 to 3 hours across all lesions, with improved tumor-to-kidney ratios over time. The tracer also demonstrated low background uptake, including in salivary glands and kidneys, which was significantly lower than that of PSMA-targeted tracers. Notably, a patient with both prostate and rectal cancers showed strong uptake in the prostate tumor (SUV_{max} 44), but no uptake in the rectal lesion, further establishing the tracer's superior specificity. No adverse events were observed. **Conclusions:** We have shown that ^{68}Ga -FC516 has high ACP3-targeting specificity, low background uptake and excellent imaging performance in preclinical and first-in-human clinical studies. These findings support the potential of ACP3 as a differentiated biomarker for prostate cancer diagnosis and patient stratification, complementing PSMA PET and addressing unmet needs in PSMA-low or PSMA-treated patient populations. The clinical validation study was approved by the Ethics Committee of the First Affiliated Hospital of Jinan University (KY-2025-254). Research Sponsor: FindCure Biosciences Co., Ltd. Clinical trial information: KY-2025-254. Research Sponsor: None.

Explainable machine learning for continuous transcriptomic modeling of metastatic risk in prostate cancer (MET-score).

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Background: Metastatic progression is the leading cause of mortality in prostate cancer, yet clinicopathological stratification incompletely identifies primary tumors with latent metastatic potential. Emerging evidence supports metastatic competence as a gradual transcriptional reprogramming, motivating molecular tools that capture continuous risk states. **Methods:** Transcriptomes from primary and metastatic prostate tumors ($n = 766$; PRIMARY = 507, MET = 259) spanning 16,234 gene features were integrated to train an interpretable XGBoost model. SHapley Additive exPlanations were used to derive a minimal 30-gene signature and define a continuous metastasis-likeness transcriptomic score (MET-score). MET-score was applied to primary tumors to quantify metastasis-likeness and characterize associated biology. External validation was performed in an independent primary prostate cohort profiled with exon microarrays (GSE21034) without model retraining. **Results:** The minimal 30-gene signature captured metastasis-associated signal with high discriminative performance (ROC AUC ≈ 0.98). In primary tumors ($n = 507$), MET-score exhibited a right-skewed continuous distribution (mean 0.0079, SD 0.0640; range 0.0023–0.9953), consistent with heterogeneous degrees of metastasis-like transcriptional activity within primary disease. Using a prespecified high-risk threshold at the 0.85 quantile (cutoff 0.002603), 81/507 (16.0%) primary tumors were classified as HIGH MET-score and 426/507 as LOW, identifying a subset with transcriptomic profiles most closely resembling metastatic disease. MET-score generalized robustly to GSE21034 while preserving its continuous structure and enabling molecular stratification despite platform differences and partial gene loss: 26/30 signature genes were present in the microarray cohort (missing C15orf40, ADIRF, CTC1, NTPCR). However, prognostic validation against clinical endpoints could not be performed because the publicly available metadata did not include clearly annotated time-to-event and event-status variables. **Conclusions:** An explainable 30-gene MET-score was developed to quantify metastasis-likeness as a continuous transcriptomic trait in primary prostate cancer. The score identifies a high-risk primary subset and transfers to an independent external cohort (GSE21034) without model retraining, supporting cross-platform robustness and prioritizing MET-score for clinical outcome validation in RNA-seq-annotated cohorts. Research Sponsor: None.

cfDNA-based signatures of nucleosome organization to enable prostate cancer subtyping.

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Background: Neuroendocrine prostate cancer (NEPC) can arise from prostate adenocarcinoma (PRAD) via therapy-associated lineage plasticity and is characterized by reduced AR signaling and activation of neuroendocrine (NE) regulatory pathways. Nucleosome positioning, inferable from cell-free DNA (cfDNA) fragmentation patterns, reflects lineage-specific gene regulation. Recent studies have shown that active, open chromatin is associated with specific nucleosome spacing patterns, leading to an enrichment of longer cfDNA fragments, including di-nucleosome fragments. We hypothesized that fragmentomic signatures reflecting nucleosome positioning could distinguish PRAD from NEPC, providing a simple means to detect lineage plasticity from cfDNA. **Methods:** We analyzed cfDNA samples from 47 patients (8 with NEPC, 39 with PRAD) with hybrid-capture sequencing. Baits were designed to target adenocarcinoma (AC, 715 sites) and NE-associated regulatory elements (508 sites). For each sample, fragments overlapping each enhancer set were aggregated into 5-bp binned fragment-length distributions (18–500 bp). We quantified di-nucleosome (250–400 bp) and mono-nucleosome (120–180 bp) fragment counts at NE and AC regulatory elements. We calculated the log-ratio of NE versus AC di/mono values: $\log_2[(\text{di/mono})_{\text{NE}}/(\text{di/mono})_{\text{AC}}]$. We also computed a position-free Transcriptional Activation Score (pFTAS) for each enhancer set using a published framework for estimating enhancer activity from cfDNA fragment size distributions, deriving an analogous log-ratio: $\log_2[\text{pFTAS}_{\text{NE}}/\text{pFTAS}_{\text{AC}}]$. We tested if these ratios could distinguish NEPC versus PRAD, evaluating the area under the receiver operating characteristic curve (AUC) in the full cohort and by leave-one-out cross-validation (LOOCV). **Results:** The enhancer-specific di/mono log-ratio achieved complete separation between PRAD (median: -0.209; range: -0.449 to -0.090) and NEPC (median: 0.030; range: -0.056 to 0.218), yielding an AUC of 1.00 both in-sample and by LOOCV. The pFTAS log-ratio was also discriminative, with an AUC of 0.99 in-sample and an AUC of 0.89 by LOOCV. Overall, nucleosome fragmentation patterns provide a chromatin-based fragmentomic signal that enables accurate discrimination between PRAD and NEPC. **Conclusions:** Leveraging hybrid-capture cfDNA, we identified a biologically grounded chromatin-based signature that robustly discriminates NEPC from PRAD. By reflecting lineage-associated nucleosome positioning, this liquid biopsy-based approach provides a cost-effective and non-invasive molecular metric derived from routinely generated cfDNA sequencing data. It may be particularly useful in clinically challenging settings, including cases with mixed morphology or when a biopsy is difficult to obtain. Research Sponsor: None.

Randomized phase 1 trial of cisplatin-based chemotherapy with or without sodium thiosulfate for men with metastatic germ cell tumor (GCT).

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Background: Cisplatin-induced ototoxicity remains a major survivorship issue in men with metastatic GCT. Sanchez et al., demonstrated that among adult GCT survivors, 78% develop hearing loss, with severity associated with cumulative cisplatin exposure. Sodium thiosulfate (STS; PEDMARK) was FDA-approved in 2022 to reduce the risk of cisplatin-associated ototoxicity in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors. However, prospective data in adults with metastatic GCT receiving curative intent cisplatin-based therapy are lacking. This study aims to address this gap in men with metastatic GCT, and potentially improve long-term quality of life. **Methods:** This open-label, single-center, randomized phase 1 trial evaluates sodium thiosulfate for reducing the incidence of cisplatin-induced ototoxicity in adults with metastatic GCT. Eligible adults have stage II–III GCT and are planned for first- or second-line cisplatin-based chemotherapy; patients receiving second-line therapy require a ≥ 4 -week cisplatin washout to establish a new audiometric baseline. Key exclusions include baseline moderate or greater hearing loss, hypersensitivity to sodium thiosulfate or related compounds, chronic systemic corticosteroid use, concurrent non-cisplatin ototoxic medications, and comorbidities requiring sodium restrictions. Participants are randomized 2:1 to receive cisplatin-based chemotherapy with sodium thiosulfate versus chemotherapy alone, with a target enrollment of 39 patients. Sodium thiosulfate is administered intravenously at 20 g/m² over 30 minutes, beginning 6 hours after completion of cisplatin infusion and at least 10 hours before the next cisplatin dose, consistent with FDA-approved multi-day dosing schedules. The primary endpoint is the incidence of clinically meaningful ototoxicity, defined by trial parameters using American Speech-Language-Hearing Association criteria relative to baseline audiometry. Secondary endpoints include incidence of high-frequency ototoxicity, ototoxicity severity, safety per Common Terminology Criteria for Adverse Events (CTCAE) v5.0, and 2-year progression-free survival. Ototoxicity monitoring is performed using serial high-frequency audiometry (testing 250–12,500 Hz) at baseline and 1, 3, and 6 months following completion of cisplatin therapy. Ototoxicity incidence will be compared between arms using a one-sided Fisher's exact test under a modified intention-to-treat framework. Enrollment has begun. Clinical trial information: NCT07218913. Research Sponsor: Fennec Pharmaceuticals Inc.

Protocol for ADHERE: A randomised controlled trial evaluating a digital exercise intervention with virtual supervised group exercise sessions compared to standard of care for patients receiving androgen deprivation therapy for prostate cancer.

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Background: In the UK, supervised exercise is recommended by NICE for prostate cancer patients receiving androgen deprivation therapy (ADT); however, engagement in physical activity remains limited. Although high adherence is observed during supervised exercise, it is unclear whether participants maintain activity after supervision. Barriers include treatment-related side-effects and low motivation. Digital exercise interventions that include education and behaviour change support may address these barriers and promote sustained engagement in physical activity. **Methods:** The primary objective of ADHERE is to determine whether a digital exercise intervention incorporating virtual group exercise sessions improves adherence to physical activity compared with standard of care (SOC). Secondary and exploratory objectives include assessment of health-related quality of life (HRQoL), fatigue, physical function, clinical biomarkers and participant experiences, and evaluation of cost-effectiveness. ADHERE is a single-centre, phase III, two-arm randomised controlled trial. Prostate cancer patients within eight weeks of starting ADT and planned for radiotherapy will be recruited at The Royal Marsden NHS Foundation Trust. Participants will be randomised 1:1, stratified by ADT duration (≤ 6 months or > 6 months), to SOC alone or SOC plus the digital exercise intervention. The intervention includes virtual supervised group exercise sessions delivered weekly over 26 weeks, access to exercise videos, an individualised exercise programme, educational content and “patient buddy” support. Assessments will be conducted at baseline and three, six, and 12-months post-radiotherapy. Primary endpoint is adherence to physical activity guidelines at six months post-radiotherapy, assessed using device-based activity monitor and self-reported exercise diary. Secondary endpoint is HRQoL and will be measured using FACT-P. 160 participants (80 per arm) will be recruited allowing for 20% dropout. ADHERE has ethical and regulatory approval and will be conducted in accordance with Good Clinical Practice. Recruitment for this trial started in December 2025. An interim analysis will be conducted, with final analyses performed following completion of all participant follow-up. Results will be disseminated via peer-reviewed publications and conferences. Clinical trial information: NCT07243834. Research Sponsor: None.

DEPECA-1 (Defeating Penile Cancer 1): A phase II study to evaluate a first-line systemic therapy with enfortumab vedotin plus avelumab for advanced and metastatic penile carcinoma.

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Background: Squamous cell carcinoma of the penis (PeCa) is a rare malignancy with unfavorable outcomes in advanced stage. Since the 1990s, platinum-based chemotherapy has been the standard of care for the first-line treatment of metastatic disease. Unfortunately, it is characterized by a response rate of 30–40%, overall survival (OS) of 17 months and progression free survival (PFS) of 6 months at most. Thus, there is a critical medical need to assess novel systemic strategies for PeCa in the first-line setting, given that current regimens are of a limited clinical benefit while exposing patients to considerable chemotherapy-associated toxicities. In this context, the PD-1 inhibitor pembrolizumab yielded a promising activity in squamous cell carcinomas of various origins. Meanwhile, enfortumab vedotin (EV), a Nectin-4 directed antibody-drug-conjugate, in combination with pembrolizumab has been recently approved for the treatment of metastatic urothelial cancer. The incidence of ≥ 3 grade adverse events with this regimen was $> 55\%$. Notably, a PD-L1 inhibitor avelumab provided a comparable activity as pembrolizumab but a lower overall rate of endocrine adverse events in patients with urothelial carcinoma. Avelumab monotherapy yielded a response rate of 17% and a median duration of response of 16 months in males with a platinum-refractory PeCa or those unfit for platinum chemotherapy in ALPACA trial. Given that approximately 60% of PeCa tissues express both PD-L1 and Nectin-4, the combination of EV with avelumab represents a potentially synergistic therapeutic strategy, leveraging both direct cytotoxicity and immune-mediated anti-tumor activity through complementary mechanisms of action. **Methods:** The DEPECA-1 trial is an investigator-initiated, open label, single-arm, multicenter phase II trial, enrolling 25 males with locally advanced or metastatic PeCa at 10 sites in Germany. Patients must be ineligible for curative surgery and not have received any prior systemic palliative therapy. Participants (ECOG ≤ 2) will receive 1200 mg avelumab on day 1 and EV (1,25 mg/kg) on day 1 and day 8 in a 3-week cycle for a maximum of 24 months and 32 cycles. Primary endpoint is the objective response rate (ORR) assessed per RECIST 1.1. Secondary endpoints include PFS, OS, duration of response (DOR), disease control rate (DCR) and patient-related outcomes. Exploratory analysis comprises tumor biomarker profiling. DEPECA-1 has received regulatory approval on 29th October 2025. First patient was enrolled on December 16, 2025. Registration IDs: EU CT No. 2025-521644-37-00/NCT07110038. Clinical trial information: NCT07110038. Research Sponsor: Merck Healthcare KGaA; Astellas Pharma GmbH.

AcTFirst: A phase 3 trial of ^{225}Ac -PSMA-617 plus ARPI versus standard of care in adults with PSMA-positive metastatic castration-resistant prostate cancer.

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Background: In the VISION and PSMAfore trials, β -emitting radioligand therapy (RLT) with [^{177}Lu]-PSMA-617 (^{177}Lu -PSMA-617) shows superior efficacy and tolerable safety compared with standard of care (SoC) in patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC). [^{225}Ac]-PSMA-617 (^{225}Ac -PSMA-617), an α -emitting agent, may offer an alternative treatment option to SoC in mCRPC because its higher linear energy transfer increases the likelihood of higher cytotoxicity in tumor cells. **Methods:** AcTFirst (NCT06855277) is a phase 3, open-label, multicenter, randomized study to evaluate the efficacy and safety of ^{225}Ac -PSMA-617 plus androgen receptor pathway inhibitor (ARPI) in patients with PSMA-positive mCRPC. Eligible participants are adults with PSMA positron emission tomography-positive mCRPC and progressive disease on androgen deprivation therapy plus one ARPI as their last treatment in the metastatic hormone-sensitive prostate cancer (mHSPC) or earlier setting. ARPI treatment received in the mHSPC setting can be continued until cycle 1. Key exclusion criteria include previous treatment with RLT or systemic anti-cancer therapy for mCRPC. Participants with homologous recombination repair gene-mutated mCRPC who had prior exposure to poly-adenosine diphosphate ribose polymerase inhibitors (PARPi) for HSPC can be included. Participants with inadequate bone marrow, hepatic or renal function are excluded. Participants will be randomized to three treatment arms: 1) a combination of ^{225}Ac -PSMA-617 (up to six cycles) plus ARPI change (enzalutamide or abiraterone); 2) ^{225}Ac -PSMA-617 monotherapy (up to six cycles); or 3) investigator's choice of SoC (ARPI change, taxane chemotherapy or ^{177}Lu -PSMA-617). Efficacy will be assessed using a hierarchical group sequential testing strategy for the primary and key secondary objectives. The primary endpoint is radiographic progression-free survival (rPFS) by conventional imaging for the combination and SoC arms. Key secondary endpoints are overall survival (OS) for the combination and SoC arms, rPFS by conventional imaging for the monotherapy and SoC arms, OS for the monotherapy and SoC arms, and rPFS by PSMA positron emission tomography/computed tomography imaging for the combination and SoC arms. Other outcomes of interest include safety, health-related quality of life and other patient-reported outcomes. As of January 2026, patient enrollment is ongoing. Clinical trial information: NCT06855277. Research Sponsor: Novartis.

OMAHA-004: Phase 3 trial of the steroidogenesis inhibitor opevesostat versus androgen receptor pathway inhibitor (ARPI) switch in participants with metastatic castration-resistant prostate cancer (mCRPC) after a prior ARPI.

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Background: Opevesostat (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. Opevesostat showed antitumor activity in participants with heavily pretreated mCRPC in the phase 1/2 CYPIDES trial. The randomized, open-label, phase 3 OMAHA-004 trial (NCT06136650) is designed to evaluate the efficacy and safety of opevesostat in participants with mCRPC after a prior ARPI. **Methods:** Eligible participants have mCRPC that progressed during androgen deprivation therapy ≤ 6 months before screening and on or after 1 ARPI for metastatic or nonmetastatic hormone-sensitive prostate cancer (HSPC) or CRPC for ≥ 8 weeks (≥ 14 weeks with bone progression). Prior ARPI plus docetaxel for HSPC is permitted if participants received no more than 6 cycles of docetaxel without radiographic disease progression. Approximately 1314 participants will be randomized 1:1 to opevesostat 5 mg orally twice-daily plus dexamethasone 1.5 mg and fludrocortisone 0.1 mg orally once daily or abiraterone acetate 1000 mg orally once daily plus prednisone 5 mg orally twice daily (if prior enzalutamide, darolutamide, or apalutamide) or enzalutamide 160 mg orally once-daily (if prior abiraterone). Stratification factors are metastatic site (bone only vs liver vs other), androgen receptor ligand binding mutation (AR-LBDm) status (positive vs negative), and prior docetaxel treatment for HSPC (yes vs no). Once the predefined enrollment threshold for participants with either mutation status (AR-LBDm-positive, ~400 participants or AR-LBDm-negative, ~914 participants) is met, no additional participants with that mutation status will be permitted to enroll. The protocol was amended to use radiographic progression-free survival per Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1 by blinded independent central review (BICR), analyzed separately in participants with AR-LBDm-positive and -negative disease, as the primary end point and overall survival as a key secondary end point. Other secondary end points include time to initiation of first subsequent anticancer therapy or death, objective response rate and duration of response 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. Enrollment is ongoing. Clinical trial information: NCT06136650. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; Orion Corporation, who are codeveloping opevesostat.

A phase 3 randomized, double-blind, placebo-controlled study of a pasritamig plus best supportive care in metastatic castration-resistant prostate cancer.

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Background: Metastatic castration-resistant prostate cancer (mCRPC) remains an incurable disease with high morbidity and a median overall survival of 2 years. Human kallikrein 2 (KLK2) is highly and specifically expressed in normal and malignant prostate tissue, including late stage mCRPC. Pasritamig is a humanized, IgG1-based bispecific antibody that targets KLK2-expressing cells via CD3 engagement, inducing T cell-mediated targeted cytotoxicity. In a first-in-human study in participants with mCRPC refractory to standard therapies, pasritamig demonstrated a favorable safety profile (< 5% grade 3 or higher treatment-related adverse events and < 10% cytokine release syndrome, all grade 1) and encouraging efficacy at the recommended phase 2 dose with every 6-week (Q6W) outpatient dosing. **Methods:** KLK2-compAS is a double-blind, randomized, global phase 3 study to evaluate the safety and efficacy of pasritamig in participants with mCRPC who have previously received all available and suitable life-prolonging therapies including androgen receptor pathway inhibitor, taxane chemotherapy, radioligand therapy (RLT), and poly(ADP-ribose) polymerase inhibitors (for patients with BRCA mutations). Other key inclusion criteria include ECOG performance status 0–2, PSA ≥ 2 ng/mL, adequate organ function, and ongoing androgen deprivation therapy or prior orchiectomy. Key exclusion criteria include visceral metastases, prior KLK2- or CD3-directed therapies, and active autoimmune disease requiring systemic immunosuppression. Approximately 663 patients will be randomized in a 2:1 ratio to receive pasritamig plus best supportive care (BSC) or placebo plus BSC, stratified by prior PSMA-targeted RLT, number of prior taxanes, and ECOG performance status. BSC may include palliative external beam radiation, low dose steroids, pain medications, bone protective agents, and needed palliative procedures. Pasritamig is administered outpatient at a target dose of 300 mg IV Q6W with two step-up doses of 3.5 mg IV on cycle 1 day 1 and 18 mg IV on cycle 1 day 8. Pre-medications (dexamethasone, diphenhydramine, acetaminophen) will be administered for step-up and first target dose. Participants will receive treatment until confirmed radiographic progression or unequivocal clinical progression, intolerable toxicity, withdrawal, or death. The primary endpoint is overall survival. Key secondary endpoints include radiographic progression-free survival (rPFS), PFS (including clinical progression and unconfirmed bone progression), time to symptomatic progression, and time to skeletal-related events. Enrollment commenced in September 2025 and remains ongoing. Clinical trial information: NCT07164443. Research Sponsor: J&J.

BNT324-03: Phase 3, randomized, open-label trial of BNT324/DB-1311, a B7H3 ADC, versus docetaxel in patients with taxane-naïve metastatic castration-resistant prostate cancer (mCRPC).

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Background: B7H3 is highly expressed in various human cancers, including mCRPC, and overexpression is associated with a poor patient prognosis. BNT324/DB-1311 is an investigational B7H3 ADC comprised of a topoisomerase-I-inhibitor-based payload with a cleavable linker and a drug-to-antibody ratio of ~6 that received FDA Fast-Track Designation for previously treated CRPC. A phase 1/2 study (DB-1311-O-1001, NCT05914116) is currently enrolling several prostate cancer cohorts: post Lutetium-177 [¹⁷⁷Lu]-PSMA-617 radioligand (RLT) (Lu 177-RLT) mCRPC, taxane-naïve mCRPC, and castration-sensitive prostate cancer (CSPC) with suboptimal PSA response, with patients receiving BNT324/DB-1311 alone or with abiraterone or enzalutamide. This study has reported encouraging activity (median radiographic PFS 11.3 months) and a manageable safety profile in heavily pretreated mCRPC (Parsonson A, ASCO 2025 #5015), and in Lu 177-RLT pretreated mCRPC (Stein M, ASCO GU 2026 #176). The treatment landscape of mCRPC has been evolving. As first use of an androgen receptor pathway inhibitor (ARPI) has shifted to the mCSPC setting, more patients will receive docetaxel in early-line mCRPC. The use of Lu 177-RLT in taxane-naïve mCRPC has been increasing; however, outcomes with subsequent docetaxel appear suboptimal. Docetaxel remains the first-line treatment option for symptomatic or rapidly progressive mCRPC, but outcomes are poor. Overall, there is a high unmet need for novel effective and better tolerated treatment options in the post-ARPI and emerging post-RLT settings. **Methods:** BNT324-03 is an open-label, randomized, Phase 3 trial (NCT07365995) designed to determine the efficacy and safety of BNT324 compared with docetaxel in patients (> 18 years, ECOG PS 0–1) with mCRPC previously treated with 1 or 2 prior ARPIs. Patients may have received prior Lu 177-RLT but must not have received prior taxane for mCRPC (allowed in mCSPC if ≥6 months since completion without disease progression). Prior treatment with B7H3 targeted therapy is not allowed. Approximately 736 patients will be randomized 1:1 to receive either BNT324 or docetaxel (+ prednisone/prednisolone). Unless there is unacceptable toxicity or withdrawal of consent, BNT324 will be administered until PCWG3-modified RECIST v1.1-defined progressive disease and docetaxel will be administered for up to 10 cycles. Randomization will be stratified by prior Lu 177-RLT, prior taxane use, and site of metastasis. The dual primary endpoints are to assess the efficacy of BNT324 in terms of radiographic PFS and OS when compared with docetaxel. Secondary endpoints include time to first subsequent therapy, ORR and DOR by BICR, time to pain progression, time to first symptomatic skeletal-related event, PSA response and time to PSA progression, and safety. Enrollment is ongoing globally. Clinical trial information: NCT07365995. Research Sponsor: BioNTech SE in collaboration with BioNTech Shanghai Pharmaceutical Co., Ltd and DualityBio Inc.

A phase II clinical trial of ivonescimab (VEGFxPD-1 bispecific antibody) in patients with metastatic castration-resistant prostate cancer (mCRPC).

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Background: Patients with mCRPC achieve limited responses with single-agent immune checkpoint therapies (ICTs), due to tumor microenvironments (TME) characterized by few intratumoral effector T cells and high prevalence of suppressive myeloid cell populations, cytokines, and signaling pathways. In murine models of mCRPC, tyrosine kinase inhibitors (TKIs, i.e. against vascular endothelial growth factor [VEGF] receptor 2, MET, and AXL, among others) inhibited tumor infiltrating myeloid-derived suppressor cells and enhanced responses to ICTs (Lu X et al., *Nature* 2017). Consistent with this, a phase III clinical trial combining TKI and anti-PD-(L)1 demonstrated improved clinical outcomes in a subset of patients with mCRPC (Agarwal N et al., *Lancet Oncol* 2025). Ivonescimab is a first-in-class bispecific antibody simultaneously targeting PD-1 and VEGF-A that has demonstrated clinical activity across multiple tumor types. We hypothesized that ivonescimab will induce anti-tumor responses in a subset of patients with mCRPC. **Methods:** This is an open-label, single-center phase II clinical trial in patients with mCRPC with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology. The primary endpoint of the study is objective response rate per Prostate Cancer Working Group 3 (PCWG3) criteria, and secondary endpoints include duration of response (DOR), disease control rate (DCR) greater than 6 months), radiographic progression free survival (rPFS), PSA₅₀ responses (defined as confirmed > 50% decline in PSA from baseline) and incidence, severity, and duration of adverse events. Tumor biopsies are collected at baseline and prior to C2D1 for evaluation of biomarkers of response and resistance to therapy. The study is being conducted using a Bayesian optimal phase 2 (BOP2) design. A total of up to 24 patients will be enrolled on study. The study is currently open and enrolling (NCT06567314). Clinical trial information: NCT06567314. Research Sponsor: None.

A phase 3 randomized, open-label study of pasritamig (JNJ-78278343), a T-cell engager targeting human kallikrein-2, with docetaxel versus docetaxel for metastatic castration-resistant prostate cancer.

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Background: Metastatic castration-resistant prostate cancer (mCRPC) remains an incurable disease with high morbidity and a median overall survival of approximately two years. Human kallikrein 2 (KLK2) is highly and specifically expressed in normal and malignant prostate tissue, including late stage mCRPC. Pasritamig (PAS) is a first-in-class bispecific T-cell-engager that simultaneously binds KLK2 on prostate cancer cells and CD3 receptor complexes on T cells. In the Phase 1b study (NCT05818683), pasritamig was combined with docetaxel (DOCE) to treat patients with mCRPC. The safety profile of PAS+DOCE was shown to be consistent with previous studies of DOCE and no cytokine release syndrome of any grade was reported (0 of 51 patients). Promising anti-tumor activity was observed in both taxane-naïve and heavily pretreated patients. **Methods:** This global, randomized, open-label, phase 3 study (NCT07225946) evaluates the efficacy and safety of PAS in combination with DOCE versus DOCE alone in adult participants (≥ 18 years) with mCRPC. Approximately 800 participants will be randomized 1:1. Stratification factors include sites of metastases (on conventional imaging), lactate dehydrogenase, Eastern Cooperative Oncology Group performance status, and prior poly(ADP-ribose) polymerase (PARP) inhibitor use. Key inclusion criteria are histologically or cytologically confirmed adenocarcinoma of the prostate, evidence of metastatic disease, and PSA or radiographic disease progression on 1–2 novel ARPI for any stage of prostate cancer. Key exclusion criteria include prior treatment with T-cell redirecting therapies, chemotherapy, or radio-pharmaceutical therapy, uncontrolled central nervous system metastases, or significant comorbidities that could interfere with study participation. PAS is administered in the outpatient setting at a target dose of 300 mg IV Q6W with two step-up doses of 3.5 mg IV on day 1 and 18 mg IV on day 8. Participants in the DOCE alone arm will also receive continuous prednisone per label. The primary endpoint is radiographic progression-free survival assessed by blinded independent central review per Prostate Cancer Working Group 3 and RECIST v1.1 criteria. Key secondary endpoints include overall survival, time to symptomatic progression, time to subsequent therapy, and time to skeletal-related event. Safety, pharmacokinetics, biomarkers, and quality of life assessments will also be evaluated. The study is currently enrolling patients in the North and Latin Americas, European Union and Asia Pacific regions. Clinical trial information: 78278343PCR3003. Research Sponsor: None.

Phase 1/2 OMAHA-U01 substudy 01A: Oral steroidogenesis inhibitor opevesostat alone or in combination with other therapies in participants with metastatic castration-resistant prostate cancer (mCRPC).

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Background: mCRPC remains an incurable disease and therapeutic agents with novel mechanisms of action are needed for this patient population. Opevesostat (MK-5684; ODM-208), an oral steroidogenesis inhibitor, selectively inhibits cytochrome P450 11A1 (CYP11A1), a catalyst of the first and rate-limiting step of steroid biosynthesis. In the phase 1/2 CYPIDES study, opevesostat showed antitumor activity in participants with heavily pretreated mCRPC. OMAHA-U01 is an adaptive, open-label, rolling-arm, multicenter, phase 1/2 umbrella study designed to evaluate opevesostat-based investigational therapies in participants with prostate cancer. Substudy 01A (NCT06353386) will evaluate the safety and efficacy of opevesostat alone or in combination with other therapies in participants with previously treated mCRPC. **Methods:** Eligible participants have mCRPC that progressed during androgen deprivation therapy ≤ 6 months before screening, and on or after 1–2 androgen receptor pathway inhibitors for metastatic or nonmetastatic hormone-sensitive prostate cancer and nonmetastatic or mCRPC. Prior treatment with ≤ 1 taxane-based chemotherapy regimen for mCRPC is allowed. A safety lead-in phase for all opevesostat-based experimental combinations (~10 participants in each arm) will establish the recommended phase 2 dose (RP2D), followed by an efficacy phase (opevesostat alone, ≤ 100 participants; opevesostat-based combinations, ~40 participants each). Participants will be randomly assigned 1:1:1:1 to receive opevesostat 5 mg PO BID, opevesostat 5 mg PO BID plus olaparib (RP2D), opevesostat 5 mg PO BID plus docetaxel (RP2D), or opevesostat 5 mg PO BID plus cabazitaxel (RP2D). Randomization for the efficacy phase will be stratified according to AR-LBD mutation (AR-LBDm) status (positive or negative). The primary end point for the safety lead-in phase is safety and tolerability. Primary end points for the efficacy phase are safety and prostate-specific antigen response rate per Prostate Cancer Clinical Trials Working Group (PCWG) criteria. Secondary end points include objective response rate and radiographic progression-free survival per PCWG-modified RECIST v1.1 by blinded independent central review (BICR), overall survival, duration of response by BICR, time to first subsequent anticancer therapy, and time to pain progression. The predefined eligibility cap for pts with AR-LBDm-negative status has been reached, and the study is currently only enrolling pts with AR-LBDm-positive status. Clinical trial information: NCT06353386. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; Orion Corporation, who are codeveloping opevesostat.

ProTACT: A first-in-human, phase 1 dose escalation and expansion study evaluating the safety, tolerability, and anti-tumor activity of [²²⁵Ac]Ac-FL-020, a PSMA-targeted radioconjugate, in patients with mCRPC.

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Background: Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy is an emerging treatment modality for metastatic castration-resistant prostate cancer (mCRPC). However, many agents targeting PSMA have resulted in quality of life-limiting toxicities, such as xerostomia, due to expression of PSMA in salivary glands and other organs. [²²⁵Ac]Ac-FL-020 is a next-generation, PSMA alpha radioconjugate developed using the proprietary UniRDC linker-chelator technology designed to optimize biodistribution. It is intended for the treatment of patients with mCRPC and aims to enhance tumor uptake while sparing radiosensitive organs, such as salivary glands, thus potentially leading to an improved therapeutic window. **Methods:** ProTACT (FL-020-001) is a first-in-human, open-label, multicenter Phase 1 study investigating the safety, tolerability, and preliminary anti-tumor activity of [²²⁵Ac]Ac-FL-020 in patients with advanced PSMA-positive mCRPC. This study consists of 2 parts: dose escalation (Part 1) and dose expansion (Part 2). Patients eligible for enrollment must be aged ≥18 years and have: histologically confirmed mCRPC, evidence of disease progression, ≥1 PSMA-positive lesion (uptake higher than liver) on PSMA positron emission tomography/computed tomography imaging, an Eastern Cooperative Oncology Group performance status of 0 to 1, and adequate organ function. Prior treatment with androgen receptor signaling inhibitors or CYP17 inhibitors and ≥1 taxane-based chemotherapy is required, unless declined by the patient. Prior therapy with Lu-177 is allowed. Patients with extensive PSMA-negative disease are excluded. [²²⁵Ac]Ac-FL-020 will be administered intravenously at the assigned dose every 6 weeks for up to 6 cycles. Throughout the study, 10 eligible patients will receive 185 ± 20 MBq of [¹¹¹In]In-FL-020 for dosimetry evaluation ≥8 days prior to their first dose of [²²⁵Ac]Ac-FL-020. Part 1 will apply a Bayesian logistic regression model with overdose control to guide dose escalation decisions. Dose cohorts of 1–3 patients (for Cohorts 1 and 2) and 3–6 patients (for Cohorts 3 and beyond) will evaluate ascending dose levels from 1–10 MBq to determine the maximum tolerated dose and/or recommended Phase 2 dose (RP2D). Once the RP2D is established, 18 additional patients will be enrolled in Part 2 to further assess safety and explore early signals of efficacy. Primary endpoints include incidence of dose-limiting toxicities and type, frequency, and severity of adverse events/serious adverse events. Secondary endpoints include overall response rate, disease control rate, radiological progression-free survival, and pharmacokinetic parameters (eg, maximum plasma concentration). The study is active in Australia, the United States, Turkey, and China. Clinical trial information: NCT06492122. Research Sponsor: Full-Life Technologies.

TIDAL: A phase II study of the DLL3-directed T-cell engager tarlatamab in DLL3-positive metastatic prostate cancer.

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Background: T-cell engagers directed at canonical prostate adenocarcinoma surface antigens (e.g., STEAP1, KLK2) have demonstrated substantial activity in prostate adenocarcinoma; however, alternative tumor-directed targets are needed for pts whose tumors have undergone lineage plasticity. Delta-like ligand 3 (DLL3) is a surface target variably expressed across the spectrum of neuroendocrine/small cell malignancies. Tarlatamab (Imdelltra, Amgen, Thousand Oaks, CA) is a bispecific T-cell engager targeting DLL3 and CD3, with regulatory approval for small cell lung cancer, and emerging evidence of activity in DLL3-positive prostate cancer. TIDAL is a multi-center, prospective, single arm phase II trial (NCT07111507) evaluating the safety and efficacy of tarlatamab in DLL3-positive advanced prostate cancer. **Methods:** Key eligibility criteria include metastatic prostate cancer with progression on ≥ 1 prior systemic therapy in the metastatic setting and DLL3-positive disease (IHC $\geq 50\%$), irrespective of histologic subtype. Pts without measurable disease by RECIST 1.1 criteria can be enrolled; however, at least 50% of pts enrolled must have measurable disease. Pts will receive tarlatamab in 28-day cycles with a 1 mg priming dose on cycle 1 day 1 (C1D1), followed by a target dose of 10 mg on C1D8, C1D15, and days 1 and 15 of subsequent cycles. All pts are hospitalized for ≥ 24 hours of monitoring following C1D1 and C1D8 infusions. Mandatory tumor biopsy and circulating tumor DNA (ctDNA) collection are performed at screening and cycle 2, with required ctDNA and optional biopsy at end of treatment (EOT). CT and bone scan are performed every 8 weeks for the first 24 weeks, then every 12 weeks. The primary endpoint is radiographic progression-free survival at 24-weeks. Secondary endpoints include overall response rate (ORR), median duration of response, median rPFS, median composite PFS, median overall survival, and safety. Correlative studies will evaluate associations between tumor DLL3 expression, circulating immune profiles, and clinical outcomes. A subset of pts will be co-enrolled in an imaging biomarker study (NCT04199741) utilizing a novel DLL3 PET tracer (^{89}Zr -DFO-SC16.56). As of January 14, 2026, 4 of the planned 32 pts have been enrolled. Clinical trial information: NCT07111507. Research Sponsor: Amgen.

A randomized phase III trial investigating platinum and taxane chemotherapy in metastatic castration-resistant prostate cancer (mCRPC) patients with alterations in DNA damage response (DDR) genes (OPTION-DDR) CCTG-PR-25 NCT06439225.

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Background: Outcomes for patients (pts) with mCRPC after androgen receptor pathway inhibitors (ARPI) remain poor. There are numerous treatment options, including single agent docetaxel, however overall survival (OS) after ARPI is between 12–19 months. Thus, management of mCRPC post-ARPI represents an area of unmet need. 25% of pts have alterations in DDR genes, which may be a biomarker for sensitivity to treatment with platinum agents. Carboplatin has been previously evaluated in smaller trials in pts with mCRPC and shows promise in patients with DDR gene alterations. PR-25 leverages standard of care testing for DDR genes to evaluate in a rigorous manner whether addition of carboplatin to docetaxel improves overall survival (OS) in pts with DDR gene alterations and mCRPC. **Methods:** PR-25 is a phase III randomized controlled trial led by the Canadian Cancer Trials Group comparing docetaxel to docetaxel and carboplatin in pts with DDR alterations. Pts must receive prior ARPI for mCRPC and demonstrate radiographic or PSA progression prior to enrollment. Qualifying DDR gene alterations include: BRCA1, BRCA2, ATM, ATR, BRIP1, BARD1, CDK12, CHEK1, CHEK2, ERCC2, FANCA, FANCC, FANCD2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L. The primary endpoint is OS. Secondary endpoints include radiographic progression free survival (PCWG3 and RECIST 1.1), PSA response, time to next systemic therapy, patient reported quality of life and economic evaluation. Statistical design: The target accrual is 236 patients over 3.25 yrs with 2 year follow-up to detect a HR of 0.65 in OS, using a type 1 error rate of 5% (2 sided) and power of 80%. **Conduct to Date:** Study activation – October 2024. First patient enrolled – December 2024. Accrual to date: 10. Clinical trial information: NCT06439225. Research Sponsor: CIHR Grant; NCTN Grant; Canadian Cancer Society Grant.

XALience: A phase 3, open-label, multicenter, randomized study of xaluritamig plus abiraterone vs investigator's choice in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer.

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Background: In the first-in-human (FIH) study, xaluritamig, a T-cell engager directed at six-transmembrane epithelial antigen of the prostate 1 (STEAP1), demonstrated potent antitumor activity with a manageable safety profile in patients with metastatic castration-resistant prostate cancer (mCRPC).^{1,2} Preliminary data from this FIH study of xaluritamig in combination with abiraterone in chemotherapy-naïve patients with mCRPC³ supports the initiation of a phase 3 study of xaluritamig plus abiraterone with the aim of improving survival in this population. **Methods:** XALience is a randomized, multicenter, open-label, phase 3 study (NCT07213674) of xaluritamig plus abiraterone vs investigator's choice in patients with chemotherapy-naïve mCRPC. Approximately 750 eligible patients ≥ 18 years old with histologically confirmed chemotherapy-naïve mCRPC; evidence of disease progression on prior enzalutamide, apalutamide, or darolutamide; ECOG PS of 0–1; and adequate organ function and who may have previously received ≤ 6 cycles of docetaxel in the metastatic hormone-sensitive prostate cancer (mHSPC) setting will be randomized 1:1 to receive xaluritamig plus abiraterone or investigator's choice of docetaxel, cabazitaxel, or abiraterone. Patients will be stratified by prior docetaxel exposure in mHSPC, presence of liver metastases, prior treatment with prostate-specific membrane antigen radioligand therapy, and planned intention-to-treat with investigator's choice. This study consists of a 28-day screening period, treatment until radiographic progression based on Prostate Cancer Working Group 3 (PCWG3) guidelines, a safety follow-up period, and a long-term follow-up period. To mitigate the risk of cytokine release syndrome, xaluritamig will be initiated at weekly step-up dosing over four doses up to the target dose during cycle 1 followed by target dose administration every 2 weeks from cycle 2 day 1 onwards. The primary endpoint is overall survival, which will be analyzed using a stratified log-rank test at a one-sided 2.5% significance level. Key secondary endpoint is investigator-assessed radiographic progression-free survival per PCWG3. Other secondary endpoints include radiographic and prostate-specific antigen response, safety, tolerability, health-related quality of life, patient-reported outcomes, pharmacokinetics, and immunogenicity. Enrollment is ongoing and 20 patients have been enrolled as of January 19, 2026. References: Kelly WK, Danila DC, Lin CC, et al. *Cancer Discov.* 2024;**14**:76–89. Kelly WK, Appleman L, Lin C-C, et al. *Ann Oncol.* 2024;**35**: S963–S964. Data on file, Amgen; 2025. Clinical trial information: NCT07213674. Research Sponsor: Amgen Inc.

TALENT: A randomized phase 2 study of talazoparib with or without enzalutamide in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) alterations after progression on abiraterone acetate.

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Background: The phase 3 TALAPRO-2 study (NCT03395197) demonstrated superior efficacy with enzalutamide plus talazoparib vs. enzalutamide plus placebo for pts with mCRPC with tumors harboring HRR mutations. Only 8% of HRRm pts enrolled in TALAPRO-2 had prior exposure to abiraterone acetate with prednisone, and none had received an androgen receptor inhibitor. Given the evolving treatment landscape of metastatic hormone sensitive prostate cancer (mHSPC), many patients now receive ADT in combination with abiraterone acetate and prednisone until progression. It is unknown whether the synergistic effects of inhibiting PARP alongside potent AR inhibition will be maintained in those patients with tumors that have demonstrated resistance to an androgen biosynthesis inhibitor such as abiraterone. The TALENT study (NCT06844383) will address this unanswered question by randomizing pts with HRR-mutated mCRPC following progression on abiraterone acetate with prednisone to receive talazoparib in combination with enzalutamide versus talazoparib alone. We hypothesize that synergy between PARP and AR inhibition will be demonstrated in this contemporary patient population. **Methods:** TALENT will enroll approximately 126 pts with mCRPC with prior disease progression while receiving abiraterone acetate for HSPC or locally advanced disease and a confirmed mutation in one of twelve HRR genes. ATM mutations will be limited to 15%. Prior exposure to docetaxel in the mHSPC setting will be included as a stratification factor. Pts will be randomized in a 1:1 fashion to either talazoparib and enzalutamide or talazoparib alone administered along with ADT. Pts will continue treatment until disease progression, unacceptable toxicity, treatment delay > 60 days of talazoparib, protocol violation, withdrawal of consent, physician decision, study termination by the Sponsor, loss to follow-up, or death. Patients will be monitored using RECIST 1.1 and PCWG3 criteria for bone disease. The primary endpoint is investigator-assessed radiographic progression free survival (rPFS). Secondary endpoints include time to PSA50 response, time to PSA progression, overall survival, and patient reported outcomes capturing quality of life. Exploratory analyses will evaluate rPFS by HRR gene (BRCA vs non-BRCA, individual genes, and gene clusters). Pt recruitment is planned at approximately 15 sites in the US. As of January 27, 2026, 0 pts have been enrolled. Clinical trial information: NCT06844383. Research Sponsor: Pfizer Inc.

Phase I/II study to evaluate AZD9750, a novel androgen receptor proteolysis-targeting chimera, alone and in combination with other anticancer agents in patients with metastatic prostate cancer (ANDROMEDA).

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Background: The androgen receptor (AR) is a key driver of prostate cancer progression. AR pathway inhibitors (ARPIs) are standard of care for metastatic prostate cancer, but acquired resistance is inevitable and often involves reactivation of AR signaling via AR gene alterations such as amplifications or ligand binding domain mutations. The need remains for alternative strategies to target the AR. AZD9750 is a novel oral proteolysis-targeting chimera that potently degrades wild-type, mutant, and amplified forms of the AR. Preclinical data also showed significant antitumor benefit with AZD9750 as monotherapy and combined with the PARP1 selective inhibitor saruparib (AZD5305). ANDROMEDA (NCT07336446) is a first-in-human, phase I/II, open-label, multicenter study investigating the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of AZD9750 as monotherapy and combined with saruparib in patients (pts) with metastatic castration-resistant prostate cancer. **Methods:** This study follows a modular design in which pts receive AZD9750 as monotherapy (Module 1) or combined with saruparib (Module 2; Table). Each module has 2 parts: monotherapy dose escalation or combination dose finding (Part A) and dose optimization and expansion (Part B). Eligible pts are ≥ 18 years of age with histologically or cytologically confirmed adenocarcinoma of the prostate and documented metastatic disease with serum testosterone level ≤ 50 ng/dL, evidence of disease progression, and ECOG performance status of 0 or 1. Pts should have previously received ARPIs and taxane-based chemotherapy, with the exception of no prior taxane-based chemotherapy in Module 1 Part B3. Primary endpoints include occurrence of dose-limiting toxicities (Part A only), incidence of adverse events (AEs) and AEs leading to treatment discontinuation (Parts A and B), and preliminary efficacy (ie, $\geq 50\%$ decrease in prostate-specific antigen [PSA]; Part B only). Secondary endpoints include preliminary efficacy (ie, $\geq 50\%$ and $\geq 90\%$ decrease in PSA, objective response rates and progression-free survival per RECIST v1.1 and PCWG3 criteria, change in target lesion size per RECIST v1.1 criteria, time to PSA response, and time to PSA progression per PCWG3 criteria) and pharmacokinetic parameters (Parts A and B). This study is currently recruiting for monotherapy dose escalation. Clinical trial information: NCT07336446. Research Sponsor: AstraZeneca.

Study part	Module 1: AZD9750 monotherapy	Module 2: AZD9750 plus saruparib
Part A	A1. Dose escalation A2. Backfill cohorts	Combination dose finding ^a
Part B	B1. Dose optimization ^a B2. Dose expansion ^b B3. Dose expansion ^b	Combination dose expansion ^c

^aRecommended doses determined in Module 1 Part A; ^bTo be opened once recommended phase II dose identified in Module 1 Part B1; ^cTo be opened once combination dose identified in Module 2 Part A.

REINFORCE: A phase III randomized trial of treatment intensification with docetaxel in metastatic hormone-sensitive prostate cancer patients without deep PSA response after initial apalutamide therapy.

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Background: Androgen deprivation therapy (ADT) plus androgen receptor pathway inhibitors (ARPIs) is the standard of care for metastatic hormone-sensitive prostate cancer (mHSPC). However, a substantial proportion of patients fail to achieve a deep prostate-specific antigen (PSA) response, which is consistently associated with worse outcomes. Deep PSA response has emerged as a robust early prognostic marker across multiple phase III trials. Patients lacking this favorable PSA decline represent a poor-risk subgroup with limited treatment personalization. Docetaxel improves survival in high-volume mHSPC and may benefit biologically aggressive disease identified by suboptimal early PSA response. REINFORCE evaluates a PSA-guided strategy of treatment intensification with docetaxel in patients without deep PSA response after apalutamide. **Methods:** REINFORCE is an international, multicenter, open-label, phase III randomized trial. Eligible patients are men ≥ 18 years with histologically confirmed mHSPC, ECOG performance status ≤ 1 , PSA > 5 ng/ml at diagnosis of metastatic disease, ≤ 12 weeks of ADT before apalutamide, adequate organ function, who have received apalutamide plus ADT for 24–30 weeks, have not progressed, and have failed to achieve a deep PSA response. Deep PSA response is defined as PSA ≤ 0.2 ng/ml or PSA response $\geq 90\%$ in combination with a PSA ≤ 4 ng/ml. Approximately 320 patients from 85 sites located in 6 countries will be randomized 1:1 to treatment intensification with docetaxel (75 mg/m² every 3 weeks for 6 cycles) plus continued apalutamide and ADT, or continuation of apalutamide plus ADT alone. Randomization is stratified by metastasis timing (synchronous vs metachronous), presence of visceral metastases, and PSA at study entry (≤ 4 vs > 4 ng/mL). The primary endpoint is event-free survival (EFS), defined as time from randomization to PSA progression, radiographic progression of soft tissue, visceral or bone lesions, according to PCWG3, or death from any cause. Secondary endpoints include time to castration resistance, radiographic and PSA progression-free survival, overall survival, safety, PSA response rates, and patient-reported outcomes. Preliminary evidence suggests that apalutamide is associated with a $\leq 10\%$ decrease in docetaxel AUC; a dedicated pharmacokinetic sub-study will assess docetaxel drug-drug interaction and bioequivalence when co-administered with apalutamide. An independent data monitoring committee will oversee patient safety, including an early safety review after the first 18 patients included, review a pre-planned interim efficacy analysis, and evaluate pharmacokinetic data, providing recommendations to the sponsor regarding study continuation. Clinical trial information: 2025-524408-30-00. Research Sponsor: Johnson & Johnson Innovative Medicine.

An open-label, parallel-cohort, multicenter clinical study of rezvilutamide in combination with androgen deprivation therapy (ADT) with or without docetaxel in the neoadjuvant treatment of oligometastatic prostate cancer.

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Background: Oligometastatic hormone-sensitive prostate cancer (omHSPC), defined by ≤ 5 metastases, represents a distinct disease state with a more favorable prognosis, offering a critical window for treatment intensification aimed at improving long-term outcomes. Cyto-reductive radical prostatectomy (cRP) has emerged as a feasible local treatment option for select patients, with phase II data suggesting a survival benefit over systemic therapy alone. The foundation of systemic therapy for metastatic HSPC (mHSPC) is an androgen receptor pathway inhibitor (ARPI) combined with androgen deprivation therapy (ADT). Rezvilutamide, a second-generation ARPI, demonstrated superior efficacy over bicalutamide when combined with ADT in patients with mHSPC. Furthermore, the addition of docetaxel to an ARPI and ADT (triplet therapy) significantly improved survival in mHSPC, including in patients with low metastatic burden. We hypothesize that intensifying neoadjuvant systemic therapy with triplet therapy prior to cRP may maximize tumor cytorreduction and pathologic response in omHSPC. **Methods:** This is a prospective, open-label, parallel-cohort, multicenter phase II study. Patients with newly diagnosed, biopsy-proven omHSPC (≤ 5 bone or lymph node metastases on conventional imaging, no visceral metastases) who are candidates for and desire cRP are eligible. All patients undergo baseline prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA-PET/CT) prior to ADT initiation. Patients select their neo-adjuvant regimen: Cohort A receives ADT plus oral rezvilutamide (240 mg daily) for 24 weeks; Cohort B receives ADT, rezvilutamide (same dose), plus docetaxel (75 mg/m² IV q3w for 6 cycles) for 24 weeks. Upon completion of the 24-week neoadjuvant therapy, metastases are reconfirmed by conventional imaging, and a second PSMA-PET/CT assessment is performed. All patients subsequently undergo cRP with extended pelvic lymph node dissection within 6 weeks. After surgery, patients may opt to continue with ADT or rezvilutamide at their discretion until disease progression. Based on assumed pCR rates of $<10\%$ (Cohort A) and 25% (Cohort B) ($\alpha=0.05$, power=80%), 40 evaluable patients are required per cohort. Accounting for 20% dropout, 100 total patients (50 per cohort) will be enrolled. Key inclusion criteria: ECOG PS 0-1, adequate organ function. Key exclusion criteria: prior systemic therapy for PCa (except ≤ 4 weeks of ADT), prior second-generation ARPI use, and prostate pathology results indicating neuroendocrine carcinoma. As of January 15, 2026, enrollment is ongoing with 6 patients accrued to date. No data analysis has been performed. Clinical trial information: ChiCTR2400093262. Research Sponsor: the Development Center for Medical Science & Technology National Health Commission Clinical Research Project.

TRIPLE-SWITCH (SWOG/CCTG-PR26): A randomized phase III clinical trial for the addition of docetaxel to androgen receptor pathway inhibitors in patients with metastatic castration sensitive prostate cancer (mCSPC) and suboptimal PSA response (NCT06592924).

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Background: Management of patients (pts) with mCSPC remains a challenge due to its incurable nature and heterogeneous response to androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPI). Analyses of phase III ADT + ARPI trials have indicated that pts with mCSPC with suboptimal PSA response (≥ 0.2 ng/mL at 6–12 months) have a short time to castration-resistance (CRPC) and poor median overall survival (OS) of 30–36 months. There is equipoise about the use of docetaxel in mCSPC pts on ARPI because of: 1) an absence of randomized data for docetaxel in this setting; 2) toxicity of docetaxel with impact on quality of life; and 3) selection of docetaxel treatment by disease volume rather than disease biology. **Methods:** PR26 is a joint CCTG–SWOG international, open-label, randomized phase III trial comparing continuing standard ADT + ARPI with the addition of up to 6 cycles of docetaxel to ADT + ARPI in mCSPC pts with suboptimal PSA response (PSA ≥ 0.2 ng/mL after 6–12 months of ADT and ≥ 4 months of ARPI). Stratification will be based on PSA levels, ARPI type, presence of liver metastasis, disease recurrence status, and time since ADT initiation. The sample size is 830 pts to detect a targeted 33% improvement in overall survival (hazard ratio 0.75) using a 1-sided 0.025 level test with 85% power. Key eligibility criteria are: ≥ 18 years, histologically confirmed prostate adenocarcinoma, metastatic disease present and confirmed by conventional imaging (CT and/or bone scan), PSA ≥ 5.0 ng/mL prior to ADT, receipt of ADT for 6–12 months and ARPI for ≥ 4 months, PSA ≥ 0.2 ng/mL within 14 days of enrolment, adequate organ and marrow function, ECOG performance status 0–2, eligible for docetaxel chemotherapy, no evidence of disease or biochemical progression on ADT prior to enrolment. Primary endpoint is OS. Secondary endpoints include PSA response, PSA kinetics, and clinical progression free-survival. Correlative studies will explore the prognostic and predictive value of circulating tumor DNA and the association between molecular signatures and clinical outcomes. Conduct to date: Study activation, January 2025. First patient enrolled, May 2025. Accrual to date: 6. Supported by CIHR grant 39527, NCTN grant #CA180863 and CCS grant #707213. Research Sponsor: None.

EORTC GUCG 2238: “Deescalate,” a pragmatic trial to revisit intermittent androgen deprivation therapy in metastatic hormone-sensitive prostate cancer in the era of new androgen receptor pathway inhibitors.

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Background: The systemic standard of care treatment in patients with metastatic hormone-sensitive prostate cancer (mHSPC) according to international guidelines is combination therapies with androgen deprivation therapy (ADT) + androgen receptor pathway inhibitor (ARPI) +/- docetaxel. These ADT + ARPI combinations (also called maximum androgen blockade, MAB) have been shown in phase 3 randomized clinical trials to reduce the risk of death by 20–40%, delay further treatment, and improve health-related quality of life (HRQoL). Treatment usually continues until biochemical, radiological, or clinical progression, sometimes many years after treatment initiation, exposing patients to chronic side effects affecting their HRQoL. Registration trials included highly selected patients, not representative of the general population, thereby overestimating treatment adherence and effectiveness while underreporting tolerability. Several sub-analyses of the registration trials demonstrated that patients achieving a PSA ≤ 0.2 ng/ml have prolonged overall survival (OS). In this study, we hypothesized that patients with mHSPC treated with MAB reaching PSA ≤ 0.2 ng/ml may benefit from treatment interruption without compromising OS. **Methods:** The primary goal of this academic-led, open-label, pragmatic, randomized phase III study is to investigate whether intermittent MAB (iMAB) can be safely administered to mHSPC patients who reached a PSA ≤ 0.2 ng/mL at 6 to 12 months after the start of treatment (docetaxel and radiotherapy permitted as part of standard treatment), as compared to continuing MAB (cMAB). Co-primary endpoints are: 1) Feasibility: proportion of patients who do not restart their MAB within one year of interruption. 2) Efficacy: OS assuming the iMAB regimen at three years is non-inferior to continuous treatment. Secondary objectives include toxicity, HRQoL and assessing the impact on treatment resources between iMAB and cMAB. The study will randomize 1600 patients to exclude a 4% OS difference at 3 years while $<30\%$ of patients restarted MAB after one year. The study is currently active in Belgium, Croatia, Denmark, Ireland, France and Spain. The activation of the other countries (Portugal, Italy, Romania, Slovenia, Switzerland and Czech Republic) is expected by spring 2026. The study has currently recruited 109 patients (Updated January 26, 2026). Clinical trial information: NCT05974774. Research Sponsor: European Union's HORIZON-MISS-2022-CANCER-01-03; 101104574.

AMPLIFY: A phase 3 study of ^{64}Cu -SAR-bisPSMA positron emission tomography in participants with biochemical recurrence of prostate cancer.

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Background: Prostate cancer (PC) is the second most prevalent cancer in men globally. The need for improved PC imaging is reflected in a biochemical recurrence (BCR) rate of 20 to 40% after initial definitive therapy. Despite advances in technology, many patients will fail to have their recurrence accurately localized by imaging, especially at low PSA levels. Imaging modalities that are widely available and can accurately detect, monitor, and restage residual / recurrent loco-regional and metastatic disease are therefore highly desirable. Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that is strongly overexpressed in PC, making it an ideal target for imaging and therapy. ^{64}Cu -SAR-bisPSMA may offer several advantages over the currently approved PSMA positron emission tomography (PET) agents for PC due to the bivalent structure of SAR-bisPSMA and longer half-life of ^{64}Cu ($t_{1/2} = 12.7\text{h}$), compared to the approved monovalent PSMA agents utilizing ^{18}F and ^{68}Ga ($t_{1/2} < 2\text{h}$). Evidence has demonstrated prolonged tumor retention and 2–3x higher tumor uptake with detection of additional PC lesions using ^{64}Cu -SAR-bisPSMA compared to approved PSMA PET agents. **Methods:** AMPLIFY (NCT06970847) is a multi-center, single arm, open-label Phase 3 diagnostic performance study of ^{64}Cu -SAR-bisPSMA PET/CT in participants with a history of prostate adenocarcinoma and rising or detectable PSA after initial definitive treatment. The primary objective is to investigate the ability of ^{64}Cu -SAR-bisPSMA PET/CT to detect recurrence of PC, with co-primary endpoints of participant-level correct detection rate (CDR) and region-level positive predictive value (PPV) assessed independently for Day 1 and Day 2. Key secondary objectives include assessment of safety, participant-level PPV, and participant-level detection rate (DR). A total of 220 patients will be enrolled. All participants are required to have baseline conventional imaging. Eligible patients will receive a single administration of ^{64}Cu -SAR-bisPSMA (200 MBq) followed by a PET/CT scan on Day 1 (1–4h post-dose) and on Day 2 ($24 \pm 6\text{h}$ post-dose). Participants will then continue into the follow-up period to verify the ^{64}Cu -SAR-bisPSMA PET/CT findings. The Day 1 and Day 2 scans will be interpreted individually by a qualified local reader and 3 independent, blinded, central readers for the presence of abnormal ^{64}Cu -SAR-bisPSMA uptake. ^{64}Cu -SAR-bisPSMA PET/CT results on Day 1 and Day 2 will then be assessed against a composite Reference Standard by a central expert panel. The study is open for recruitment in the United States and Australia. Clinical trial information: NCT06970847. Research Sponsor: Clarity Pharmaceuticals.

A phase 2 study of androgen deprivation therapy and the androgen receptor ligand-directed degrader (BMS-986365) prior to radical prostatectomy in patients with high-risk localized prostate cancer.

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Background: Although radical prostatectomy (RP) is a curative approach for patients (pts) with high-risk localized prostate cancer (PC), recurrence rates remain high. Neoadjuvant studies of androgen deprivation therapy (ADT) plus an androgen receptor pathway inhibitor (ARPI) suggest improvement in local disease control at the time of RP and may be associated with better long-term outcomes (McKay et al. PC Prostatic Dis. 2018; McKay et al. ASCO 2023: #5095). An ongoing phase 3 study is evaluating ADT plus apalutamide for 6 months prior to RP in pts with high-risk or locally advanced PC; co-primary endpoints are pathologic complete response (pCR) and metastasis-free survival (NCT03767244). BMS-986365 is an orally administered ligand-directed degrader targeting the androgen receptor (AR) via a first-in-class dual mechanism of 1) AR degradation and 2) AR antagonism. A phase 1 study showed that BMS-986365 was well tolerated with a manageable safety profile, with antitumor activity in pts with metastatic castration-resistant PC (mCRPC) regardless of AR gene alterations (Rathkopf et al. Ann Oncol. 2025), leading to an ongoing phase 3 study in mCRPC (rechARge: NCT06764485). Due to its dual mechanism and promising data in mCRPC, we hypothesize that neoadjuvant treatment with ADT plus BMS-986365 prior to RP will result in robust pathologic response rates. **Methods:** This is a single center, phase 2, single-arm trial testing the combination of ADT plus BMS-986365 for 6 months prior to RP in pts with high-risk localized PC. Eligible pts include those who are candidates for RP and meet ≥ 1 high-risk criteria: PSA ≥ 20 ng/mL, Gleason ≥ 8 , or clinical stage $\geq$ cT3a (N1M0 disease allowed). Pts will receive degarelix SC once monthly (first dose 240mg, maintenance dose 80mg) and BMS-986365 at a dose of 300mg PO twice daily (liquid-filled capsule formulation) for 6 months; RP will occur 2 weeks after the last dose of BMS-986365. The dose of BMS-986365 was selected based on the phase 1 data and equivalent doses utilized in the ongoing phase 3 rechARge study. The primary endpoint is the rate of pCR and/or minimal residual disease (MRD, defined as tumor ≤ 5 mm) at the time of RP. A two-stage design will evaluate if pCR and/or MRD rate exceeds 0.20, which is the rate observed in historical studies of ADT and ARPI prior to RP (McKay et al. J Urol. 2021) 10 pts will be enrolled in Stage 1; if $\geq 3/10$ pts achieve a pCR and/or MRD, an additional 20 pts will be enrolled in Stage 2. If $\geq 10/30$ pts achieve a pCR and/or MRD, the treatment will be declared sufficiently active ($\alpha = 0.05$, power 0.80). Secondary endpoints include safety and time to biochemical recurrence. As part of exploratory analyses, cfDNA, pre-/post-treatment (prostatectomy) tissue, and pre-/post-treatment multiparametric MRI will be collected. The study opened to accrual in January 2026. Clinical trial information: NCT07335796. Research Sponsor: Bristol Myers Squibb (BMS); Institutional Funding supported through Philanthropy.