5000 Oral Abstract Session

Phase 3, randomized, placebo-controlled clinical trial of CAN-2409+prodrug in combination with standard of care external beam radiation (EBRT) for newly diagnosed localized prostate cancer.

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Background: Standard of care (SoC) for intermediate to high-risk localized prostate cancer (PrCa) includes surgery or external beam radiation (EBRT) +/- androgen deprivation therapy (ADT). Nearly 30% of men undergoing EBRT will experience recurrence requiring ADT and salvage therapies that negatively impact quality of life. CAN-2409 is a replication-defective adenovirus encoding the HSV-tk gene that, when combined with valacyclovir (prodrug), results in immunogenic cell death. This results in immunization against tumor antigens and long-term tumor control. **Methods:** We conducted a phase 3, multicenter, double-blinded, randomized, placebo (PBO)-controlled clinical trial in PrCa patients (pts) planning to receive EBRT+/- short course ADT (<6 mos); NCT01436968. 745 pts were randomized 2:1 (496 in CAN-2409+prodrug and 249 in PBO+prodrug) and stratified by NCCN risk group and ADT use. Three intraprostatic injections of CAN-2409 (5x10 ^{11}v/2mL) or PBO were administered, each followed by 14 days of prodrug. Follow-up included a prostate biopsy 2 years after EBRT. Primary endpoint was disease-free survival (DFS), defined as time from randomization to PrCa recurrence (local/regional failure or distant metastasis) or death in the intent-to-treat population. Median follow up time was 50.3 mos. The study was conducted under a special protocol assessment (SPA) granted by the FDA. **Results:** Treatment with CAN-2409 reduced the risk of PrCa recurrence or death by 30% (median DFS not reached vs 86.1 mos, p=0.0155, HR 0.7, 95% CI 0.52 to 0.94). PrCa-specific DFS (exclusion of non PrCa- related deaths) demonstrated an even greater effect with a 38% decreased risk in the CAN-2409 arm vs. PBO (p=0.0046; HR 0.62, 95% CI 0.44 to 0.87). Statistically significant secondary endpoints included increased percentage of patients achieving prostate-specific antigen nadir (67.1% vs 58.6%, p=0.0164) and an increase in pathological complete responses in the 2-year biopsies in the CAN-2409 arm vs. PBO (80.4% vs. 63.6%, p=0.0015). Most common treatment-related adverse events included chills (33.4% vs. 8.6%), flu-like symptoms (30.5% vs. 13.8%), and fever (25.1% vs. 3.9%), mostly Gr 1-2 and self-limited. Serious adverse events (SAEs, 5.8% vs. 7.3%) and treatment-related SAEs (1.7% vs. 2.2%) were uncommon across treatment groups. **Conclusions:** In this randomized, double-blind, Phase 3 trial, CAN-2409 significantly reduced the risk of PrCa recurrence or death when added to SoC EBRT+/- ADT. The addition of CAN-2409 was not associated with significant added toxicity. These data represent the first potentially new therapy for patients with intermediate and high risk PrCa in over 20 years. Clinical trial information: NCT01436968. Research Sponsor: Candel Therapeutics, Inc.; National Cancer Institute.

Multimodal artificial intelligence (MMAI) model to identify benefit from 2nd-generation androgen receptor pathway inhibitors (ARPI) in high-risk non-metastatic prostate cancer patients from STAMPEDE.

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Background: The STAMPEDE trials showed that adding abiraterone acetate + prednisolone (AAP) ± enzalutamide (ENZ) to standard of care androgen deprivation therapy (SOC) improves metastasis-free survival (MFS) in high-risk non-metastatic (M0) prostate cancer (PCa) patients (pts). However, variable responses & adverse events underscore the need for prognostic & predictive biomarkers. We evaluated performance of a validated MMAI algorithm (ArteraAI Prostate Test v1.2) to identify pts who benefit most from the addition of AAP ± ENZ (ARPI). **Methods:** High-risk M0 STAMPEDE pts treated with SOC+ARPI (N=555) or SOC (N=781) with sufficient quality H&E biopsy images & clinical data (T stage, age, PSA) were included. MMAI score association with PCa specific mortality (PCSM, primary outcome measure) & distant metastasis (DM) was analyzed using Fine-Gray regression & cumulative incidence curves, with other cause mortality treated as competing risks. MFS was assessed using Cox regression & Kaplan-Meier curves. An optimal cut-point was identified via grid search to maximize ARPI benefit separation across biomarker positive (pos, MMAI in top quartile) & negative (neg) subgroups. Hazard ratios [95% CI] & p values are reported. **Results:** PCSM median follow-up was 6.0 years (N=1336). Continuous MMAI scores were statistically significantly associated with poorer PCSM (1.65 [1.43-1.90], p<0.001), MFS (1.42 [1.29-1.56], p<0.001) & DM (1.54 [1.36-1.74], p<0.001). Using clinically-established prognostic cut-offs, 89% of pts were MMAI high-risk. The optimal ARPI MMAI cut-point identified 334 biomarker-pos pts who had significantly higher PCSM than biomarker-neg pts. A statistically significant biomarker-treatment interaction for PCSM (p-int=0.04) revealed that biomarker-pos pts treated with ARPI had improved PCSM (0.42 [0.24-0.74], p=0.003), while biomarker-neg pts did not derive a treatment benefit (0.85 [0.56-1.29], p=0.45). Estimated 5-year PCSM was 9% for biomarker-pos pts receiving ARPI vs. 17% with SOC, compared to 4% & 7% for biomarker-neg pts, respectively, with similar results observed in M0N0 pts (Table 1). **Conclusions:** For the first time, we demonstrate that a validated MMAI algorithm can identify high-risk non-metastatic PCa pts most likely to benefit from the addition of ARPI. Notably we identify a positive biomarker-treatment interaction in the highest MMAI score quartile, which in cases of clinical equipoise could inform clinical decision-making. We highlight MMAI's potential to optimize treatment decisions & spare biomarker-neg pts from unnecessary therapy & toxicities. Clinical trial information: NCT00268476. Research Sponsor: Prostate Cancer Foundation; Artera, Inc.; John Black Charitable Foundation; UK Medical Research Council; Prostate Cancer UK; Cancer Research UK; Sanofi Aventis; Janssen; Astellas; Novartis.

Estimated 5-yr absolute risk reduction from ARPI vs SOC-treated patients by biomarker groups in M0 (M0N0) pts.

	Biomarker-neg	Biomarker-pos
PCSM	3% (1%)	8% (9%)
MFS	2% (-1%)	17% (16%)
DM	5% (3%)	12% (15%)

Prognostic significance of PSA>0.2 after 6-12 months treatment for metastatic hormone-sensitive prostate cancer (mHSPC) intensified by androgen-receptor pathway inhibitors (ARPI): A multinational real-world analysis of the IRONMAN registry.

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Background: Phase III post-hoc analyses show poor prognosis of PSA >0.2 in mHSPC treated by androgen deprivation therapy (ADT) and ARPI, but it remains unclear 1) when PSA cutoffs should be interpreted for prognostic significance, and 2) how PSA cutoffs may differ in real-world multinational data. IRONMAN (International Registry for Men with Advanced Prostate Cancer) prospectively enrolled mHSPC patients from 16 countries and is a unique large data set to investigate these questions. **Methods:** Patients with mHSPC who received ADT, ARPI +/- docetaxel with PSA data enrolled in the IRONMAN registry were included. 3 PSA strata (>0.2, 0.02 to 0.2, and <0.02ng/ml) were defined at 6- and 12-months (primary analysis) after treatment start. Multivariable Cox proportional hazard regression models were constructed for overall survival (OS) and progression-free survival (PFS, as defined by any of biochemical, radiographic or clinically progression) with adjustment for disease characteristics. A 12-month landmark population was constructed to determine conditional OS and PFS in each PSA stratum. **Results:** 1288 patients received ADT and ARPI within 90 days of IRONMAN enrolment and met inclusion. Key characteristics were median age 70 years, 69.5% de-novo metastatic, 59% Gleason 8-10, 73% Caucasian, 8.2% Black, 1.5% Asian, 7.3% lung metastases, 3.4% liver metastases, and 53.2% enrolment from centers outside US/Canada. Intensification agents were: abiraterone acetate (576, 44.7%), apalutamide (283, 22.0%), darolutamide (135, 10.5%), or enzalutamide (294, 22.8%), and 122 (8.7%) received docetaxel in addition to ADT-ARPI. PSA at 6, 12 month landmarks respectively were: <0.02 (10%, 21%); 0.02-0.2 (41%, 45%); >0.2 (49%, 34%), with 70% of patients with 6-month PSA >0.2 retained at 12-months. Outcome data in the 12-month landmark cohort are detailed in Table 1, with 3-year OS for the PSA >0.2 stratum significantly worse than the PSA<0.02 stratum (45.3 vs 92.7%, p<0.001), representing a 7-fold mortality risk in the Cox model adjusted hazard ratio (aHR) and 8-fold risk of progression. **Conclusions:** IRONMAN provides large real-world data validating the poor prognosis of mHSPC with PSA>0.2 after 6-12 months ADT-ARPI treatment and these patients could be targeted for intensification in future trials. Conversely, PSA<0.02 at 6-12 months defines the best prognosis and may be of interest for de-intensification strategies. Research Sponsor: Movember Foundation; Amgen, Astellas, AstraZeneca, Bayer, Janssen, Merck, Novartis and Sanofi.

OS and PFS outcomes by 12-month PSA strata.

12-mo PSA (ng/ml)	n	3-yr OS [95%CI]	3-yr PFS [95% CI]	OS Cox model mortality risk [95% CI]
>0.2	264	45.3% [36.7-55.9]	36.7% [28.6-47.1]	aHR 7.34 [3.66-14.71]
0.02-0.2	585	80.0% [74.5-85.9]	72.9% [66.9-79.1]	aHR 2.16 [1.06-4.41]
<0.02	439	92.7% [87.9-97.8]	93.0% [88.6-97.5]	reference

5003 Oral Abstract Session

Transcriptome classification of PTEN inactivation to predict survival benefit from docetaxel at start of androgen deprivation therapy (ADT) for metastatic prostate cancer (PC): An ancillary study of the STAMPEDE trials.

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Background: Docetaxel (Doce) is effective for metastatic (M1) PC but its effect is varied. Combining Doce and hormone therapy can improve overall survival (OS) but is not appropriate for all. We previously reported the mRNA Decipher test predicts benefit from Doce. We then used transcriptome-wide data to interrogate differential associations with outcome for biologically-relevant pathways. **Methods:** PTEN inactivation using a previously described signature (Liu et al JCI, 2021; active score <= 0.3, inactive: score > 0.3) and Decipher score (high > 0.8, lower <= 0.8) was determined from transcriptome-wide expression data generated in a clinically-accredited lab on prostate tumor from M1 patients (pts) randomized 1:1 to ADT vs ADT + Doce +/- zoledronic acid (ZA) or ADT vs ADT + Abi (abiraterone acetate + prednisone) in the STAMPEDE protocol (Oct 2005-Jan 2014). Cox survival models were fitted with an interaction between treatment allocation and PTEN activity, adjusted for age, WHO PS, pre-ADT PSA, Gleason score, T-stage, N stage (N0, N1), metastatic volume (CHAARTED definition, high [HV] or low [LV]). Hypotheses were tested using partial likelihood ratios. Primary endpoint was OS. **Results:** We generated transcriptome-wide profiles on 832 M1 pts with no notable differences from the full M1 trial cohort (N=2224). 657 (79%) were reported to have died. 50% of tumors were classified as PTEN inactive (N=419). PTEN mRNA score distribution was similar across HV and LV disease (p=0.310). PTEN inactivity associated with shorter OS in pts allocated ADT+Abi (N=182; HR=1.56, 95%CI: 1.06-2.31) but not in pts allocated ADT+Doce+/-ZA (N=279; HR=0.93, 95%CI: 0.70-1.24). We found strong evidence (p=0.002) of an interaction between PTEN inactivation and Doce sensitivity: PTEN inactive pts benefited from Doce (HR=0.57, 95% CI 0.42-0.76) unlike PTEN active pts (HR=1.05, 95% CI 0.77-1.43). This was consistent in LV (N=244; PTEN inactive HR=0.53, 95% CI 0.33-0.86; PTEN active HR=0.82, 95% CI 0.48-1.40) and HV (N=295; PTEN inactive, HR=0.59, 95% CI 0.39-0.88; PTEN active HR=1.23, 95% CI: 0.83-1.81). In pts randomized to Abi, treatment effect was uniform (PTEN inactive HR=0.52, 95% CI 0.36-0.73; PTEN active HR=0.55, 95% CI 0.39-0.77; p=0.784). We estimated adding Doce for tumors classified as PTEN inactive and high Decipher reduced the hazards of death by 45% (HR 0.55, 99% CI 0.34-0.89). **Conclusions:** Prostate tumors classified as high Decipher and PTEN inactive have a 45% reduction in hazard of death when Doce is added to ADT. This biomarker should be tested in pts considered for triplet therapy of ADT + Abi + Doce. Research Sponsor: Prostate Cancer UK; National Institute for Health Research UK; Veracyte; Medical Research Council; Prostate Cancer Foundation; John Black Charitable Foundation; Cancer Research UK; Prostate Cancer Research; U.S. National Institutes of Health; Department of Defence; Orchid; The Benioff Initiative.

5004 Oral Abstract Session

Health-related quality of life (HRQoL) outcomes with darolutamide in the phase 3 ARANOTE trial.

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Background: Effective and well tolerated treatments to maintain HRQoL are essential for patients with metastatic hormone-sensitive prostate cancer (mHSPC). Darolutamide (DARO) + androgen deprivation therapy (ADT) significantly reduced the risk of radiological progression or death (primary endpoint) by 46% (hazard ratio [HR] 0.54; 95% confidence interval [CI] 0.41–0.71; $P<0.0001$) vs placebo (PBO) + ADT in ARANOTE (NCT04736199). The incidence of adverse events (AEs) was low and similar to PBO, with fewer study drug discontinuations due to AEs in the DARO vs PBO group (6.1% vs 9.0%). We report HRQoL and pain outcomes in ARANOTE. **Methods:** Patients were randomized 2:1 to DARO 600 mg twice daily or PBO, with ADT. HRQoL was measured using the Functional Assessment of Cancer Therapy–Prostate (FACT-P). Deterioration in FACT-P total score by ≥10 points was a prespecified exploratory endpoint; deteriorations in FACT-P subscales by ≥3 points were analyzed *post hoc*. Pain was assessed using the Brief Pain Inventory–Short Form (BPI-SF), including the pain severity and pain interference subscales. Pain progression (secondary endpoint) was defined as an increase of ≥2 points in BPI-SF worst pain score (WPS) from nadir observed at 2 consecutive evaluations ≥4 weeks apart or initiation of opioid use for ≥7 consecutive days. Association of HRQoL and pain progression with prostate-specific antigen (PSA) response was assessed *post hoc*. HRs and 95% CIs were calculated using a Cox regression model, stratified by visceral disease (present vs absent) and prior local therapy (yes vs no) for FACT-P total score and pain progression, unstratified for FACT-P and BPI-SF subscales and association with PSA. **Results:** DARO extended time to deterioration in FACT-P total score (overall well-being) by 5.1 months vs PBO: median 16.6 vs 11.5 months; HR 0.76, 95% CI 0.61–0.93. The treatment benefit of DARO in FACT-P total score was strongly driven by longer time to deterioration in the subscales of social/family well-being (HR 0.79, 95% CI 0.64–0.98), functional well-being (0.78, 0.63–0.96), and urinary symptoms (0.78, 0.61–0.99). Additionally, DARO extended time to pain progression vs PBO: HR 0.72, 95% CI 0.54–0.96. In patients treated with DARO, achievement of PSA response <0.2 ng/mL at any time was associated with longer time to deterioration in FACT-P total score and longer time to pain progression vs detectable PSA response (≥0.2 ng/mL) at any time. **Conclusions:** To our knowledge, DARO is the first and only androgen receptor inhibitor to demonstrate clinically meaningful delays in deterioration of important patient-relevant HRQoL outcomes vs PBO in men with mHSPC. Patients treated with DARO had improvements in overall well-being (FACT-P total score), social/family well-being, functional well-being, urinary symptoms, and pain. Combined with the efficacy and safety profile, these findings suggest that DARO also confers a positive impact on HRQoL. Clinical trial information: NCT04736199. Research Sponsor: Bayer and Orion Pharma.

5005 Oral Abstract Session

ARCHES: 5-year follow-up overall survival (OS) analysis of enzalutamide (ENZA) plus androgen-deprivation therapy (ADT) in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC).

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Background: In 2021, final prespecified OS (key secondary endpoint; defined as time from randomization to death from any cause) analysis of the global phase 3, randomized, double-blind, placebo (PBO)-controlled ARCHES trial (NCT02677896) demonstrated that ENZA + ADT significantly reduced risk of death by 34% versus PBO + ADT in pts with mHSPC (medians not reached [NR]; hazard ratio [HR] 0.66; 95% confidence interval [CI]: 0.53–0.81; p<0.0001; median follow-up, 44.6 months). To assess long-term efficacy of ENZA + ADT, we report an updated OS analysis as of July 31, 2024 (median follow-up, 61.4 months). **Methods:** In ARCHES, 1150 enrolled pts with mHSPC were randomized 1:1 to ENZA (160 mg once daily) + ADT or PBO + ADT. After primary analysis of radiographic progression-free survival (primary endpoint), ARCHES was unblinded to allow eligible patients who were randomized to PBO + ADT to cross over to ENZA + ADT in an open-label extension. Using extended follow-up data with median follow-up >5 years (cut-off date: July 31, 2024), Kaplan–Meier method was used to summarize the OS endpoint by treatment, with two-sided 95% CIs calculated by the Brookmeyer–Crowley method. HRs relative to PBO + ADT were determined using Cox regression model stratified for prior docetaxel use and disease volume. **Results:** ENZA + ADT (n=574; median [range] age = 70.0 [46–92] years) and PBO + ADT (n=576; median [range] age = 70.0 [42–92] years) cohorts had similar baseline characteristics. 184 (31.9%) PBO + ADT pts crossed over to open-label ENZA + ADT (median [range] age = 69.0 [51–89] years). After a median follow-up of 61.4 months, ENZA + ADT extended survival compared with PBO + ADT (medians NR; HR 0.70; 95% CI: 0.58–0.85; p=0.0003), with consistently improved survival across clinically relevant subgroups analyzed (Table), including a 36-month improvement in median OS in high-volume patients. **Conclusions:** Long-term follow-up of ARCHES demonstrated results consistent with previous OS analyses, with marked benefit in all study subgroups, including high- and low-volume patients, despite a substantial cross-over cohort. These findings further support ENZA + ADT as a standard-of-care for pts with mHSPC. Clinical trial information: NCT02677896. Research Sponsor: Astellas Pharma Inc.; Pfizer Inc.

Subgroup	ENZA + ADT N (events)	ENZA + ADT (median months)	PBO + ADT N (events)	PBO + ADT (median months)	HR (95% CI)
All	574 (191)	NR	576 (223)	NR	0.70 (0.58–0.85)
Age <65 years	148 (46)	86.4	152 (55)	NR	0.63 (0.42–0.93)
Age ≥65 years	426 (145)	NR	424 (168)	NR	0.73 (0.58–0.91)
Low-volume disease	220 (50)	NR	203 (57)	NR	0.71 (0.49–1.05)
High-volume disease	354 (141)	83.1	373 (166)	47.6	0.70 (0.56–0.88)
No prior docetaxel	471 (157)	NR	474 (179)	NR	0.71 (0.57–0.88)
Prior docetaxel	103 (34)	83.1	102 (44)	59.5	0.67 (0.43–1.05)
Synchronous (de novo): ≤90 days	438 (161)	86.4	439 (186)	58.9	0.71 (0.57–0.88)
Metachronous (relapsed): >90 days	132 (29)	NR	136 (37)	NR	0.66 (0.41–1.08)

LBA5006 **Oral Abstract Session**

Phase 3 AMPLITUDE trial: Niraparib (NIRA) and abiraterone acetate plus prednisone (AAP) for metastatic castration-sensitive prostate cancer (mCSPC) patients (pts) with alterations in homologous recombination repair (HRR) genes.

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5007 Oral Abstract Session

A multicenter, randomized, phase 2, investigator-initiated ETCTN trial of olaparib + radium-223 vs. radium-223 in men with castration-resistant prostate cancer (CRPC) with bone metastases (BM) (COMRADE): Initial efficacy and biomarker analysis.

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Background: Radium-223 is an α-emitting radioisotope which has improved overall survival (OS) in men with CRPC with BM. PARP inhibitors demonstrate synergy with radiation. Our phase 1 trial established olaparib 200 mg twice daily + radium-223 (55 kBq/kg IV q4weeks x 6) as the recommended phase 2 dose. Here, we report the phase 2 results (NCT03317392). **Methods:** Patients were randomized 1:1 to olaparib + radium-223 (Arm A) vs. radium-223 (Arm B), stratified by prior docetaxel and BM extent ($\leq$20/$>$20). Crossover was permitted in Arm B. Eligibility included any line of prior therapy, $\geq$2 BM by CT/MRI or bone scan, and at least 1 BM without prior radiation. Visceral metastases or lymphadenopathy $>$ 4 cm were excluded. Bone protecting agents (BPA) were required unless contraindicated. Homologous recombination repair gene (HRR) mutation status was determined using FoundationOne Monitor with algorithmic clonal hematopoiesis determination from baseline plasma (reported here) and Oncopanel assay from baseline biopsy or archival tissue. The primary endpoint was radiographic progression-free survival (rPFS). With 120 patients, the study was designed to have 88% power to detect an improvement in rPFS from 6.0 to 10.5 months (1-sided α=0.10). **Results:** 120 patients enrolled across 9 centers (Arm A=61, B=59). 96% received prior ARPI, 53% prior docetaxel, 32% with nodal disease, 46% had $>$ 20 BM, and 90% with concurrent BPA. Of the 103 evaluable patients, 18.5% in Arm A and 26.5% in Arm B had an HRR gene alteration by ctDNA, with 7.4% and 10.2% with *BRCA1/2* mutations, respectively. Olaparib + radium-223 had a significant improvement in rPFS vs. radium-223 (median 8.6 vs. 4.0 months, HR 0.51, 80% CI 0.37-0.70, 2-sided p=0.005). Secondary endpoints are in Table 1. The addition of olaparib improved rPFS regardless of HRR status (HRR+: HR 0.52, 80% CI 0.26-1.04; HRR-: HR 0.54, 80% CI 0.38-0.77). 56% of patients in Arm A and 35% of patients in Arm B had grade $\geq$3 treatment-related adverse events, the most common on Arm A/Arm B being: anemia (22.0%/18.0%), lymphocyte decrease (30.5%/9.1%), platelet decrease (6.8%/3.6%), and neutrophil decrease (5.1%/7.3%). **Conclusions:** In this phase 2, multicenter trial, olaparib + radium-223 demonstrated superior rPFS to radium-223, in both HRR+ and HRR- groups, with manageable side effect profile in CRPC patients with BM. Tissue and serial ctDNA analyses are underway and will be presented. Clinical trial information: NCT03317392. Research Sponsor: National Cancer Institute.

	Arm A median (months)/%	Arm B median (months)/%
rPFS	8.6	4.0
rPFS (HRR+)	5.5	3.8
rPFS (HRR-)	8.8	4.5
PSA response (confirmed)	13.1%	13.6%
Alkaline phosphatase response (confirmed)	49.2%	50.8%
Time to PSA progression	3.6	3.3
Time to Alkaline phosphatase progression	7.9	7.4
Time to next treatment	12.0	7.7
1-year symptomatic skeletal event	11.0%	22.1%
12-month OS	74%	71%

5008 Oral Abstract Session

C3NIRA: Randomized phase II study of carboplatin-cabazitaxel-cetrelimab (anti-PD-1) induction followed by niraparib +/- cetrelimab maintenance in men with aggressive variant prostate cancers (AVPC).

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Background: AVPC have limited therapeutic options and a dismal prognosis. Although early data indicate that adding carboplatin (Carb) to cabazitaxel (Cab) benefits men with AVPC, responses are short-lived. In a previous study (NCT03263650) a subset of AVPC patients had long-term responses to CabCarb induction followed by PARP inhibitor maintenance. Tumor tissue analyses revealed upregulation of inflammatory and immune pathways in post-CabCarb treated tumors from prolonged responders. We therefore hypothesized that adding anti-PD-1 (cetrelimab, Cet) would increase the efficacy of CabCarb induction plus niraparib (Nira) maintenance in AVPC patients, and that correlates would expose tumor cell intrinsic and microenvironment pathways implicated in therapy response and resistance. **Methods:** In a single-institution study, men with CRPC meeting $\geq$ 1 of 9 AVPC criteria (listed in https://clinicaltrials.gov/study/NCT04592237) and ECOG performance status 0-2 received 6 cycles of Cab 20-25mg/m^2 and Carbo (AUC 3-4). Cet (360mg) was added to Cycles 2-6 of CabCarb. Men completing 6 cycles without progressive disease (PD) were randomized 1:1 to Nira 300mg BID $\pm$ Cet. The primary endpoint was progression free survival (PFS) in randomized patients. Subgroup comparisons between patients with PD in the first 6 cycles (Early PD) vs. patients who achieved randomization (Randomized) were made with chi-square and Kruskal-Wallis tests. Paired tumor biopsies were obtained after 1 cycle of CabCarb and 2 cycles of CabCarbCet. **Results:** 120 patients started CabCarb. Their median age was 68 years (30-83). Most were White/non-Hispanic (78%) and had not received prior docetaxel (58%). Of the 120, 20 (16.7%) went off study for reasons other than PD and 40 (33.3%) had Early PD and were not randomized. The Early PD group did not differ from the Randomized group in terms of age, race ethnicity, prior docetaxel, or baseline PSA. Post randomization median follow up was 20.5 months; median PFS was 3.4 months (95% confidence interval: 2.0, 4.4) with Nira (n=30) and 5.6 (3.7, 16.8) months with Nira+Cet (n=30, p=0.01); median overall survival was 10.2 (6.4, 19.6) with Nira and 24.3 (9.5, not reached) months with Nira+Cet (p=0.01). Single-cell RNA sequencing of paired biopsies revealed increased progenitor-like exhausted CD8+ T cells and decreased FoxP3+ Treg cells in Randomized patients (n=5) while Early PD patients (n=5) showed the opposite following the addition of Cet to CabCarb. **Conclusions:** A subset of men with AVPC derive meaningful benefit from the addition of anti-PD-1 to PARP inhibitor maintenance following platinum-taxane-anti-PD-1 induction. Ongoing correlates aim to identify biomarkers to select patients for this treatment strategy and reveal candidate mechanisms of resistance to guide future therapeutic combinations. Clinical trial information: NCT04592237. Research Sponsor: U.S. Department of Defense; W81XWH-20-1-0257; Janssen Scientific Affairs, LLC.

5009 Clinical Science Symposium

Lutetium-177-PSMA-617 in oligo-metastatic hormone sensitive prostate cancer (BULLSEYE trial).

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Background: [^{177}Lu]Lu-PSMA-617 (Pluvicto) is a novel treatment for patients with metastatic castration resistant prostate cancer. In a phase 1 dosimetry study, we previously showed that [^{177}Lu]Lu-PSMA-617 could be offered to patients with PSMA-expressing, recurrent, oligometastatic hormone-sensitive prostate cancer (oHSPC) with encouraging outcomes (Privé et al, CCR 2021). We here report the results of the following randomized phase 2 trial. **Methods:** This was an investigator initiated, international, multicenter, open-label, randomized phase 2 trial (NCT04443062). Fifty-eight oHSPC patients ineligible for salvage treatments, were randomized in a 1:1 fashion to [^{177}Lu]Lu-PSMA-617 vs. the standard of care (SoC) of deferred androgen deprivation therapy (ADT). Eligibility consisted of fast-progressing oHSPC (prostate specific antigen [PSA] doubling time <6 months) following radical prostatectomy or radiotherapy, with a maximum of 5 metastases on PSMA-PET/CT. Patients received 2 (+2 optional) cycles of 7.4 GBq [^{177}Lu]Lu-PSMA-617. The primary outcome was progression-free survival (i.e. time without ADT). Progressive disease (PD) was defined as a 100% increase in PSA since randomization, radiographic or clinical progression or earlier necessitation of subsequent therapy (e.g. ADT). Secondary outcomes were PSA response, adverse events and quality of life. **Results:** Between April 20, 2020 and July 29 2024, 58 of 78 screened men were eligible. Data cut-off was set on December 24th 2024. Median age was 72 years (range 51-82) with a median baseline PSA of 3.6 (1.2-29). Two patients received 2 cycles whereas 27 patients underwent 4 cycles of [^{177}Lu]Lu-PSMA-617. At a median follow-up time of 7 months (range 1-31), 93% (27/29) and 38% (11/29) of the SoC and arm, respectively, reached the definition for PD. The median progression free survival was 5 months (95% CI 4-6 months) for the SoC group whereas the median progression free survival was not reached for the [^{177}Lu]Lu-PSMA-617 group (HR, 0.07 [95% CI, 0.02 to 0.19]; P <.001). The median percentage PSA change was +125% vs. -91% in the SoC vs. [^{177}Lu]Lu-PSMA-617 arm, respectively. Twenty-one percent (6/29) of [^{177}Lu]Lu-PSMA-617 arm patients had a complete remission. The most common treatment-related adverse events were grade (G) 1 dry mouth (59%), G 1 fatigue (55%), G 1 nausea (48%), G 1 bone marrow toxicity (24-30%) which generally normalized during follow-up. G ≥2 adverse events were seldom observed (<15%) and not clinically relevant. **Conclusions:** [^{177}Lu]Lu-PSMA-617 showed promising efficacy as monotherapy in oligometastatic hormone sensitive prostate cancer patients to defer from androgen deprivation therapy, with minimal and mostly transient side effects. Following surgery and external beam radiotherapy, could become a third metastases-directed therapeutic option for oligometastatic prostate cancer patients to prolong ADT-free interval. Clinical trial information: NCT04443062. Research Sponsor: Novartis; Dutch Prostate Cancer Foundation.

First-in-human results of terbium-161[^{161}Tb]Tb-PSMA-I&T radioligand treatment in patients with metastatic castration-resistant prostate cancer (VIOLET): A single-centre, single-arm, phase I/II study.

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Background: Terbium-161 (^{161}Tb) is a novel radionuclide emitting beta-radiation comparable to lutetium-177 (^{177}Lu), with additional higher-energy, ultra-short path-length Auger electrons which may better target micrometastases. ^{161}Tb has superior in-vitro and in-vivo efficacy in comparison with ^{177}Lu. We aim to evaluate the safety and effectiveness of [^{161}Tb]Tb-PSMA-I&T in patients with metastatic castration-resistant prostate cancer (mCRPC). **Methods:** Eligible patients in this investigator-initiated, single-centre, single-arm, phase I/II trial had progressive mCRPC previously treated with taxane chemotherapy (unless medically unsuitable) and an androgen receptor pathway inhibitor, PSMA-positive disease on PSMA PET/CT (SUVmax ≥20), no sites of discordance on FDG PET/CT, adequate bone marrow, hepatic and renal function, and ECOG performance status ≤2. The dose-escalation followed a 3+3 design to establish safety of three prespecified administered radioactivities of [^{161}Tb]Tb-PSMA-I&T (4.4, 5.5, and 7.4 GBq). Up to six cycles of [^{161}Tb]Tb-PSMA-I&T were administered intravenously every six weeks, with each subsequent radioactivity per cycle reduced by 0.4 GBq. The co-primary objectives were to establish the maximum tolerated dose (MTD) and safety profile (CTCAE v5.0) of [^{161}Tb]Tb-PSMA-I&T. Key secondary objectives for this interim analysis were PSA ≥50% and ≥90% response rates (PSA50-RR and PSA90-RR), PSA and radiographic progression-free survival (PSA-PFS and rPFS). **Results:** Between October 14, 2022 and February 15, 2024, 30 eligible patients were enrolled. Median (IQR) age 69.0 years (66.0-74.8), median baseline PSA 26.9 ng/mL (10.1-70.0), PSMA SUVmean 8.2 (7.4-10.8) and 20 patients (67%) had received prior docetaxel. There were no dose-limiting toxicities. The MTD and recommended phase 2 dose was 7.4 GBq. There were no treatment-related deaths and few grade 3 or higher treatment-related adverse events, which included pain flare and lymphopenia only. The remaining AEs are summarised in the table. PSA50-RR and PSA90-RR occurred in 21 (70% [95%CI 51-85]) and 12 (40% [95%CI 23-59]). Median PSA-PFS and rPFS were 9.0 months (95% CI 5.7-15.1) and 11.1 months (95%CI 6.6-11.7) with median follow-up of 11.2 and 11.0 months, respectively. **Conclusions:** [^{161}Tb]Tb-PSMA-I&T displayed highly encouraging efficacy with few Grade 3 or 4 adverse events. An additional cohort to assess a higher administered radioactivity is planned. Clinical trial information: NCT05521412. Research Sponsor: Prostate Cancer Foundation; Peter MacCallum Cancer Foundation; National Health and Medical Research Council; Isotopia Molecular Imaging.

Main treatment-related adverse events.

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Total
Lymphocyte count decreased	8	10	1	0	19 (63%)
Pain	3	0	1	0	4 (13%)
Anemia	16	4	0	0	20 (67%)
Neutrophil count decreased	3	3	0	0	6 (20%)
Fatigue	12	1	0	0	13 (43%)
Dry mouth	21	0	0	0	21 (70%)
Nausea	7	0	0	0	7 (23%)
Platelet count decreased	6	0	0	0	6 (20%)
Any adverse event	13	14	2	0	29 (97%)

Predictive and prognostic value of baseline PSMA-PET total tumor volume and SUV mean within ENZA-p, a randomized phase II trial of enzalutamide versus enzalutamide plus [^{177}Lu] Lu-PSMA-617 (ANZUP1901).

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Background: [^{68}Ga]Ga-PSMA-11 PET (PSMA-PET) standardized uptake value (SUV)mean and total tumor volume (PSMA-TTV) have been respectively identified as predictive and prognostic of response to [^{177}Lu]Lu-PSMA-617 (LuPSMA) monotherapy. The addition of LuPSMA to enzalutamide (enza + LuPSMA) improved overall survival (OS) compared to enza-alone in mCRPC in the ENZA-p trial. This pre-specified sub-study of ENZA-p evaluated baseline PSMA-PET quantitative parameters as predictive and prognostic biomarkers for enza+ LuPSMA and enza-alone. **Methods:** ENZA-p is an open-label, randomized, phase 2 trial. Participants (pts) with mCRPC not previously treated with chemotherapy or AR antagonist (abiraterone permitted) and [^{68}Ga]Ga-PSMA-avid disease were randomized (1:1) to either enza-alone or enza + LuPSMA using adaptive-dosed [^{177}]Lu LuPSMA-617 7.5 GBq for (2 or 4 doses). All pts had a baseline [^{68}Ga]Ga-PSMA-11 PET/CT to assess eligibility (SUVmax >14 at a single site and SUVmax >10 at all larger tumor sites). PSMA-PET were quantified with semi-automated software to derive PSMA-TTV and SUVmean. The pre-specified tertiary study objective was to evaluate associations between quantitative parameters on the baseline PSMA-PET and both PSA progression-free survival (PSA-PFS) and OS. Prespecified cut-points were based on SUVmean highest quartile (Q4 vs Q1-3) and PSMA-TTV median at baseline. We used the Kaplan-Meier method and Cox regression models. **Results:** This sub-study included the 160 of 162 randomized pts who received study treatment. Median follow-up was 34 months with 96 OS events. Baseline PSMA-PET SUVmean Q4 was 9.8 and median PSMA-TTV was 234 mL. Median OS for PSMA-TTV above or below the median for enza-alone were 20 vs 39 months respectively ($p<0.001$). The corresponding median OS for enza + LuPSMA were 28 vs 35 months (p=0.18). The test for interaction between PSMA-TTV and treatment arm for OS was p=0.008. Median OS for SUVmean Q4 vs Q1-3 for enza alone were 29 vs 25 months (p=0.59). For enza + LuPSMA median OS for SUVmean Q4 vs Q1-3 were 32 vs 34 months (p=0.56). The test for interaction between SUVmean (Q4 vs Q1-3) and treatment for OS was p=0.88. Results for PSA-PFS are also tabulated below. **Conclusions:** Baseline PSMA-TTV was prognostic of shorter OS with enza-alone, but not with the addition of LuPSMA-617. In contrast to LuPSMA-617 monotherapy, PSMA SUVmean was neither predictive nor prognostic of improved OS, nor of PSA-PFS when LuPSMA-617 was given together with enza as first line treatment for mCRPC. Clinical trial information: NCT04419402. Research Sponsor: Prostate Cancer Research Alliance (PCRA): An Australian Government and Movember joint alliance and Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP); GenesisCare, Roy Morgan Research; St Vincent's Clinic Foundation; Cancer Australia; Astellas and Endocyte - a Novartis Company Pharmaceutical/ Biotech Company.

Treatment Arm	SUVmean Q4	SUVmean Q1-3	P	Interaction	PSMATTV >234mls	PSMATTV <234mls	p	Interaction
Enza-alone OS	29mo	25mo	0.59		20mo	39mo	0.001	
Enza+LuPSMA OS	32mo	34mo	0.56	**0.88**	28mo	35mo	0.18	**0.008**
Enza-alone PSA-PFS	7.8mo	5mo	0.55	**0.17**	3mo	11mo	0.001	**0.017**
Enza+LuPSMA PSA-PFS	15mo	13mo	0.22		11mo	15mo	0.11	

LBA5012 **Rapid Oral Abstract Session**

An open label randomized non-inferiority trial comparing adjuvant platinum plus paclitaxel to platinum plus 5-FU after curative resection in high-risk penile carcinoma.

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5013 Rapid Oral Abstract Session

Docetaxel with androgen deprivation therapy (ADT) and radiotherapy (RT) for high-risk localized prostate cancer (HRLPC): An ICECaP individual patient-data (IPD) meta-analysis of randomized controlled trials (RCTs).

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Background: There is no established role for the use of docetaxel with ADT and RT for HRLPC, with mixed results seen in prior RCTs. Prior work from ICECaP (Ravi et al, Eur Urol 2024) has shown that patients (pts) with very high-risk disease (i.e. 2 or 3 risk factors [RFs]: Gleason ≥8, PSA >20, ≥cT3 and/or cN1) have the poorest outcomes with RT+ADT for HRLPC, with 5-year metastasis-free survival (MFS) of ≤80%. We aimed to perform an IPD meta-analysis of the role of docetaxel with ADT+RT for HRLPC and specifically evaluate whether patients with very high-risk disease benefit from the addition of docetaxel. **Methods:** IPD from RCTs involving pts with HRLPC treated with RT+ADT +/- docetaxel collated by ICECaP were analyzed. "High-risk" disease was defined as presence of 1 RF and "very high-risk" disease as 2-3 RFs and/or cN1 disease. The primary outcomes of interest were MFS and overall survival (OS). Hazard ratios (HR) for MFS and OS were estimated using Cox regression, stratified by year of randomization and adjusted for age at randomization and ECOG performance status. 5-year MFS and OS rates were estimated using the Kaplan-Meier method. Subgroup analyses were performed according to the severity of disease (high- and very high-risk), and p-values for interaction were tested using the likelihood ratio test. **Results:** 1690 pts treated on 4 RCTs (GETUG-12, DFCI 05-043, STAMPEDE, RTOG-0521) between 2002-2015 were eligible. Median age was 65, median PSA was 23 (IQR 10-48); 154 (9%) pts had cN1 disease and 1444 (85%) received long-term ADT with RT. Median follow-up was 10 years (range: <1-15). Overall, the addition of docetaxel to RT+ADT was not associated with a significant benefit in MFS (HR=0.89 [0.76-1.05], p=0.160) or OS (HR=0.88 [0.74-1.05], p=0.167). Though there was some evidence for favoring docetaxel in pts with very high-risk disease (n=1054; MFS HR=0.86 [0.71-1.05]; OS HR=0.85 [0.68-1.07]) compared to high-risk disease (n=636; MFS HR=0.97 [0.74-1.27]; OS HR=0.95 [0.71-1.28]), there was no evidence of a significant difference in treatment effect by risk group (p-interaction >0.1). 5- and 10-yr MFS and OS in pts with high- and very high-risk disease, stratified by receipt of docetaxel, are shown in the Table. **Conclusions:** Some HRLPC pts with very high-risk disease may benefit from the addition of docetaxel to RT+ADT. Biomarker evaluation within this group may identify those who are candidates for treatment intensification with docetaxel with RT+ADT (+/- androgen receptor pathway inhibitors) in HRLPC. Research Sponsor: PCF.

	High risk		Very high-risk	
% (95% CI)	RT+ADT	RT+ADT+docetaxel	RT+ADT	RT+ADT+docetaxel
5yr MFS	87 (82-90)	90 (86-93)	74 (71-78)	80 (76-83)
5yr OS	90 (86-93)	93 (90-96)	84 (80-86)	89 (86-92)
10yr MFS	67 (61-72)	71 (65-76)	51 (46-55)	55 (49-60)
10yr OS	74 (69-79)	77 (72-82)	62 (57-67)	67 (62-72)

Intensified hormonal blockade with SBRT in PSMA-PET detected oligometastatic prostate adenocarcinoma: Results from the phase II Metacure trial cohorts B2 and the B2 expansion.

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Background: Metastasis directed therapy (MDT) with stereotactic body radiotherapy (SBRT) is a standard of care in patients with oligometastatic hormone-sensitive prostate cancer (HSPC) and can delay the use of ADT. Combining SBRT with a defined period of systemic therapy may lead to durable control of oligometastatic disease and is often used in this setting, however the optimal intensity and duration of hormonal blockade with SBRT remains unclear. **Methods:** Metacure is a multi-center, multi-arm randomized phase 2 trial that tests novel systemic therapies in the context of a multimodality approach, including SBRT to oligometastatic sites. The B2 and B2 expansion cohorts of Metacure tested SBRT +/- salvage RT to prostate bed/nodes with time-limited ADT+ARPI hormonal blockade in patients (pts) with PSMA-PET detected metachronous oligometastatic HSPC. Eligible pts had biochemical recurrence or persistence (PSA >0.2) after prostatectomy with metastases treatable within max 3 RT plans. Cohort B2 randomized pts to metastasis-directed SBRT with either 10 months of ADT + apalutamide + abiraterone acetate plus prednisone (ADT+APA+AAP) or ADT + apalutamide (ADT+APA). In the B2 expansion cohort pts received 6 months of ADT+APA with SBRT. The primary endpoint was proportion of pts with undetectable PSA (PSA<0.1) at 12 months from treatment start in pts with recovered testosterone (T). Secondary objectives included PSA<0.1 at 24 months, time to PSA progression (PSA 0.2), time to T recovery, rPFS, and PFS (PSA, radiographic, or clinical progression or death). **Results:** 36 pts were treated in the combined B2 (10 pts) and B2 expansion (26 pts) cohorts. Median follow-up was 35 months for cohort B2 and 19 months for the B2 expansion. T recovery (>150ng/dl) at 12 months from treatment start occurred in 3/5 (60%) ADT+APA+AAP and 2/5 (40%) ADT+APA pts on cohort B2 and 14/26 pts (54%) on the B2 expansion (ADT+APA). Of those, 2/2 (100%) B2 ADT+APA+AAP pts, 3/3 (100%) B2 ADT+APA and 11/14 (79%) B2 expansion pts had PSA <0.1. This met the pre-specified threshold for activity for the B2 expansion of 4 pts. Median time to PSA progression and PFS was 26 months for the B2 ADT+APA+AAP arm and not reached for the B2 ADT+APA arm or B2 expansion cohort. Median rPFS was not reached in any group. At 12 months, all patients on B2 and B2 expansion were progression free. At 18 months, PFS for B2 was 100% (ADT+APA) and 60% (ADT+APA+AAP) and was 85% for the B2 expansion. At 24 months, PFS was 60% for ADT+APA and 60% for ADT+APA+AAP pts on cohort B2. Median T recovery was 3.0 and 5.5 months for the B2 and B2 expansion cohorts. Grade 3 TRAEs were seen in 0/10 B2 and 1/26 B2 expansion subjects (lymphopenia). **Conclusions:** SBRT with short course intensified hormonal blockade was well tolerated and led to durable disease control in pts with PSMA PET-detected metachronous oligometastatic prostate cancer. Clinical trial information: NCT03436654. Research Sponsor: Janssen.

5015 Rapid Oral Abstract Session

DB-1311/BNT324 (a novel B7H3 ADC) in patients with heavily pretreated castrate-resistant prostate cancer (CRPC).

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Background: There is a high unmet need for effective therapy for patients (pts) with heavily pretreated CRPC. B7H3 ADCs have reported early clinical activity in CRPC, including DB-1311/BNT324, an investigational B7H3 ADC that received FDA Fast-Track Designation for previously treated CRPC. **Methods:** This phase 1/2 study (NCT05914116) enrolled pts with advanced/metastatic solid tumors, including previously treated CRPC (post docetaxel/hormonal therapy). Dose optimization cohorts randomized pts to receive 6 mg/kg or 9 mg/kg Q3W DB-1311/BNT324 until progression or unacceptable toxicity. The primary endpoints were objective response rate (ORR, based on investigator assessment per RECIST 1.1 and PCWG3 criteria) and safety. Secondary endpoints included disease control rate (DCR), duration of response (DOR) and radiographic progression-free survival (rPFS). **Results:** As of 3 Jan 2025, of 393 pts treated with DB-1311/BNT324, there were 65 pts with CRPC. Median age was 71 years (range 45–84), 49%/34%/14% were White/Asian/Black, 32%/37%/31% from Australia/USA/East Asia, 71% had ECOG PS 1, 29% had bone only disease. Median number of prior lines was 3 (range 1–14) and 28% had ≥5 prior lines. Most pts received prior docetaxel (93.8%) and hormonal therapy (96.9%); other therapies included PARP inhibitors (PARPi, 15.4%), Lutetium-177 (Lu-177, 15.4%), immunotherapy (IO, 13.8%). Among 43 response-evaluable pts (measurable disease at baseline per RECIST 1.1), best overall response was PR in 12 pts and SD in 29 pts for an unconfirmed ORR of 27.9% (95% CI 15.3, 43.7; 12/43, 8 confirmed) and DCR of 95.3% (95% CI 84.2, 99.4). Median DOR was not reached (95% CI 4.2, ne). After a median follow-up of 5.7 months (m) (range 0.6–16.0), median rPFS (N=57) was 8.3 m (95% CI 6.7, ne) with a 6-m rate of 86.6% (95% CI 67.8, 94.8). Outcomes were similar by dose (6 mg/kg [ORR 26.3%, DCR 100%, 6-m rPFS rate 88.7%], 9 mg/kg [ORR 29.2%, DCR 91.7%, 6-m rPFS rate 80.0%]), by line of treatment (≤3L [ORR 33.3%, DCR 77.8%], ≥4L [ORR 26.7%, DCR 100%]), and by type of prior treatment (ORR/DCR: Lu-177 [25.0%/100%], IO [33.3%/100%], albeit lower for PARPi [16.7%/100%]). The CRPC safety profile (N=65) is supported by the safety in the larger overall population (N=393). Treatment-related adverse events (TRAEs) occurred in 56 (86.2%) and 343 (87.3%) pts and were Grade ≥3 (G≥3) in 26 (40.0%) and 156 (39.7%) pts, respectively. TRAEs led to dose reduction in 8 (12.3%) and 39 (9.9%) pts, to discontinuation in 4 (6.2%) and 23 (5.9%) pts, and to death in 0 and 2 (0.5%) pts, respectively. Nausea and hematological events, primarily G1–2, were the most common TRAEs. Hematological TRAEs occurred more frequently with 9 mg/kg vs 6 mg/kg, both in the CRPC and overall populations. **Conclusions:** DB-1311/BNT324 showed encouraging efficacy and a manageable safety profile in heavily pretreated CRPC and is currently being evaluated in post Lu-177 CRPC and in taxane-naïve CRPC. Clinical trial information: NCT05914116. Research Sponsor: Sponsored by Duality Biologics and conducted in collaboration with BioNTech SE.

^{177}Lu-PSMA-617 with ipilimumab (ipi) and nivolumab (nivo) in metastatic castration-resistant prostate cancer (mCRPC): An investigator-initiated phase 2 trial (EVOLUTION; ANZUP2001).

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Background: LuPSMA improves progression-free survival (PFS) and overall survival (OS) in patients with mCRPC. Immune checkpoint inhibitors (ICI) have limited single-agent activity in mCRPC. Radiation may enhance ICI activity by inducing immunogenic tumor cell death and altering the tumor microenvironment. We evaluated the activity and safety of ipi plus nivo plus LuPSMA in mCRPC. **Methods:** Eligibility: prior androgen receptor pathway inhibitor therapy, PSMA-positive disease, normal organ function, no contraindications to ICIs, <= 1 line of chemotherapy. Randomized (1:2) to LuPSMA alone (7.4 GBq every 6 weeks, up to 6 doses) or LuPSMA plus induction ipi (3 mg/kg every 6 weeks for 4 doses) and nivo (1 mg/kg every 3 weeks for 8 doses) followed by maintenance nivo (480 mg every 4 weeks for 18 doses) (LuPSMA+ICI). Primary endpoint: PSA PFS at 12 months (PSA-PFS 12m). Secondary endpoints: PSA response rate (PSA-RR), adverse events (AEs), radiographic-PFS (rPFS), PSA-PFS, and OS. **Results:** 93 of 100 planned participants (pts) were randomized from July 2022 to July 2023. Recruitment was stopped early due to 4 cases of treatment-related myocarditis in pts assigned LuPSMA+ICI. Of 93 randomized, 30 pts received LuPSMA, 57 pts received LuPSMA+ICI. 6 pts who did not receive assigned LuPSMA+ICI (1 ineligible; 5 ceased ICI at the direction of the central study team) were excluded from the efficacy intention to treat analysis. However, 5 were included in the safety analysis. Median age was 70 years [range: 45-83]; 80% had prior docetaxel. The median follow-up was 18 months (IQR: 16-22). PSA-PFS 12m was higher in pts assigned LuPSMA+ICI than LuPSMA-alone (33% vs. 17%, see table). Grade 3-4 AEs were reported in more pts assigned LuPSMA+ICI than LuPSMA-alone (75% vs 29%). Among those assigned LuPSMA+ICI, Grade 3-4 AEs in ≤5% were: colitis (19%), anemia (11%), hypophysitis (14%), lung infection (9%), fatigue (7%), thrombocytopenia (7%), hepatitis (7%), pneumonitis (7%), thromboembolic event (5%) and rash (5%). Myocarditis was reported in 4 pts (7%) assigned LuPSMA+ICI. There were 2 deaths during LuPSMA+ICI treatment: myocarditis (treatment related) and sepsis (not treatment related). **Conclusions:** LuPSMA+ICI was associated with improved PSA-PFS 12m in mCRPC. The spectrum of AEs were keeping with established toxicities however significantly higher with LuPSMA+ICI, and frequency of ICI-related myocarditis lead to early trial cessation. Clinical trial information: NCT05150236. Research Sponsor: Bristol Myers Squibb; Novartis; Cancer Australia; Prostate Cancer Foundation of Australia (PCFA); Australasian Radiopharmaceutical Trials Network (ARTnet); MIM Software Inc.; ANSTO.

	LuPSMA+ICI (N=57)	LuPSMA alone (N=30)
Median (IQR) LuPSMA cycles	5 (4-6)	6 (4-6)
Median (IQR) cycles of ipi	2 (1-3)	
Median (IQR) cycles of nivo	3 (2-5)	
PSA-PFS 12m, %	33	17
PSA-PFS, median, months	7.6 (95% CI: 6.5, 11)	7.1 (95% CI: 4.9, 10)
HR (95% CI)	0.70 (0.43, 1.13)	
PSA 50% (95% CI)	75% (62, 85)	67% (47, 82)
PSA 90% (95% CI)	46% (33, 59)	43% (26, 62)
Pts with grade 3-4 AEs	43/57* (75%)	10/35* (29%)

*Safety population.

5017 Rapid Oral Abstract Session

Phase 1 study results of JNJ-78278343 (pasritamig) in metastatic castration-resistant prostate cancer (mCRPC).

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Background: Human kallikrein 2 (encoded by the *KLK2* gene and hereafter referred to as KLK2) is a novel target expressed on PC cells with limited normal tissue expression. Pasritamig is a first-in-class T-cell-redirecting bispecific antibody that simultaneously binds KLK2 on PC cells and CD3 receptor complexes on T cells. We report dose escalation and expansion results from a first-in-human study (NCT04898634) evaluating pasritamig in pts with mCRPC. **Methods:** Pasritamig target doses (TDs) were escalated from 0.5-2000 mg SC and 150-900 mg IV QW-Q6W, with various step-up (SU) dosing schedules. Pre-medication with dexamethasone (16 mg) was required in SU and 1st TD. The primary objective was to determine the safety and RP2D. Secondary objectives included preliminary assessment of antitumor activity. **Results:** As of October 7, 2024, 174 pts (median [range] age 69 [36-89] years) had received ≥1 pasritamig dose (Table). Pts had a median of 4 prior therapies (range 1-13; 99.4% ARPI, 78.2% taxane chemotherapy, 17.2% lutetium Lu 177 vipivotide tetraxetan). There were no pasritamig-related deaths. One pt experienced a DLT of transient Gr 3 ALT/AST elevation after 50 mg SU2 SC administration. While most pts reported ≥1 TRAE (82.2% overall; 68.1% IV; 92.2% SC), these were mostly low grade, with only 9.2% of pts (6.9% IV; 10.8% SC) experiencing a Gr ≥3 TRAE. In the RP2D safety population (n=45; 3.5 mg [Day 1], 18 mg [Day 8], 300 mg Q3W or Q6W IV), the most common TRAEs were infusion-related reactions (22.2%; Gr 1/2), fatigue (15.6%; Gr 1/2), and CRS (8.9%; all Gr 1, no tocilizumab was administered), no TRAEs led to treatment discontinuation, no ICANS was observed, and 2 serious TRAEs (Gr 1 CRS) were reported. In the RP2D efficacy population (n=33; 3.5 mg [Day 1], 18 mg [Day 8], 300 mg Q6W IV), PSA50 was 42.4% (14/33) and median rPFS was 6.77 (95% CI 2.89, NE) months with 39.4% of pts ongoing (13/33). ORR in the 85 pts with measurable disease was 16.1% (n=5/31) in pts with lymph node +/- bone and 3.7% (n=2/54) in pts with visceral disease, with a median DOR of 11.27 (95% CI 3.58, NE) months. **Conclusions:** Pasritamig was very well tolerated (<10% of pts experienced CRS [all Gr1] at the RP2D) with promising antitumor activity, demonstrating proof of concept for KLK2 as a target amenable to T-cell redirection. These results address an unmet need for a targeted T-cell based therapy that is safe to administer in an outpatient setting with clinically meaningful benefit in mCRPC. Phase 3 trials are planned. Clinical trial information: NCT04898634. Research Sponsor: Johnson & Johnson.

	Total N=174	SC n=102	IV n=72	RP2D n=45[a]
TRAEs leading to treatment discontinuation, n (%)	1 (0.6)	1 (1.0)	0	0
Gr ≥3 TRAEs, n (%)	16 (9.2)	11 (10.8)	5 (6.9)	2 (4.4)
CRS, n (%)	43 (24.7)	31 (30.4)	12 (16.7)	4 (8.9)
Gr 1	37 (21.3)	28 (27.5)	9 (12.5)	4 (8.9)
Gr 2	6 (3.4)	3 (2.9)	3 (4.2)	0
Radiographic PFS, months, median (95% CI)	4.40 (3.35, 6.47)	4.07 (2.79, 4.93)	5.88 (3.15, NE)	6.77 (2.89, NE)[b]

[a]RP2D safety pop.=TD 300 mg Q3W/Q6W.
[b]RP2D efficacy pop.=TD 300 mg Q6W (n=33).

CA209-8TY trial, a randomized phase 2 trial of nivolumab and ipilimumab with or without stereotactic body radiation therapy in metastatic castration-resistant prostate cancer.

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Background: Metastatic castration-resistant prostate cancer (mCRPC) is among the leading causes of cancer related mortality in men worldwide. Treatment options include chemotherapy and androgen receptor pathway inhibitors (ARPIs). Prostate cancer is considered an immunosuppressive tumor. As of today, immune checkpoint inhibitors (ICIs) have not demonstrated effect in patients with mCRPC. The use of stereotactic body radiation therapy (SBRT) may increase the expression of tumor associated antigens and enhance potential immune responses following systemic therapy. **Methods:** Patients with mCRPC, who had previously progressed on at least one taxane regimen and one ARPI, were screened for the trial. Eligible Patients were randomized to receive either ipilimumab 1mg/kg and nivolumab 3mg/kg every 4 weeks for the first 12 weeks followed by nivolumab monotherapy 480mg every 4 weeks for up to 52 weeks (arm B), or the same ICI with SBRT of a metastasis, 24Gy in 3 fractions (arm A). The co-primary endpoints were prostate specific antigen (PSA) response rate, defined as a ≥50% decline in PSA compared to baseline, confirmed after ≥4 weeks, and objective response rate (ORR) according to modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and Prostate Cancer Working Group (PCWG) 3. Secondary endpoints included overall survival (OS), radiologic progression free survival (rPFS), and toxicity. **Results:** Between November 2019 and January 2024, 91 patients were randomized in the CheckPRO trial (NCT 05655715). A total of 81 patients received at least one treatment cycle and were eligible for evaluation. The confirmed PSA response rate was 21.6% in arm A and 20.5% in arm B. ORR was 16.7% (95% CI [4.7-37.4] %) and 22.2% (95% CI 10.1-39.2) in arm A and B, respectively. Median OS was 10.2 months (95% CI [7.1-14.1] %) in arm A and 9.2 months (95% CI [7.1-14.1] %) in arm B. rPFS was 2.1 months and 1.9 months in arm A and B, respectively. Serious adverse events related to ICIs occurred in 29.7% of patients in arm A and 31.8% in arm B. **Conclusions:** Objective responses were demonstrated in patients with mCRPC treated with combination ICI, however PFS was short and treatment-related toxicity significant. While the addition of SBRT was safe, it did not improve treatment outcomes in this study. Further analyses are ongoing to identify patients with mCRPC, who are most likely to respond to ICI. Clinical trial information: NCT05655715. Research Sponsor: Bristol Myers Squibb.

5019 Rapid Oral Abstract Session

Exploratory analyses of homologous recombination repair alterations (HRRm) by gene subgroup and potential associations with efficacy in the HRR-deficient population from TALAPRO-2.

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Background: In TALAPRO-2, talazoparib (TALA) + enzalutamide (ENZA) significantly improved radiographic progression-free survival (rPFS) and overall survival (OS) vs ENZA + placebo (PBO) in patients (pts) with mCRPC harboring HRRm assessed prospectively. Here we report exploratory biomarker analyses which assessed HRR by gene subgroup and potential associations with efficacy in pts enrolled in the HRR-deficient cohort from TALAPRO-2. **Methods:** Pts were randomized 1:1 to TALA 0.5 mg (N=200) or PBO (N=199) + ENZA 160 mg QD. HRRm testing used a 12-gene HRR panel (HRR12; clinical trial assays based on FoundationOne CDx and FoundationOne Liquid CDx). HRRm status categorization by gene incorporated all available tumor and prescreening/screening ctDNA records using an algorithm similar to that previously used by others (Fallah et al, JCO 2024 PMID: 38484203). For non-*BRCA* gene analyses, pts with co-occurring *BRCA1/2* alterations were excluded. For *BRCA1*, pts with co-occurring *BRCA2* alterations were excluded. The efficacy endpoints assessed were overall response rate (ORR), rPFS, and OS. Data cutoff Sept 3, 2024. **Results:** For all HRRm pts, TALA + ENZA was superior to ENZA + PBO across all efficacy endpoints: ORR, 69.4% vs 39.1% (odds ratio [OR], 0.28 [95% CI, 0.13–0.61]); rPFS, median 30.7 vs 12.3 months (mo) (hazard ratio [HR] =0.47 [0.36–0.62]); OS, median 45.1 vs 30.8 mo (HR=0.60 [0.46–0.78]). TALA + ENZA vs ENZA + PBO demonstrated benefit for *BRCA2m* across endpoints: ORR, 86.4% vs 31.0% (OR, 0.07 [95% CI, 0.01–0.35]); rPFS, median not reached (NR) vs 10.9 mo (HR=0.25 [0.15–0.42]); OS, median NR vs 28.5 mo (HR=0.47 [0.29–0.76]). Similar rPFS and OS benefit was seen for *BRCA1m* and *PALB2m* (allowing for small n in the groups); for ORR, evaluable n of 8 across arms for each gene was too low to meaningfully assess ORR differences. Benefit for TALA + ENZA was also evident for *CDK12m*: ORR, 63.6% vs 22.2% (OR, 0.16 [95% CI, 0.01–1.61]); rPFS, 19.3 vs 13.8 mo (HR=0.36 [0.19–0.70]); OS, 36.4 vs 22.8 mo (HR=0.41 [0.23–0.74]). *ATMm* also showed benefit for TALA + ENZA: ORR, 75.0% vs 33.3% (OR, 0.17 [95% CI, 0.02–1.32]); rPFS, 30.4 vs 18.3 mo (HR=0.66 [0.37–1.18]); OS, 45.1 vs 39.5 mo (HR=0.70 [0.38–1.29]). *CHEK2m* showed modest overall benefit for TALA + ENZA: ORR, 53.3% vs 42.9% (OR, 0.66 [95% CI, 0.07–5.59]); rPFS, 24.8 vs 18.3 mo (HR=0.65 [0.34–1.22]); OS, 34.2 vs 39.5 mo (HR=0.96 [0.51–1.81]). The remaining six HRR12 genes could not be meaningfully assessed for efficacy benefit by gene with TALA + ENZA vs ENZA + PBO due to low mutational prevalence. **Conclusions:** An efficacy benefit was evident for TALA + ENZA vs PBO + ENZA across multiple mutational subgroups assessed by gene, and was most pronounced for the *BRCA1-PALB2-BRCA2* axis and *CDK12*, with benefit also apparent for *ATM*. Analyses of additional efficacy endpoints are planned and will be presented. Clinical trial information: NCT03395197. Research Sponsor: Pfizer.

Clonal hematopoiesis (CH) in participants with metastatic castration-resistant prostate cancer (mCRPC) receiving ^{177}Lu-PSMA-617 or cabazitaxel: An exploratory post-hoc analysis of a randomized phase II trial (TheraP; ANZUP 1603).

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Background: The prostate-specific membrane antigen (PSMA)-targeted radioligand [^{177}Lu] Lu-PSMA-617 (^{177}Lu-PSMA-617) is an effective new standard-of-care for mCRPC. Since radiation may cause CH, an age-related preleukemic condition, we hypothesized that ^{177}Lu-PSMA-617 drives an increase in CH compared to other mCRPC treatments. Here, we explored CH in the TheraP trial randomizing participants (pts) with docetaxel-refractory mCRPC to cabazitaxel or ^{177}Lu-PSMA-617 (NCT03392428). **Methods:** We performed targeted DNA sequencing with a CH gene panel on blood samples from trial baseline (n = 176) and disease progression (n = 103; 56 post-^{177}Lu-PSMA-617, 47 post-cabazitaxel). Baseline CH mutations were detected in both cell-free DNA (cfDNA) and leukocyte DNA with variant allele frequency (VAF) ≥0.25%. Progression leukocyte DNA was unavailable at analysis, so progression CH mutations were identified via cfDNA only. We used Fisher's exact test to compare proportions, and the Mann-Whitney U test for changes in VAF. **Results:** Data was evaluable in 174/176 pts with baseline samples, and 103/103 with progression samples. Median time between baseline and progression blood draws was 28 and 27 weeks for ^{177}Lu-PSMA-617 and cabazitaxel arms, respectively. CH was detected in 77% (135/174) of pts at baseline (median age: 72). 71 (41%) pts had baseline CH mutations with VAF≥2%. The most commonly mutated genes at baseline were *DNMT3A* (n = 67 pts, 38%), *TET2* (n = 44, 25%), *PPM1D* (n = 26, 15%) and *ASXL1* (n = 19, 11%), with no difference in gene mutation frequency between arms. At progression, new mutations of presumed CH origin were detected in 83% and 46% of ^{177}Lu-PSMA-617 and cabazitaxel pts, respectively (47 vs 22 pts, p=0.0001). The most frequently mutated gene at ^{177}Lu-PSMA-617 progression was the DNA damage repair gene *PPM1D*; and new *PPM1D* CH mutations were 8 times more common after ^{177}Lu-PSMA-617 than cabazitaxel (p = 0.00032). Progression mutations in *ATM* or *CHEK2* were also 5 times more commonly observed after ^{177}Lu-PSMA-617 (p = 0.01). Among CH variants concordantly detected at baseline and progression on ^{177}Lu-PSMA-617, the median VAF change for mutations in DNA damage repair genes was higher than in canonical CH genes *DNMT3A*, *TET2* and *ASXL1* (1.53% *vs.* 0.15%, p = 0.01). **Conclusions:** ^{177}Lu-PSMA-617 was associated with a greater number of new CH mutations, especially in DNA damage repair genes, compared to cabazitaxel. Whilst the clinical relevance of this finding in a population of patients with heavily-treated mCRPC is unclear, CH emergence and expansion may have implications as radioligand therapy is used as an earlier line of therapy. Clinical trial information: NCT03392428. Research Sponsor: Prostate Cancer Foundation of Australia (PCFA); Australian Nuclear Science and Technology Organisation (ANSTO); Endocyte Inc. (A Novartis company); It's a Bloke Thing; Movember; The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP); Terry Fox New Frontiers Program Project Grant; Canadian Cancer Society Challenge Grant; The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP); The Distinguished Gentleman's Ride; CAN4CANCER; Prostate Cancer Foundation Challenge Award.

Association of hormone therapy usage with adverse cardiovascular events in prostate cancer patients of the All of Us Research Program cohort.

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Background: Hormone therapies (HT) such as GnRH agonists, GnRH antagonists, and/or anti-androgens have led to improved overall survival for prostate cancer patients. However, the usage of these drugs may also increase cardiovascular (CV) risk. **Methods:** This study examined participants in the All of Us Research Program who were diagnosed with prostate cancer, had no prior history of adverse cardiovascular events (ACE), and were either treated or not treated with HT. We defined ACE as myocardial infarctions, strokes, or heart failure. Covariates used in our analysis were age, dyslipidemia, type 2 diabetes, hypertension, chronic kidney disease, peripheral vascular disease, statin usage, and smoking history. Time-to-ACE was defined using longitudinal electronic health record data. Participants who did not develop ACE were right censored at the date of their last medical visit. We evaluated whether HT use affected the risk of ACE using a Cox proportional hazards model with adjustment for established CV risk factors as covariates. **Results:** The final cohort included 5156 *All of Us* participants. Of these participants, 851 received HT treatment, 624 received only non-HT treatment (other medical, radiation, or surgical treatment for their prostate cancer), and 3681 received no known treatment. In our overall survival analysis, HT was associated with increased risk of ACE (HR, 1.22; 95% CI, 1.01-1.48; P = 0.03). In participants with pre-treatment dyslipidemia (Table), HT usage was associated with increased risk of ACE (HR, 1.52; 95% CI, 1.19-1.95; P <0.001). In participants without pre-treatment dyslipidemia, no association was found between HT usage and ACE (HR, 0.96; 95% CI, 0.71-1.30; P = 0.81). **Conclusions:** In a study cohort with no prior history of ACE, HT was associated with increased risk of ACE in participants with pre-treatment dyslipidemia. These results suggest that risk stratification by dyslipidemia status may help improve CV outcomes when selecting treatment regimens for prostate cancer patients. Research Sponsor: NHGRI.

Cox model for adverse cardiovascular time-to-event stratified by pre-treatment dyslipidemia.

	Pre-treatment Dyslipidemia (n=2377)		No Pre-treatment Dyslipidemia (n=2779)	
	Hazard Ratio (95% CI)	P-Value	Hazard Ratio (95% CI)	P-Value
Hormone Therapy	1.52 (1.19-1.95)	<0.001	0.96 (0.71-1.30)	0.81
Type 2 Diabetes	1.34 (1.07-1.70)	0.01	1.18 (0.79-1.76)	0.41
Hypertension	1.68 (1.31-2.15)	<0.001	1.43 (1.15-1.78)	0.001
Chronic Kidney Disease	1.96 (1.46-2.62)	<0.001	1.45 (0.85-2.47)	0.18
Peripheral Vascular Disease	1.47 (1.02-2.01)	0.04	1.10 (0.54-2.26)	0.79
Age	1.05 (1.03-1.06)	<0.001	1.04 (1.03-1.05)	<0.001
Statin Usage	0.72 (0.59-0.89)	0.002	0.90 (0.65-1.23)	0.50
Smoking History	1.18 (0.96-1.45)	0.11	1.20 (1.00-1.44)	0.05

Comprehensive genomic profiling of Black and non-Hispanic White (NHW) men with prostate cancer (PCa).

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Background: Racial disparities are evident in PCa, with Black men experiencing a higher incidence and worse survival compared to NHW patients (pts). The molecular alterations that distinguish these groups remain incompletely characterized. Herein, we investigate the clinical-genomic features that potentially contribute to the differences in outcomes between Black and NHW pts with PCa. **Methods:** Comprehensive next-generation sequencing of DNA (592-gene panel/whole exome) and RNA (whole transcriptome) was performed at Caris Life Sciences on PCa tissue samples (n = 5,412), collected from 2015 to 2023. Transcriptomic signatures – Androgen Receptor (AR), Neuroendocrine PCa (NEPC) scores – were calculated. Real-world overall survival (OS) data was obtained from insurance claims and was analyzed using Kaplan-Meier estimation. **Results:** Overall, 1,078 pts with PCa identified as Black, while 4,334 were NHW. Black pts were younger at biopsy collection than NHW pts (median age 66 vs 71 years, $P < 0.001$). The proportion of metastatic samples was higher in Black pts compared to NHW pts (43% vs 38%, $P < 0.01$). The prevalence of castrated PCa specimens was similar between Black and NHW pts (26.0% vs 25.4%, P = 0.72). Among non-castrated PCa tumors, tumors from NHW pts had more frequent alterations in *TP53*, *PTEN*, *PIK3CA*, and *CHEK2*, while tumors from Black pts had more *SPOP* and *CTNNB1* mutations. In the castrate setting, *TP53* and *PTEN* alterations were more frequent in tissue samples from NHW pts, while *CDK12* and *SPOP* mutations were more frequent in tumors from Black pts. *TMPRSS2* fusions were more prevalent in the NHW cohort across both castrated and non-castrated tumors. Tumors from Black pts had higher *FOLH1*/*PSMA* and *STEAP1* expression, elevated AR scores, but lower *CD276*/*B7H3* expression and NEPC scores. In the overall cohort, Black pts demonstrated a shorter median OS from diagnosis compared to NHW pts (86 vs 94 mos, P = 0.03). Black pts had a significantly longer time on treatment with enzalutamide in both the non-castrate (HR 0.82, P= 0.04) and castrate subgroups (HR 0.77, P= 0.03). Among pts with homologous recombination repair (HRR) deficiency-harboring tumors, PARP inhibitors provided a numerically longer survival benefit in Black pts than in NHW pts (21 vs 13 mos, P = 0.09). **Conclusions:** This multi-institutional study reveals distinct molecular profiles between Black and NHW pts with PCa. Despite having molecular features associated with better prognosis, Black men demonstrated worse survival outcomes, pointing to multifaceted determinants of disease outcomes. Notably, Black pts had improved outcomes on enzalutamide and showed potential benefit from PARP inhibitors in the presence of HRR mutations. These findings highlight genomic differences in diverse PCa populations and suggest therapeutic opportunities to address outcome disparities.
Research Sponsor: None.

Prognostic impact of brain metastases on survival rates in patients with metastatic testicular cancer: A comprehensive registry-based analysis.

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Background: Testicular cancer (TC) is a rare malignancy that accounts for less than 1% of all cancers. Advances in the treatment paradigm have improved survival rates. However, oncologic outcomes may vary based on the extent and location of metastasis. Brain metastases (BM) are rare but may lead to worse survival outcomes. We aimed to conduct the largest retrospective study of patients with metastatic TC (mTC) to evaluate the prognostic impact of brain metastasis on survival rates in patients with IGCCC intermediate or poor risk mTC. **Methods:** We utilized the National Cancer Database (2010-2021) to identify patients with mTC(T1-4, any N0-2, M1). Patients with isolated lung metastases were excluded, as lung involvement alone was considered a surrogate marker for patients with good risk disease. We utilized Kaplan Meier analysis and cox proportional hazard modelling to study the impact of BM on survival outcomes in patients with mTC. **Results:** A total of 4,076 patients with mTC met our study criteria, of which 11.14% (454) had BM. Among these, 36.11% (1,472) had seminoma, 27.16% (1,107) had non-seminomatous histology, and 36.73% (1,497) had mixed germ cell tumors. The 2- and 5-year survival rates for patients without BM were 82.63% (95% CI: 81.26–83.91) and 78.26% (95% CI: 76.72–79.71), respectively. For patients with BM, the 2- and 5-year survival rates were 51.01% (95% CI: 45.99–55.79) and 42.78% (95% CI: 37.72–47.72), respectively. In our adjusted analysis, patients with BM had 2.35-fold increased risk of death (HR: 2.35, 95% CI: 1.96–2.82, $p<0.001$), compared to those without BM. Additionally, compared to seminoma, non-seminomatous histology had a 1.72-fold increased hazard of death (HR: 1.72, 95% CI: 1.42–2.09, $p<0.001$), while mixed germ cell tumors had a 1.34-fold increased hazard of death (HR: 1.34, 95% CI: 1.10–1.62, $p = 0.003$). **Conclusions:** In this large-scale retrospective cohort study, patients with BM had 135% increased risk of death in patients with mTC compared to patients without BM. Additionally, non-seminomatous and mixed germ cell histology were associated with significantly worse outcomes compared to seminoma. These findings highlight the importance of aggressive, tailored treatment strategies to address the higher mortality risk posed by BM in patients with intermediate and poor risk metastatic testicular cancer. Research Sponsor: None.

Cox proportional hazard model in patients with mTC.

Variable	HR (95% CI)	P-value
Histology: Seminoma	Ref	
Non seminoma	1.72 (1.42–2.09)	< 0.001
Mixed germ cell	1.34 (1.10–1.62)	0.003
Brain Metastasis: No	Ref	
YES	2.35 (1.96–2.82)	< 0.001
Bone Metastasis No	Ref	
YES	1.43 (1.20–1.71)	< 0.001
Liver Metastasis: No	Ref	
YES	1.65 (1.40–1.96)	< 0.001

Use of GIP and GLP-1 receptor agonists in prostate cancer patients.

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Background: The use of glucagon-like peptide 1 receptor agonist (GLP-1 RA) and dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA (GIP/GLP-1 RA) classes has increased over the past several years. The GLP1 receptor is expressed in metastatic prostate tissue, and GLP-1 RA and GIP/GLP-1 RA medications may have an impact on prostate cancer (PCa) outcomes. However, a use analysis among patients with prostate cancer in a large, diverse, current, real-world database has not been published. **Methods:** This national, retrospective study analyzed adult patients in the Epic Cosmos database with an active diagnosis of PCa who initiated a GLP-1 RA or GIP/GLP-1 RA medication from January 1, 2015, to December 31, 2024. The primary endpoint was percent use and change in use over time. Secondary endpoints included factors associated with use. Data were reviewed from Epic Cosmos, a Health Insurance Portability and Accountability Act-defined limited data set using deidentified electronic health record (EHR) data from more than 293 million patients served by 1,633 hospitals and more than 37,900 clinics. **Results:** This study includes 1,533,762 patients with a median age of 75. 30.3% (464,477) of the patients had a concurrent diagnosis of T2DM. The percentage of PCa patients utilizing a GLP-1 RA or GIP/GLP-1 RA increased from 0.43% in 2015 to 6.1% in 2024. Odds of receiving a GLP-1 RA or GIP/GLP-1 RA in PCa patients with a T2DM diagnosis were higher among those with a low social vulnerability index (SVI) percentile (<25) compared to patients with an SVI 75 or above (OR 1.20, 95% CI 1.16, 1.24) and among obese compared to non-obese (OR 1.88, 95% CI 1.85, 1.90). Odds were lower in PCa patients with T2DM 65 years and above compared to those under 65 (OR 0.41, 95% CI 0.40, 0.42). Odds of an opioid medication were higher in T2DM PCa patients receiving a GLP-1 RA or GIP/GLP-1 RA compared to those who weren't (OR 1.14, 95% CI 1.12, 1.16). While most PCa patients who received a GLP-1 RA or GIP/GLP-1 RA had T2DM, the percentage with neither T2DM nor obesity has increased (Table 1). **Conclusions:** This study showed that GLP-1 RA and GIP/GLP-1 RA use is on the rise. Use is associated with age and social vulnerability and may impact opioid receipt. Ongoing and future investigations examine the impact of GLP-1 RA and GIP/GLP-1 RA use on PCa progression. Research Sponsor: U.S. National Institutes of Health; 5P30CA056-036; U.S. National Institutes of Health; 1L30CA284329-01.

PCa patients receiving GLP-1 RA or GIP/GLP-1 RA by year.

Year	PCa	T2DM*	BMI ≥30*	No T2DM+BMI<30*
2016	2,085	1,905 (91.37)	1,497 (71.80)	31 (1.49)
2017	3,436	3,168 (92.20)	2,448 (71.25)	50 (1.46)
2018	5,594	5,183 (92.65)	3,946 (70.54)	77 (1.38)
2019	8,594	7,975 (92.80)	5,861 (68.20)	109 (1.27)
2020	11,881	11,086 (93.31)	7,494 (63.08)	129 (1.09)
2021	18,460	17,033 (92.27)	11,820 (64.03)	298 (1.61)
2022	28,850	25,986 (90.07)	18,232 (63.20)	581 (2.01)
2023	47,596	40,638 (85.38)	31,230 (65.61)	1,393 (2.93)
2024	69,808	56,649 (81.15)	46,241 (66.24)	3,033 (4.34)

*Data displayed as absolute number and as percentage of PCa population for each characteristic.

5025 Poster Session

Barbados' first next-generation sequencing of a prostate cancer sample.

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Background: According to the WHO (2022), Prostate cancer is the most frequent of all cancers in Barbados. In 2022, it accounted for over 45% of the reported cancer cases on the island, second being colorectal cancer at an alarming, contrasted prevalence rate of 13.5%. Today, cancer is fought at the cellular level across the globe. Reportedly nearly 40% of prostate cancer may be attributed to inherited genetic susceptibility, yet only hand full of clinically relevant genes have been associated with risk and/or adverse outcomes after diagnosis with this type of cancer (NCI, 2025). NGS is not widely available in Barbados. The primary aim of this research was to evaluate the feasibility of providing Next Generation Sequencing capability to the patients and practitioners on the island and to discover more about the genomics of the prostate cancer present on the island at molecular, ethnic, and geographic levels. **Methods:** A genomic sequencing protocol was conducted to determine the feasibility of delivering Next Generation Sequencing to patients receiving oncological care on the island. A Barbadian multidisciplinary team inclusive of a pathology group, prostate cancer surgical center and healthcare system partnered with their South American medical equipment distributor and a global genomics and human health innovation company to conduct the pilot study. Forty prostate cancer archive tissue samples were identified from a local tissue bank. The samples were donated to future use research by previously treated surgical cases. Patients provided written consent to future use research. Of the forty samples, 25 were batched and shipped to a genomics laboratory for DNA extraction. DNA was then shipped to Illumina Laboratories in Baltimore where the NGS sequencing was performed. The OncoReveal Multi-Cancer with CNV & RNA Fusion Panel on the Illumina MiniSeq system was utilized. **Results:** OncoReveal Multi-Cancer with CNV & RNA Fusion Panel had the capability to detect 60 variants and CNVs detected from DNA. Of the 25 cases sequenced, new actionable data were found on 52% (13 of 25) with 33.3% (3 of 12) of tests detecting a ATM. The remaining data found following variants APC, CDKN2A, JAK3 V722I, PIK3CA, TP53, PTEN, SMO, CDKN2A, TP53, ERBB2 and PTEN. All of which were 7.6% (1of 13) in therapeutics actionability. **Conclusions:** Next Generation Sequencing in Barbadian men is not performed as part of routine diagnostic care due to a lack of access to this companion diagnostic resource. Providing NGS to local patients was proven to be feasible utilizing a central laboratory transport and testing model. OncoReveal Panel performed on a random sample revealed new actionable data were found on 52% (13 of 25) with 33.3% (3 of 12) of tests detecting a ATM. This suggests approximately 50% of this male population may find clinical utility in the use of NGS as a companion diagnostic and more research is needed in the region to better understand the high prevalence of the ATM variant. Research Sponsor: None.

BEP in intermediate- and poor-risk advanced non-seminomatous germ cell tumor (NSGCT): Standing the test of time.

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Background: Bleomycin, etoposide, and cisplatin (BEP) has been the cornerstone of treatment for advanced NSGCT for decades. With the advent of newer regimens such as VIP (Etoposide, ifosfamide and cisplatin) and improved outcomes over the years, it is imperative to assess whether BEP has truly stood the test of time, especially for those in the intermediate and poor risk. **Methods:** This was a retrospective analysis of a prospectively collected dataset of NSGCT patients treated at a comprehensive cancer care centre in India. Adolescent and adult males with intermediate or poor-risk as per IGCCCG were included. The progression-free survival (PFS) and overall survival (OS) were calculated from date of diagnosis to date of progression and death respectively. Log-rank method was used to compare outcomes between BEP and VIP. **Results:** A total of 351 patients were analysed. The median age was 28 years (IQR: 23-34 years) (Table 1). Primary high-inguinal orchidectomy (HIO) was done in 208 (59.3%) and after completion of chemotherapy in 63 (17.9%) patients. There were 209 (59.5%) patients with poor-risk. Forty-seven (13.4%) received less than 4 cycles of chemotherapy. Retroperitoneal lymph node dissection (RPLND) was done in 195 (55.6%) patients. Overall, 45 (12.8%) patients had toxicities requiring hospitalization. Viable residual disease was seen in 33 (9.4%) patients. The median follow-up of the cohort was 58.9 + 3.6 months (95% CI: 51.9 – 65.9 months). Patients who received BEP had better 7-year PFS (68.4% vs 47.5%, $p < 0.001$) and 7-year OS (77.9% vs 55.2%, $p < 0.001$) as compared to VIP albeit higher lung toxicities and deaths due to chemotherapy. The cohort which received VIP had higher percentage of smokers, mediastinal primary, visceral metastases and S3 tumor markers. **Conclusions:** BEP has stood the test of time and remains the standard of care. However, for patients who are smokers, or have aggressive disease, VIP is a good alternative. Research Sponsor: None.

Patient, disease and treatment characteristics.

Characteristics	BEP (n = 226)	VIP (n = 125)	p-value
Age group (years)			**0.217**
< 35	181 (80.1%)	93 (74.4%)	
> 35	45 (19.9%)	32 (25.6%)	
ECOG PS			**0.004**
0-1	216 (95.6%)	110 (88%)	
2-3	10 (4.4%)	15 (12%)	
Smokers	19 (8.4%)	20 (16%)	**0.034**
Primary site			**< 0.001**
Testis	206 (91.2%)	95 (76%)	
Retro-peritoneum	12 (5.3%)	3 (2.4%)	
Mediastinum	8 (3.5%)	27 (21.6%)	
Tumor markers (S)			**0.061**
Sx	6 (2.7%)	1 (0.8%)	
S0	3 (1.3%)	0	
S1	11 (4.9%)	8 (6.5%)	
S2	124 (54.9%)	53 (43.1%)	
S3	82 (36.3%)	61 (49.6%)	
Sites of metastases			
None	53 (23.4%)	5 (4%)	**< 0.001**
Non-regional lymph nodes	92 (40.7%)	62 (49.6%)	**0.108**
Pulmonary	115 (50.9%)	86 (68.8%)	**0.001**
Non-pulmonary visceral	43 (19.0%)	28 (22.4%)	**0.074**
Less than 4 cycles chemotherapy	31 (13.7%)	16 (12.8%)	**0.809**
Toxicities			
Grade 3-4 febrile neutropenia	54 (23.9%)	42 (33.6%)	**0.214**
Grade 3-4 hematological toxicities	93 (41.1%)	77 (61.6%)	**0.003**
Lung toxicities	29 (12.8%)	2 (1.6%)	**< 0.001**
Toxicities requiring hospitalization	29 (12.8%)	16 (12.8%)	**0.806**
Deaths	5 (2.2%)	1 (0.8%)	**0.328**
Viable residual disease after chemotherapy	17 (7.52%)	16 (12.8%)	**0.041**

Epidemiology, treatment patterns, and survival outcomes of spermatocytic seminoma: A National Cancer Database analysis.

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Background: Spermatocytic seminoma (SS) is a rare germ cell tumor, representing 2-5% of seminomas. Unlike classical seminomas, SS primarily affects older men (median age: 55 years) and exhibits low metastatic potential, though rare sarcomatoid transformations can lead to aggressive behavior. Treatment typically involves orchiectomy, with adjuvant therapies reserved for advanced cases. Despite its distinct clinical behavior, SS remains understudied, with limited data on its epidemiology, demographic patterns, and socioeconomic influences. Leveraging the National Cancer Database (NCDB) could provide critical insights into its epidemiology and management. **Methods:** A retrospective cohort study using the 2004–2020 NCDB identified patients with histologically confirmed SS (ICD-O-3 code 9063). Demographic, socioeconomic, and clinical variables were analyzed descriptively, with incidence trends evaluated via regression analysis. **Results:** A total of 541 patients with histologically confirmed SS were identified in the NCDB from 2004–2020. The incidence rate remained stable (R^2 = 0.012). All patients were male, with a mean age of 58.9 years (SD = 16.6). The cohort was predominantly White (91.5%) and non-Hispanic (89.6%), with 49.2% privately insured and 38.6% covered by Medicare. Most patients (55.1%) resided in metropolitan areas, and treatment was primarily delivered at comprehensive community cancer programs (43.5%) and academic/research programs (26.1%). Most patients (67.8%) were diagnosed at Stage I, with 82.4% having a Charlson-Deyo comorbidity score of 0. Surgery was performed in 98.9% of cases, with 95.2% achieving no residual tumor. Radiation therapy (18.3%) and chemotherapy (5.9%) were rarely used. The 30-day mortality rate was 0.6%, and the 90-day mortality rate was 1.0%. Survival rates were 98.0% (2-year), 96.0% (5-year), and 91.5% (10-year). **Conclusions:** This represents the first NCDB in-depth demographic analysis of spermatocytic seminoma (SS), addressing a significant gap in the literature on this rare malignancy. The study shows that SS predominantly affects males, with a strong predilection for non-Hispanic White individuals, consistent with prior case reports and small-scale studies. Additionally, this analysis provides novel insights into the socioeconomic profile of SS patients, revealing a tendency toward higher income brackets, residence in urban metropolitan areas, and treatment at community-based cancer programs rather than academic institutions. Future research should explore how demographic and socioeconomic factors influence diagnostic pathways, treatment decisions, and survival outcomes in this patient population. Research Sponsor: None.

Racial and socioeconomic disparities in testicular cancer survival outcomes: A SEER database analysis.

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Background: Testicular cancer, the most common malignancy in men aged 15 to 45 years, has a high cure rate exceeding 95% with early diagnosis and proper treatment. However, these favorable outcomes are not equitably distributed across all racial and socioeconomic groups. This study aims to analyze these disparities in testicular cancer survival outcomes from 2014 to 2021. **Methods:** The Surveillance, Epidemiology, and End Results (SEER) database was queried to identify patients diagnosed with testicular cancer (ICD-O-3 site codes C620-C629) from 2014 to 2021. Variables including stage, treatment, ethnicity, income level, and geographic location (urban/rural) were extracted. Patients with missing data were excluded from the analysis. Statistical methods included chi-square tests, Kaplan-Meier survival curves, and Cox proportional hazards models. Analyses were conducted using R (v4.4.1). **Results:** A total of 20,508 patients were included in the study. The population was predominantly White (87%), followed by Asian/Pacific Islanders (5%) and African Americans (3%). The majority of patients were aged 20–39 years (60%), with T1 disease (42.89%) and no nodal involvement (N0-53.93%). Seminomas accounted for 52.7% of cases, followed by mixed germ cell tumors (25.88%) and embryonal carcinoma (7.73%). Primary treatments included surgery (95%) and chemotherapy (38%). Advanced disease stages (T3–T4, M1, Stage II–III) and extensive nodal involvement were significantly associated with poor survival outcomes ($p<0.001$). Multivariate stratified analyses revealed higher overall mortality (OM) among African Americans (HR = 1.75, $p < 0.001$) and Asian/Pacific Islanders (HR = 1.25, $p = 0.003$) compared to White patients. The Hispanic population exhibited an 8.8% higher hazard compared to non-Hispanics (HR = 1.088, $p = 0.02$). Patients with annual incomes below $40,000 had significantly elevated OM (HR = 2.41, $p < 0.001$), whereas those with incomes of $120,000 or more demonstrated better survival outcomes (HR = 0.77, $p = 0.019$) compared to the reference group ($40,000-$120,000). Multivariate analyses of cancer-specific mortality (CSM) revealed similar findings, with African American patients (HR = 1.69, $p < 0.001$) and individuals in lower-income brackets (HR = 2.12, $p < 0.001$) experiencing worse outcomes. **Conclusions:** This study highlights racial and socioeconomic disparities in testicular cancer survival outcomes, with African American patients and individuals in lower-income brackets experiencing significantly worse overall and cancer-specific mortality. It underscores the need for future research to investigate structural inequities and insurance-related barriers contributing to these disparities and develop actionable strategies to achieve equity in cancer outcomes. Research Sponsor: None.

5029 Poster Session

Therapeutic decisions and outcome of patients with stage I testicular germ cell tumor: Single-centre experience.

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Background: Testis cancer (TC) is the most common solid neoplasm affecting men aged 15 to 40, with most of diagnosis occurring at stage I. Despite excellent prognosis, optimal post-surgical management remains controversial, comprising adjuvant therapy (AT) or active surveillance (AS). **Methods:** Our study aimed to compare relapse-free survival (RFS) in patients (pts) with stage I TC undergoing AT [chemotherapy (CT) or radiotherapy (RT)], versus AS, between 2000 and 2023. Evolution of AT choices for seminomas was evaluated over different time periods (before 2014, 2014-2018, after 2018). Clinical histories of stage I TC treated at our institution were retrospectively collected. Traditional histopathological prognostic factors for relapse were assessed, and seminomas were reclassified according to the new EAU risk group classification. Overall survival (OS) was a secondary endpoint. Pts with inadequate follow-up, insufficient information, or histologies other than seminoma and nonseminoma were excluded. **Results:** Out of 240 cases, 184 (129 seminomas, 54 non-seminomas, 1 burned-out tumor) were eligible. AT was administered to 58.1% of seminomas and 57.4% of nonseminomas. In seminomas, AT was represented by CT in 40.3% and RT in 17.8% of cases. RT administration significantly decreased over time, representing 66.7% of AT before 2014, 9.1% between 2014 and 2018, and 0% after 2018. With a median follow-up of 56.9 months, 5-yr RFS rate was 94.6% and 84.7% for pts undergoing AT and AS, respectively ($p=0.005$). Particularly, 5-yr RFS rate was 92.5% vs 86.7% in seminomas ($p=0.07$), and 100% vs 79.9% in nonseminomas ($p=0.015$). Proportion of seminomas undergoing AT was 20.7% among those with $T<4$ cm and no rete testis invasion, 56.4% among those with 1 risk factor, and 82.2% among pts with 2 risk factors. AT was received by 3.2% and 96.8% of nonseminomas without and with lymphovascular invasion, respectively. In the new EAU classification, 31.4%, 48.8% and 19.8% of seminomas were classified into the very low, low, and high risk categories (8 cases not evaluable). Compared to the traditional classification, a lower proportion of pts resulted in the poorest risk category (19.8% vs 34.9%). AT receipt significantly increased with risk: very low 27.0%, low 67.8%, high 83.3% ($p<0.001$). 5-yr OS rate was 98.1% (99.1% in seminoma and 95.1% in nonseminoma). **Conclusions:** AT was associated with higher RFS rates across both histological types. AS and AT are both associated to excellent survival. A temporal trend in reduction of RT was observed. Further evaluations are needed to individualize treatment decisions. Histopathological risk factors and the new EAU risk classification provide valuable prognostic information, aiding in treatment stratification. Additionally, the EAU risk group classification emerges as a potential tool to better stratify seminoma pts and support the implementation of AS in lower risk categories. Research Sponsor: None.

5030 Poster Session

Risk factors and causes of early death among patients with germ cell testis tumors (GCTs): An international collaborative study supported by the Global Society of Rare Genitourinary Tumors.

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Background: GCTs are the most common solid tumor in young men aged 20 to 40 years and are curable in most cases. However, a small proportion of patients with very advanced or aggressive disease, die early after starting chemotherapy. These patients are often not included in clinical trials and therefore accurate data on their risk factors and causes of death are critically lacking. **Methods:** This retrospective cohort study included patients with GCTs who died within 3 months from the completion of first-line systemic chemotherapy. Anonymized patients were included in an international database from tertiary cancer centers. Inclusion criteria were age ≥18 years, diagnosis between 2000-2024, death within 3 months from the last cycle of first-line chemotherapy, and treatment with systemic anticancer therapy and/or intention to treat. The database included data on patient and tumor characteristics, treatment and outcomes. **Results:** We identified 94 patients who experienced early death. Majority had IGCCCG poor prognosis and 16 (17%) had extragonadal GCTs. The proportion of these patients ranged from 0.4% to 2.1% of all patients treated with first line chemotherapy. Median time from starting of platinum based-therapy to death was 32 days (range: 2-301 days). Initial chemotherapy dose was reduced in 44.3% of patients. The most common causes of death were acute respiratory failure (ARF) due to acute respiratory distress syndrome (35.1%), disease progression (18.1%), febrile neutropenia (FN) with septic shock (13.8%), fatal extrapulmonary hemorrhage (13.8%), venous thromboembolism and myocardial infarction, each with an incidence of 2.1%. Approximately 11.7% of patients died from other causes and in 3.2% of cases the cause of death remains unknown. Factors associated with ARF development were older age (median age 43 years), lung involvement >50%, resting dyspnea and hemoptysis, but not choriocarcinoma histology, and less likely received bleomycin and/or initial dose reduction. Death within 30 days from starting chemotherapy (n=47, 50.0%) was associated with liver metastases, lung involvement >50%, beta-HCG > 50,000 mIU/mL, ECOG performance status 2-3, higher neutrophil/lymphocyte ratio and intensive or ventilated care (all $p<0.05$). Beyond ARF, fatal extrapulmonary hemorrhage (19.6%) and FN with septic shock (17.4%) were the most common cause of death within 30 days of starting therapy, while disease progression (29%) was more common in patients who died later. **Conclusions:** The proportion of patients with early death is low, but this group presents significant clinical challenges. Among advanced GCTs, high beta-HCG levels, liver metastases, massive lung involvement, poor ECOG and/or need of intensive care are associated with a higher risk of early death and need targeted intervention to improve their therapeutic outcomes. Research Sponsor: None.

TROP-2 expression in germ cell tumors (GCT).

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Background: Trophoblast cell surface antigen 2 (TROP-2) is a tumor associated antigen overexpressed in several malignancies including breast and urothelial cancer. The TROP-2 antibody-drug conjugate (ADC) Sacituzumab govitecan is approved for treatment of metastatic breast cancer. The expression of TROP-2 in GCT is unknown. We present immunohistochemistry results of TROP-2 expression in GCT. **Methods:** Patients who underwent resection for GCT at Indiana University were included. Sixty formalin-fixed paraffin-embedded (FFPE) GCT samples were available. FFPE slides were selected from differing GCT histology and surgical sites including primary tumor, retroperitoneal lymph node, and distant metastases. Immunohistochemical (IHC) staining for TROP-2 (clone 1, mouse monoclonal, Enzo Life Sciences) was conducted and scored by intensity on a 0-3 scale by an experienced pathologist. **Results:** Samples from 60 individual specimens were available for IHC analysis. TROP2 expression was detected in 29 (48%) of these samples. Intensity expression differed from pure seminoma, mixed non-seminoma (NSGCT), teratoma, yolk sac tumor, and choriocarcinoma samples. Both primary and metastatic samples had TROP-2 expression of varying degrees. **Conclusions:** TROP-2 expression varies across histology in GCT. Seminoma appears to have the lowest expression of TROP-2. Higher TROP-2 expression was noted in choriocarcinoma and yolk sac tumor samples indicating potential as a target in these histologic subtypes in future clinical trials. Research Sponsor: John Cleland Fellowship.

Detectable TROP-2 by histology.

Sample histology (N)	Total detectable TROP-2 expression (%)	3+	2+	1+
Seminoma (20)	3 (15)		2	1
NSGCT (19)	12 (63)	9 (6*)	2*	1*
Teratoma (9)**	6 (66)	3*	3*	
Yolk sac (9)	5 (56)	2	3	
Choriocarcinoma (3)	3 (100)	1	1	1

*In epithelial elements of teratoma.
**Three negative samples with only small fragments of teratoma and false negative may be present.

Clinical utility of a tumor-naïve circulating tumor DNA (ctDNA) test to predict outcomes in patients with advanced testicular germ cell tumors.

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Background: Serum tumor markers (STM) used in the management of Testicular Germ Cell Tumors (TGCT) lack sufficient specificity and are not altered in up to 60% of patients (pts). We evaluated the clinical utility of a tumor-naïve ctDNA test to predict outcomes in pts with advanced TGCT. We also analyzed the correlation between ctDNA detection and STM levels. **Methods:** Blood samples were collected from 31 pts before and after first-line treatment (chemotherapy, primary radiotherapy or retroperitoneal lymphadenectomy). ctDNA detection was performed using a ddPCR assay to identify copy number gains in chromosome 12p, present in 90% of TGCTs. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier curves and the log-rank test. The correlation between ctDNA status and STM alterations was analyzed using Pearson's correlation test. **Results:** The median age of participants was 31 years, 81% were non-seminoma, 48% stage III, 45% IGCCCG intermediate-poor risk, 39% Sx-S0 stage, 83% received first-line chemotherapy, and the median follow-up time was 53 months. The ddPCR assay showed 88% sensitivity and 100% specificity for ctDNA detection. ctDNA detection before first-line treatment significantly correlated with altered LDH levels ($r=0.78$, $p<0.001$) but did not correlate with altered AFP ($r=0.33$, $p=0.16$) or bHCG levels ($r=-0.03$, $p=0.88$). Detection of ctDNA before first-line treatment was significantly associated with a shorter 2-year PFS rate (ctDNA positive 64% vs. ctDNA negative 100%, $p=0.022$) and 2-year OS rate (ctDNA positive 64% vs. ctDNA negative 100%, $p=0.014$). None of the patients who tested negative for ctDNA detection experienced disease progression or died. Elevated STM levels before first-line therapy were not significantly associated with PFS ($p=0.07$) or OS ($p=0.053$). Detection of ctDNA after first-line therapy did not significantly correlate with PFS ($p=0.27$) and OS ($p=0.29$), and was not predictive of viable tumor or teratoma in the surgical specimen. **Conclusions:** This is the first study to use a tumor-naïve ctDNA test to assess outcomes in pts with TGCT. ctDNA detection before first-line therapy may serve as a valuable prognostic biomarker, complementing STM for pts with advanced TGCT. Further prospective studies are needed to validate our findings. Research Sponsor: Hospital Sírio-Libanês.

Initiation of high dose chemotherapy at rising tumor markers compared with radiographic progression in patients with relapsed germ-cell tumors (GCT).

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Background: Patients with GCT who relapse after first-line therapy can be cured with salvage high-dose chemotherapy (HDCT). We evaluate the outcomes of patients who received HDCT based on tumor maker rise only compared to radiographic progression only or both. **Methods:** The Indiana University Testicular Cancer database was queried for pts with GCT who were treated with salvage HDCT between 2004-2024. 2-yr progression free survival (PFS) and overall survival (OS) were analyzed among subgroups of patients who had tumor markers rise only (group 1) at start of HDCT compared to those who had radiological progression only or both (group 2). The Kaplan-Meier method was used to analyze PFS and OS. Comparisons between groups were done using the log-rank test. **Results:** 316 pts with GCT treated with salvage HDCT between March 2004 and May 2024 and had detailed information regarding progression leading to HDCT were included. Median age was 32.05 (16-70). Histology was non-seminoma in 237 (75.0%) pts and seminoma in 79 (25.0%) pts. Primary site was testis in 273 (86.4%) pts, retroperitoneum in 20 (6.3%) and mediastinum in 23 (7.3%). 156 (49.4%) pts had IGCCCG good risk disease at diagnosis, 28 (8.9%) had intermediate risk disease, and 132 (41.8%) had poor risk disease. 101 (32.0%) patients were platinum refractory at start of HDCT. HDCT was 2nd line therapy in 264 (83.5%) pts, 3rd line in 49 (15.5%), 4th line in 2 (0.6%) and 5th line in 1 (0.3%). At initiation of HDCT, 98 (31.0%) pts had tumor marker (AFP and/or hCG) rise only, 69 (21.8%) had radiographic progression only, and 149 (47.2%) had both. Median follow-up from start of HDCT was 3.67 years (0.03-19.5). For the overall population, 2-yr PFS was 62.4 with 95% CI (56.7-67.5) and 2-yr OS was 71.9 with 95% CI (66.3-76.8). 60 (59.4%) of patients in group 1 had platinum refractory disease compared to 41 (40.6%) in group 2. 2-yr PFS for group 1 was 44.8% (34.6-54.4%) vs 70.3% (63.6-76%) for group 2 ($P<0.001$). 2-yr OS was 58.8% (47.5-68.6%) for group 1 vs 77.4% (70.9-82.7%) for group 2 (P=0.001). **Conclusions:** Patients with relapsed GCT with rising tumor markers only at time of initiation of salvage HDCT had inferior 2-yr PFS and OS likely due to higher rates of platinum refractory disease in this population. Research Sponsor: None.

Treatment of poor-risk non seminomatous germ-cell tumors (NSGCT) adapted by tumor marker decline: A 7-year multicenter real-world experience.

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Background: Since 2014, adaptation of chemotherapy based on tumor marker decline after the cycle of BEP (Bleomycin, Etoposide, Cisplatin) is a standard for patients with IGCCCG poor-risk NSGCT based on data from the GETUG-13 phase 3 trial (Fizazi et al, Lancet Oncol 2014; J Clin Oncol 2024). The aim of this multicenter study was to evaluate the GETUG-13 algorithm when used in routine practice. **Methods:** We collected data from all poor-risk NSGCT patients treated consecutively in 13 expert centers from 2013 to 2019. After one cycle of BEP, tumor marker levels were assessed at day 18-21. Pts with a favorable decline continued with BEP for 3 additional cycles (Fav group), whereas those with an unfavorable decline received up to 4 cycles of dose-dense chemotherapy (Unfav group). Data was analysed descriptively, and the Kaplan-Meier method was used to estimate progression-free (PFS) and overall survival (OS). **Results:** Data from 146 patients were collected (46 with PS $\geq$ 2, 35 with mediastinal NSGCT): 111 (76%) had an Unfav decline and 35 (24%) had a Fav decline. More pts with hCG $>$ 50 000 UI/L and AFP $>$ 10 000 were in the Unfav group (44.9% vs 17.6%, p=0.0045, and 26.9% vs 8.8%, p=0.0282). Surgery of residual masses was performed in 85.7% and 74.3% in the Fav and Unfav groups, and the procedure was complete in 83.3% and 59%, respectively. With a median follow-up of 5.8 years (95% CI,63.2-77.2), 5-year PFS rates were 68.6% (95% CI, 50.5-81.2) and 61.1% (95% CI, 51.2-69.6) in the Fav and Unfav groups, respectively. Five-year OS rates were 73.8% (95% CI, 55.6-85.4) and 64.6% (95% CI, 54.6; 73.0), respectively. In the short term, neuropathy, anemia and thrombopenia were more frequent in the Unfav group. Treatment-related deaths were reported in 2 (5.7%) and 5 (4.5%) (including 2 post-surgery deaths) pts in the Fav and Unfav groups, respectively. Peripheral neuropathy evolved favorably, with 4 (5.9%), 2 (3.8%) and no pts in the Unfav group reporting grade 3 toxicity at 6 months, 1 year and at last follow-up, respectively. Long-term side effects were infrequent with only one pt with grade 3 cardiovascular toxicity in the Unfav group. Late grade 2 toxicities included cardiovascular toxicity (1.4%), hypoacousia (1.4%), peripheral neuropathy (4.2%), chronic renal failure (CRF) (9.9%) in the Unfav group, and grade 2 CRF (8.3%) in the Fav group. In both groups, almost 80% pts had returned to work. Among pts with progression or relapse, salvage high-dose chemotherapy with stem-cell transplant was used in 4/11 (36.4%) and 13/33 (43.3%) in the Fav and Unfav groups, respectively. **Conclusions:** The GETUG-13 algorithm can be safely used in routine practice by expert centers, with a high cure rate similar to that reported in the original phase 3 trial and rare long-term toxicity. This data confirms that this algorithm is standard for poor-risk NSGCT. Research Sponsor: None.

Predicting teratoma histology in postchemotherapy residual lesions of non-seminoma testicular cancer (NSTC) patients using integrated CT radiomics and circulating MicroRNAs modelling.

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Background: Chemotherapy is the primary treatment for metastatic NSTC, but patients often have residual masses afterward. Accurate non-invasive models are needed to predict the histology of these masses, guiding treatment and reserving surgery for those with teratoma. This study aims to enhance predictive accuracy by integrating CT-driven radiomics features with miRNAs 371 and 375 (miR371-375) to distinguish between teratoma and non-teratoma histologies in post-chemotherapy residual masses. **Methods:** We retrospectively reviewed 52 patients with teratoma (n=56), fibrosis/necrosis (n=34), vGCT (n=11), and seminoma (n=10) lesions, divided into training (N=78) and test (N=33) cohorts with equal class distribution. Lesions included lymph nodes (n=68 retroperitoneum, n=11 mediastinum, n=4 pelvic, n=4 neck), lung (n=21), and brain (n=3) with a median size of 1.6 cm (Q1-Q3 interval=1.2-2.73 cm). Using 3D Slicer version 5.6.1, metastatic masses >1 cm (short axis) were segmented and radiomics features were extracted from venous phase CT images. Plasma miR371 and miR375 levels were measured by RT-PCR before resection. Four machine learning models evaluated the predictive value of radiomics alone (R-only) and combined with miR371/miR375 levels for teratoma histology, and the best performer, Cat Boosting (CB) method, is reported. **Results:** The analysis of datasets revealed a consistent pattern of superior performance in training sets compared to test sets across all metrics. The CB model R+371+375 dataset demonstrated the most robust overall performance, with the highest AUC values (0.96 [95% CI 0.88-1.0] for training, 0.83 [95% CI 0.68-0.98] for test) and a well-balanced sensitivity (0.71) and specificity (0.76) in the test set for predicting teratoma histology. R+375 followed closely with an AUC of 0.82 (95% CI 0.66-0.97). **Conclusions:** Combining miR 371 and 375 with CT-driven radiomics features improves the accuracy of classifying teratoma histology in metastatic NSTCs. This method can help characterize teratoma in residual metastatic disease, aiding treatment decisions and minimizing under or over-treatment risks. Further refinement, including the integration of clinical features, will be reported. Research Sponsor: None.

Survival outcomes of patients with mNSGCTs with and without teratoma in the primary tumor: An international retrospective study.

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Background: Recent studies have reported conflicting findings on the outcomes of patients with metastatic nonseminomatous germ cell tumors (mNSGCT) and the presence of teratoma in the primary tumor. To further investigate this association, we conducted an analysis using data from a distinct multicenter hospital databases. **Methods:** Clinical-pathological data of mNSGCT patients whose primary tumors were available for histologic review and who underwent cisplatin based chemotherapy between 1992-2014 were retrospectively collected from the IRB approved Dana Farber Cancer Institute (DFCI), Vall D'Hebron University Hospital (VHIO), University Hospital Virgen Del Rocio (HUVR) and Instituto Nacional Cancerologia (INC), GCT databases. We stratified NSGCT patients by the presence or absence of teratoma in the primary tumor(T+ vs T-) Demographic, clinical and pathological characteristics were analyzed using X2 test for categorical variables and T test for continuous variables. Kaplan-Meier methods estimated survival. **Results:** A total of 662 patients were included with a median follow-up of 8 years. 305 (46.1%) patients had teratoma in the primary tumor. Median ages were 28,7 (+- 8,61) and 31,0 years (+- 9,19) in T+ in T- groups respectively. The T+ group was more likely to have a testicular primary (94,4% vs 86,3%, p=0.003). There were no major differences in IGCCCG risk between the two groups, T+ vs T-, good: 155 (50,8%) versus 190 (53.2%); intermediate: 75 (24,6%) versus 60 (16,8%); poor: 66 (21,6%) versus 87 (24,4%), p=0.041. First line chemotherapy consisted of bleomycin, etoposide and cisplatin (BEP) in 233 (76,4%) and 286 (80,1%) of each group. The T+ group had more post- chemotherapy retroperitoneal lymph node dissections and other local resections n=211, 69,2% (95% CI: 59% - 74%) compared to the T- group n=160, 44,8% (95% CI: 37%-50%). There was no significant diference in 10-year survival between T+ and T- patients 79% (95%CI: 77% - 89%) vs. 82% (95% CI: 80% - 91%), p= 0,976 (log-rank). **Conclusions:** The presence of teratoma in the primary tumor was not an adverse prognostic factor in a series of 662 patients with mNSGCT with a median follow-up of 8 years treated in the modern era with predominantly BEP. Longer follow-up beyond 10 years is needed to see if there is an increased incidence of teratoma related deaths in patients with T+. Research Sponsor: None.

5037 Poster Session

Bilateral germ cell tumor of the testis (TGCT): Implications for a stem cell versus genetic origin of cancers.

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Background: Bilateral TGCT provides a unique opportunity to elucidate a stem cell versus genetic origin of cancer. Comparison of the epigenetics and genetics of disparate tumors in either synchronous or metachronous bilateral TGCT from the same patients is feasible and may be informative. **Methods:** We examined the clinical characteristics and natural history of 38 patients with bilateral TGCT. We performed reduced representation bisulfite sequencing (RRBS) of FFPE DNA and whole exon sequencing (WES) of 9 of those patients whose tumor samples were available for the study. **Results:** From the database at MDACC, we identified 38 patients with bilateral TGCT, who underwent their first orchiectomy between January 1984 and April 2022 and the second between August 1997 and April 2022. Median follow-up was 134.2 months (IQR 69.5–222.1 months). Seven patients had synchronous, while 31 had metachronous bilateral TGCT. There were 13 bilateral seminomas, 14 bilateral nonseminomas, and 11 bilateral seminoma and nonseminoma. For those patients with metachronous bilateral TGCT, the median time between the two TGCT was 47.7 months (IQR 19.6–108.9). Out of approximately 20,000 genes investigated, 189 (<1%) had a detectable mutation in the 9 paired cases (n=18). A total of 8 genes were mutated in more than 1 sample, including KIT (n=4, 22%) and KRAS (n=6, 33%). Among the 4 bilateral TGCT showing a similar methylation profile in the RRBS analysis, the pattern of single nucleotide variants and type of specific genetic mutations were dissimilar between the right and left TGCT from the same patients in the WES study. Among the 5 bilateral TGCT that did not cluster in the RRBS study, there was differential methylation of the JUP and MAGE-A4 genes between the right and left TGCT from the same patients. **Conclusions:** The clinical course of our patients with synchronous and metachronous bilateral TGCT and the results of our RRBS and WES reaffirmed that a preponderance of TGCT was curable and suggested that epigenomic findings may supplement, if not complement, genomic data to elucidate a stem-cell versus genetic origin and nature of GCT and cancers in general. Research Sponsor: None.

Spatial transcriptional dynamics of CD74⁺ B cells in tertiary lymphoid structures and effects on immune evolution in penile squamous cell carcinoma.

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Background: Antitumor immunity has become a critical focus in improving Penile squamous cell carcinoma (PSCC) patient outcomes. Among various immune features, tertiary lymphoid structures (TLS) have emerged as crucial players in tumor immunity. Nevertheless, the specific role of B cells within TLS and their interaction with naive T cells in PSCC remain largely unclear. Therefore, this study aims to elucidate the role of CD74⁺ B cells in TLS and their impact on immune regulation in PSCC. **Methods:** Spatial transcriptomics produced 519,608 cellular profiles from tumor samples of 18 patients. Additionally, scRNA-seq on tissues from 21 patients yielded 150,540 cells. Bulk RNA-seq was performed on tissues from 55 patients. TLS were identified and visualized using the DBSCAN algorithm, which clusters B cells, T cells, and DCs. Survival analyses were conducted to examine the association between TLS density and patient outcomes. Moreover, immune activity and cell infiltration were assessed via AUCell and CIBERSORT, while pseudotime analysis was used to explore dynamic gene expression changes during cell development. Additionally, pathway enrichment analysis identified key signaling pathways, and intercellular signaling was analyzed through cell communication models. **Results:** TLS, accurately identified using the DBSCAN algorithm, were significantly associated with improved prognosis in PSCC patients (Internal cohort, n = 152, $P < 0.01$; External cohort, n=63, $P < 0.05$). The spatial distribution, a high density of B cells was observed within the TLS regions. Notably, CD74⁺ B cells were enriched within TLS, particularly during early developmental stages. Mapped the spatially in situ developmental trajectory of CD74⁺ B cells and uncovered the dynamic changes in gene expression throughout their maturation process, we observed that CD74⁺ B cells within the TLS of PSCC patients predominantly exhibited features of early developmental stages. In line with this, scRNA-seq data further validated these observations. These cells, through their HLA molecules, interacted with CD4/CD8 ligands on naive T cells, thereby activating critical transcription factors such as NFKB1, NFKB2, NFATC1, NFATC2, FOS, and RUNX1. This interaction ultimately amplified immune responses within the tumor microenvironment. Furthermore, patients with higher CD74⁺ B cell expression exhibited better responses to immunotherapy (pCR : $P < 0.01$and CR: $P < 0.01$) and underscoring the therapeutic relevance of these cells. **Conclusions:** By activating naive T cells through antigen presentation, CD74⁺ B cells within TLS significantly enhance local immune responses in PSCC. Thus, CD74⁺ B cells not only serve as a promising biomarker but also represent a potential therapeutic target, providing novel insights into the immunological mechanisms underlying PSCC progression and response to immunotherapy. Research Sponsor: Shenzhen Science and Technology Innovation Commission Outstanding Youth Basic Research Project; Shenzhen People's Hospital Clinical Scientist Cultivation Project.

Long-term outcomes of dynamic sentinel lymph node biopsy in clinically node-negative penile cancer.

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Background: Dynamic sentinel lymph node biopsy (DSLNB) has emerged as a viable alternative in management of clinically node-negative (cN0) penile cancers owing to the high morbidity associated with radical inguinal lymphadenectomy. However, data on efficacy of DSLNB in penile cancer is limited. This study analyses the long-term outcomes of DSLNB in patients with cN0 penile cancer. **Methods:** A retrospective analysis of patients who underwent DSLNB with dual technique (blue dye + radiocolloid) for cN0 penile cancer was done. Data was collected between 2010 to 2018 from a prospectively maintained database with a median follow up of 70.36 months (range - 4 to 150 months). Patients under all risk groups of the European Association of Urology (EAU) Risk Stratification were included. **Results:** The study included 168 consecutive patients who underwent DSLNB (307 groins). Glans penis was the commonest site of disease (92.9%). Partial penectomy was the most common type of surgery for the primary (72.1%). Median number of sentinel nodes identified was three. Based on the EUA risk stratification, 57.2% of the cases were in the high-risk group. Identification rate with dual technique DSLNB in our study was 98.5%. Clavien-Dindo score of 2 or more was seen in 3.57% of patients. A nodal recurrence was seen in 8 groins (8 patients) with a mean time to recurrence of 430 days (69 to 1355 days). This corresponds to a DSLNB false negative rate of 2.6% with median inguinal node recurrence-free survival of 74.4 months. **Conclusions:** In our institution, DSLNB was done with a false negative rate of 2.6% and an acceptable morbidity. The low rate of inguinal nodal recurrence shows the utility of SLNB in staging cN0 groins. By using DSLNB we have avoiding a potentially morbid inguinal dissection in 81.4% of patients with clinically node negative disease. Research Sponsor: None.

Dedicated resources for veteran clinical trial participation: The Prostate Cancer Analysis for Therapy Choice (PATCH) program.

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Background: The Veterans Affairs (VA) hospital system is the most extensive integrated healthcare system in the United States. It serves 9.1 million Veterans and has over 170 healthcare centers and 1,193 outpatient sites. Traditionally, clinical trial access has been limited at the VA. The Prostate Cancer Foundation (PCF) and the VA worked together to create the Precision Oncology Program for Cancer of Prostate (POPCaP) within the VA Healthcare System. By 2021, they had funded 21 Centers of Excellence. The program not only strived to bring cutting-edge clinical trials to Veterans but also sought to develop careers for VA investigators and encourage clinical trial participation by a more diverse group of men. **Methods:** PCF and VA-funded sites paid for genomic testing and established clinical trial infrastructure. PATCH developed centralized clinical trial resources- biostatistics, scientific advisory committees, and young investigator development meetings. PATCH also created a budget working group and hired a research nurse to help open complicated investigator-sponsored studies. POPCaP/PATCH provided two monthly meetings for investigators to discuss their research and for industry partners to review trials and drugs in the pipeline. Here, we report on the change in Veteran participation in clinical trials and the demographics of this population from December 2022 to October 2024. **Results:** Since the development of POPCaP/PATCH, Veteran participation in clinical research has rapidly increased from 100 to 400 men enrolled in clinical trials. The number of clinical trials increased from eight clinical trials to 21. Using an existing database containing genomic results, it enrolled patients in trials requiring specific genomic mutations (e.g., MSI-H, BRCA2). We efficiently screened patients for clinical trials, and more than half of those screened enrolled in trials (60%). Patients of different races and ethnicities participated- white 52.6%, black 36.1%, Hispanic/Latino 4.9%, Asian 2.2%, Native American 1.7%, unknown 2.5%. VA stations opened all phases of clinical trials. Through collaboration with other specialties, interventions included targeted oral therapies, immunotherapies, chemotherapies, radiation, and radiopharmaceuticals. **Conclusions:** The VA has dramatically increased clinical trial opportunities and participation over the past two years. We used VA databases of genomic results to enroll patients in studies with restrained eligibility requirements, such as the presence of microsatellite instability (3%). Sixty percent of patients screened for studies ultimately enrolled in those studies. The diversity of VA trials relative to other US prostate cancer trials makes the results of VA studies more generalizable to the US population. Research Sponsor: Prostate Cancer Foundation; Veterans' Affairs.

5041 Poster Session

Cardiovascular (CV) event risk in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide (ENZA) or abiraterone acetate (AA) in the United States (US).

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Background: Prior studies suggest that chemotherapy-naïve pts with mCRPC treated with AA have a higher CV event-related hospitalization risk than those treated with ENZA. To further explore this association, this real-world, comparative causal inference study used a large US dataset to assess CV event risk in chemotherapy-naïve pts with mCRPC who initiated treatment (Tx) with ENZA or AA and provide outcome data based on history of (h/o) CV disease (CVD). **Methods:** Using US Medicare fee-for-service claims (Jan 2010–Dec 2022), we identified chemotherapy-naïve pts aged ≥65 years with mCRPC who initiated ENZA or AA between Sep 2014 and May 2017. The primary endpoint was a 4-point major adverse CV event (MACE-4; composite of acute myocardial infarction [AMI], stroke, unstable angina/revascularization [UA/R], and heart failure). Atrial fibrillation (AFib), venous thromboembolism (VTE), and all-cause death were also analyzed. Groups were propensity score matched (PSM) to adjust for differences in pt characteristics, assessed using standardized mean difference (SMD). Cause-specific Cox proportional hazards models were used to comparethe risk of CV outcomes between intention-to-treat cohorts, with death as a competing event. Subgroup analyses were conducted based on h/o CVD. Sensitivity analysis was performed with a MACE-5 endpoint, defined as MACE-4 or CV-related death. **Results:** Of 6319 pts in the total study population (ENZA: 2934; AA: 3385), 2913 PSM pts were included from each group. The ENZA and AA cohorts had similar baseline characteristics even before PSM (SMD<0.1), with a mean (standard deviation) age of 78.8 (7.3) years; 76% of pts had prior CVD. Compared with pts on ENZA, pts on AA had a significantly higher risk of experiencing MACE-4—particularly UA/R—as well as a higher risk of AFib and VTE (Table). Similar results were found in the subgroup of pts with a h/o CVD and the sensitivity analyses. Additionally, pts on AA had a higher risk of all-cause death than pts on ENZA, regardless of CVD history (h/o CVD hazard ratio [HR]: 1.14, 95% confidence interval [CI]: 1.07–1.21, *P*=0.0001; no h/o CVD HR: 1.12, 95% CI: 1.01–1.26, *P*=0.036). **Conclusions:** This matched analysis of US Medicare beneficiaries showed an increased risk for MACE-4, AFib, and VTE in pts with mCRPC treated with AA compared to ENZA, in the overall pt population and pts with a h/o CVD. The risk of all-cause death was higher with AA in all pts. These findings provide insights into Tx decision-making for pts with mCRPC, especially those at high risk of CV events. Research Sponsor: Astellas Pharma Inc.; Pfizer Inc.

Outcomes	HR* (95% CI)	*P*-value
MACE-4	1.12 (1.02–1.24)	**0.028**
AMI	1.01 (0.76–1.32)	0.987
Stroke	0.92 (0.70–1.20)	0.505
UA/R	1.13 (1.01–1.26)	**0.041**
Heart failure	1.19 (0.90–1.58)	0.237
AFib	1.73 (1.31–2.29)	**0.0001**
VTE	1.37 (1.02–1.85)	**0.037**
All-cause death	1.13 (1.07–1.19)	**0.0001**

*ENZA = reference group.

A phase Ia/Ib study of talazoparib in combination with tazemetostat in metastatic castration-resistant prostate cancer (mCRPC).

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Background: Enhancer of zeste homolog 2 (EZH2) is frequently overexpressed in metastatic castration-resistant prostate cancer (mCRPC), and is linked to lineage plasticity and therapy resistance. In pre-clinical studies, EZH2 directly regulates DNA damage repair (DDR) gene expression, and inhibition of EZH2 sensitizes prostate cancer cells to genotoxic stress as induced by poly-ADP ribose polymerase (PARP) inhibition. Here we report results of a Phase 1a/1b study of the combination of the PARP inhibitor talazoparib (tala) with the EZH2 inhibitor tazemetostat (taz) in mCRPC. **Methods:** Eligible patients (pts) had progressive disease after at least one secondary hormonal therapy and taxane-based chemotherapy (or felt not to be more appropriate for taxane), disease evaluable for response (PSA $\geq$ 2 ng/ml or measurable disease by RECIST 1.1) and a metastatic lesion amenable to biopsy adequate for next generation sequencing. The starting dose level (DL 0) in Phase 1a was tala 0.75 mg QD + taz 600 mg BID with dose escalation/de-escalation of both agents by up to 2 dose levels based on a 3+3 design to define the recommended phase 2 dose (RP2D). In Phase 1b, an additional 20 pts were treated at the RP2D to assess preliminary safety and efficacy. **Results:** 12 pts were treated in Phase 1a, of whom 2 of 11 DLT-evaluable pts experienced DLT (both Grade 4 thrombocytopenia): 0 of 3 at DL 0, 1 of 6 at DL +1 (tala 0.75 mg QD + taz 800 mg BID), and 1 of 2 at DL +2 (tala 1 mg QD + taz 800 mg BID). The other pt treated at DL +2 experienced Grade 3 anemia requiring transfusion just outside the DLT period, so DL +1 was selected as the RP2D. 27 pts were treated at the RP2D: 7 in Phase 1a (1 of whom was replaced due to progression prior to completion of the DLT period) and 20 pts in Phase 1b. Median PSA at enrollment was 21.8 ng/ml (range 0-3287), and median number of prior treatments was 4 (range 1-10). Grade $\geq$3 treatment-related AEs were reported in 59% of pts (16/27), including thrombocytopenia (8/27, 29.6%), anemia (8/27, 29.6%), fatigue (4/27, 14.8%), neutropenia (3/27, 11.1%), lymphopenia (1/27, 3.7%), and hyperglycemia (1/27, 3.7%). 14 of 27 pts (51.8%) required dose reduction. Confirmed PSA50 response was seen in 3 of 23 PSA-evaluable pts (13.0%), and PSA30 in 4 of 23 (17.4%). 1 of 12 pts with measurable disease (8.3%) experienced unconfirmed radiographic response, and 6 of 27 pts (22.2%) remained on study treatment for $>$ 270 days. **Conclusions:** In a heavily pretreated biomarker-unselected population, the RP2D of talazoparib 0.75 mg daily and tazemetostat 800 mg BID was associated with expected myelosuppression but otherwise acceptable safety profile, with clinical benefit seen in a minority of patients. Companion blood and tissue-based correlative studies to characterize pharmacodynamic biomarkers of combined PARP+EZH2 inhibition and biomarkers of response and resistance are ongoing. Clinical trial information: NCT04846478. Research Sponsor: Pfizer; Prostate Cancer Foundation; Ipsen (drug only); National Cancer Institute; P50CA272390.

Does cytoplasmic AR-V7 circulating tumor cell (CTC) detection add utility in predicting AR pathway inhibitor benefit in men with mCRPC? A retrospective analysis of the PROPHECY study.

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Background: Androgen receptor splice variant-7 (AR-V7) is a constitutively active truncated protein that emerges during hormone therapy resistance in prostate cancer. We have shown that circulating tumor cell (CTC) AR-V7 nuclear localization is strongly associated with worse responses, PFS, and overall survival with AR pathway inhibitors (ARPIs) such as abiraterone or enzalutamide in the metastatic castration-resistant prostate cancer (mCRPC) setting. The measurement of cytoplasmic AR-V7, however, has unclear predictive value and we thus sought to determine whether an AR-V7-agnostic CTC scoring criterion would identify more patients with ARPI resistance as compared to nuclear AR-V7 in the PROPHECY study (NCT02269982). **Methods:** Blood samples were available from 110 of 118pre-ARPI mCRPC patients and evaluated for both nuclear and cytoplasmic CTC only AR-V7 detection utilizing Epic's CTC platform and associated with confirmed PSA50 response, overall survival (OS), and progression-free survival (PFS). We also assessed the correlation between AR overexpression and AR-V7 detection. The proportional hazards model was utilized to explore the prognostic significance of nuclear, cytoplasmic AR-V7 in predicting OS and PFS adjusting for Halabi clinical risk score and CellSearch CTCs≥5. **Results:** At baseline, 11/107 (10%) mCRPC samples had AR-V7 nuclear expression, 15/107 (14%) had cytoplasmic only AR-V7 detection, and thus 26/107 (24%) cases were CTC AR-V7 positive. All of the nuclear AR-V7 positive cases had AR overexpression, while only 67% of cytoplasmic AR-V7 positive cases exhibited AR overexpression. We observed a confirmed PSA50 in 0%, 13%, and 29.6% of nuclear V7+, cytoplasmic V7+, and V7- patients. See the table for PFS and OS outcomes. **Conclusions:** Cytoplasmic AR-V7 detection in CTCs is more prevalent than nuclear only scoring. Cytoplasmic AR-V7 positive cases appear to have worse PFS, PSA50, and OS as compared to AR-v7 negative cases. However, men with cytoplasmic only CTC AR-V7 detection were more likely to have post-ARPI short term PSA declines and improved overall survival, despite a similar poor PFS as compared to nuclear AR-V7 positive patients with mCRPC. Knowledge of both CTC nuclear and cytoplasmic AR-V7 status could be helpful for improved risk stratification of patients with mCRPC prior to ARPI therapy. Clinical trial information: NCT02269982. Research Sponsor: None.

N=107 baseline	Median (95% CI), months	Univariate HR (95%CI)	Multivariate HR (95%CI)
OS based on AR-V7 status			
Nuclear AR-V7	8.4 (7.0, NR)	3.6 (1.9, 7.0)	3.7 (1.7, 8.4)
Cytoplasmic AR-V7 only	14.7 (10.8, 27.3)	2.0 (1.1, 3.6)	1.2 (0.6, 2.5)
AR-V7 negative	21.8 (18.9, 29.2)	Reference	Reference
PFS based on AR-V7 status			
Nuclear AR-V7	3.7 (2.3, NR)	2.6 (1.4, 5.1)	2.9 (1.3, 6.2)
Cytoplasmic AR-V7 only	3.8 (2.7, 8.5)	2.2 (1.2, 3.9)	1.7 (0.8, 3.4)
AR-V7 negative	7.4 (5.5, 9.0)	Reference	Reference

Effect of HLA class I expression on the tumor immune microenvironment and prognosis in prostate cancer.

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Background: Human leukocyte antigen (HLA) class I comprises a family of peptide-binding proteins that regulate T-cell interactions. Here, we examined HLA class I mRNA expression and gene zygosity in prostate cancers (PCs), exploring associations with clinical outcomes, molecular features, and tumor microenvironment. **Methods:** We analyzed 10,790 PC samples, of which 8,040 (75%) contained HLA transcription data, and 2,792 (26%) contained HLA genotypes in the Caris Life Sciences database. Samples were stratified into HLA-high (>75th percentile) and -low (<25th percentile) groups. Genomic and transcriptomic alterations were compared at an adjusted significance level of 0.05. Immune cell fractions were inferred by quanTIseq. Overall survival was obtained from insurance claims data and computed using Cox proportional hazards. **Results:** Among 66 cancer types, PC ranked 2nd, 11th, and 19th lowest with respect to HLA-A, HLA-B, and HLA-C expression. In PC, genes related to AR signaling, immunoglobulins, and cell-surface antigens (CTLA4, PD-L1, TROP2, B7-H3, and PSMA) were significantly increased in HLA-high tumors. HLA-high status was associated with increased interferon-gamma scores and more cytotoxic and regulatory T cells, B cells, and NK cells. HLA-high tumors also exhibited a 2-fold depletion in CDK12 and AR/FOXA1 mutations but were enriched in tumor suppressor gene (RB1, PTEN) alterations. HLA-A high tumors exhibited increases in MSI-H/dMMR status (4.8% vs. 3.3% and 5.1% vs 3.1%, p=0.04 and 0.01), while dMMR was also increased in HLA-B high tumors (5.1% vs. 3.4%, p=0.03). HLA class I expression was generally lower in metastatic biopsies (Bx) compared to primary prostate Bx. Upon examining the zygosity of HLA alleles, metastatic Bx exhibited a higher proportion of homozygous HLA-B (7.2% vs. 5.1%, p=0.03) compared to prostate Bx. Last, worse overall survival was seen in prostate Bx that were high in HLA-A or HLA-B (HR = 1.36, 1.21, p<0.0001, 0.008) or metastatic Bx that were HLA-A high (HR = 1.18, p = 0.019). **Conclusions:** HLA class I expression is lower in PCs compared to other cancers, but elevated HLA class I levels correlate with immune cell activity, somatic alterations, and clinical outcomes. Unexpectedly, HLA-A and HLA-B high tumors portended shorter survival, perhaps due to significant enrichment of PTEN/RB1 alterations. Altogether, HLA status, immunogenicity, and tumor suppressor alterations should be considered in tandem when considering patient prognosis. Research Sponsor: University of Minnesota.

Updated prostate cancer risk groups by PSMA-PET PROMISE (PPP2): Results from an international multi-centre registry study.

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Background: We previously established prognostic two-tier risk nomograms based on PSMA-PET and Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria in a large single-centre cohort. Here, we validate three-tier risk stratification by PSMA-PET PROMISE (PPP2) in a large international multi-centre registry study for prostate cancer survival. **Methods:** We included prostate cancer patients who underwent PSMA-PET at 20 hospitals in EU, USA or Australia between 2013 and 2022. PSMA-PET was standardized by PROMISE version 2 (V2). Total lesion count, total tumour volume, PSMA expression score, and overall survival follow-up were obtained. Investigator sites were split 2:1 into development and validation cohorts, considering site characteristics. In the development cohort we assessed PPP predictors and created version 2 for visual and quantitative PPP nomograms (PPP2) based on Cox regression models with least absolute shrinkage and selection operator penalty for overall survival. Performance of both nomograms was measured in the validation cohort using Harrell´s C-index and calibration plots. Head-to-head comparison to the National Comprehensive Cancer Network (NCCN) risk score was examined by ROC-curves. **Results:** We analyzed 6128 male patients (4044 development and 2084 validation cohorts) across all disease stages with 1915 (31·2%) reported deaths and median follow-up of 4·8 years (IQR 3·4-6·4). Predictors in the visual PPP2 nomogram were presence of distant metastases (extrapelvic nodal metastases [M1a], bone metastases [M1b; oligometastatic, disseminated or diffuse marrow involvement], and visceral metastases [M1c]), PSMA expression score, and total lesion count. Predictors in the reassessed quantitative PPP2 nomogram were distant metastases (M1a, M1b, and M1c), total tumour volume, and PSMA expression score. C-indices (95% CI) in the validation cohort were 0·80 (0·78-0·82) for the visual and 0·80 (0·79-0·82) for the quantitative nomogram, respectively. In the validation cohort for three-tier stratification (high, intermediate, low risk), accuracy of both PPP2 nomograms was superior when compared to the NCCN risk score (n=1034, AUC 0·84 vs. 0·76; p<0·0001, respectively). Performance of both PPP2 nomograms was independent from radiopharmaceutical (68Ga vs. 18F) or PROMISE version (V1 vs. V2; n=2084, visual: both AUC 0·79, respectively, p=0·11; quantitative: both AUC 0·79, respectively, p=0·56). **Conclusions:** PSMA-PET PROMISE nomograms were improved in an international multi-centre study to accurately stratify high vs. intermediate vs. low risk for overall survival across all stages of prostate cancer. PPP2 yields superior accuracy compared to the NCCN risk score. Follow-up continues in the PROMISE Registry (NCT06320223, promise-pet.org). Research Sponsor: Prostate Cancer Foundation; Innovative Health Initiative Joint Undertaking; AstraZeneca.

Safety and pharmacokinetics of mevrometostat (M) in combination with enzalutamide (E) in patients with metastatic castration-resistant prostate cancer (mCRPC).

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Background: M is a potent and selective small molecule inhibitor of enhancer of zeste homolog 2 (EZH2). In the randomized dose-expansion part of a phase 1 study, M (1250 mg BID on an empty stomach) + E (160 mg QD) improved outcomes versus E alone, with a manageable safety profile in patients (pts) with mCRPC (NCT03460977). We report safety and pharmacokinetics for M at 875 mg with food + E from this study. **Methods:** This was an open-label, phase 1 dose escalation and dose expansion study. Pts with mCRPC who received prior treatment with abiraterone or E, with evidence of progression per modified Prostate Cancer Working Group 3 criteria were included. Pts received M (875 mg BID with food) + E (160 mg QD) + androgen deprivation therapy. Safety and pharmacokinetics of the food effect cohort were primary and secondary endpoints, respectively. **Results:** As of Nov 15, 2024, 29 pts received M at 875mg with food + E. Median (interquartile range [IQR]) duration of treatment was 5.5 (4.1–7.4) months. Overall, 28 (96.6%) pts experienced a treatment-emergent adverse event (TEAE; Table). The most common TEAEs of any grade related to M were diarrhea (41.4%), thrombocytopenia (41.4%), and dysgeusia (37.9%). Serious TEAEs related to M were reported in 3 (10.3%) pts (anemia, ECG QT prolonged, and hemorrhagic enterocolitis), all were grade 3. There were no grade 4 TEAEs. TEAEs led to withdrawal from M in 4 (13.8%) pts. One patient had a fatal event of osteonecrosis of the jaw (present at baseline) that was not considered related to M. Plasma exposures of M + E after multiple doses were comparable between M 1250 mg on an empty stomach (n=51) and M 875 mg with food (n=12) (geometric mean [coefficient of variation]: AUC_{tau}, h*ng/mL: 1250 mg, 8690 [54]; 875 mg, 8984 [48]; C_{max}, ng/mL:1250 mg, 2371 [54]; 875 mg, 1868 [85]). **Conclusions:** In pts with mCRPC treated with M + E, M 875 mg with food had an improved safety profile compared with M 1250 mg on an empty stomach. M 875 mg with food has similar plasma exposures to M 1250 mg on an empty stomach. M 875 mg with food + E was selected as the recommended dose for pivotal phase 3 studies. Clinical trial information: NCT03460977. Research Sponsor: This study is sponsored by Pfizer Inc. Enzalutamide for the study was provided by Astellas Pharma Inc. Editorial support was provided by Megan Christian, MBiolSci, and Rosie Henderson, MSc, of Onyx (a division of Prime, London, UK), funded by Pfizer Inc.

	M (875 mg with food) + E (n=29)		M (1250 mg on an empty stomach) + E (n=41)[†]	
n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	28 (96.6)	10 (34.5)	40 (97.6)	22 (53.7)
TEAE related to M	28 (96.6)	7 (24.1)	39 (95.1)	20 (48.8)
Serious AE	8 (27.6)	6 (20.7)	14 (34.1)	13 (31.7)
Most common TEAEs that occurred in ≥30% of pts[‡]				
Diarrhea	13 (44.8)	0	32 (78.0)	7 (17.1)
Thrombocytopenia	13 (44.8)	2 (6.9)	12 (29.3)	1 (2.4)
Dysgeusia	12 (41.4)	0	24 (58.5)	0
Decreased appetite	10 (34.5)	0	24 (58.5)	0
Nausea	9 (31.0)	0	17 (41.5)	0

[†]Data presented at ASCO-GU 2025. Data cut-off Sept 2, 2024. Median (IQR) duration of treatment: 7.6 (3.7–12.8) months.
[‡]For pts treated with M (875 mg with food) + E.

5047 Poster Session

Final overall survival (OS) with talazoparib (TALA) + enzalutamide (ENZA) as an initial treatment in unselected patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) in the China cohort of the phase 3 TALAPRO-2 trial.

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Background: In the China cohort of the TALAPRO-2 study, unselected pts with mCRPC who received TALA + ENZA had improved radiographic progression-free survival per BICR (rPFS; HR=0.30; 95% CI, 0.17–0.56; $P<0.0001$; data cutoff: Nov 15, 2023), consistent with the global population (HR=0.63; 95% CI, 0.51–0.78; $P<0.0001$; data cutoff: Aug 16, 2022). In final prespecified analyses, TALA + ENZA significantly improved OS vs PBO + ENZA in the global population. Here we report final OS, a descriptive update of rPFS, and an extended follow-up of secondary outcomes in the China cohort. **Methods:** The China cohort includes pts from the unselected cohort 1 of TALAPRO-2 and China extension (unselected homologous recombination repair [HRR] gene status). Pts had asymptomatic/mildly symptomatic mCRPC, received ongoing androgen deprivation therapy, and were prospectively tested for HRR alterations in tumor tissue. Pts were randomized 1:1 to TALA 0.5 mg/day (moderate renal impairment 0.35 mg/day) or placebo (PBO); all pts received ENZA 160 mg/day. Primary endpoint was rPFS by BICR. OS was a key secondary endpoint. Other secondary endpoints included BICR-assessed objective response rate (ORR), time to prostate-specific antigen (PSA) progression, safety, and pt-reported outcomes. All reported P values are 2-sided. **Results:** Overall, 125 pts were randomized (TALA + ENZA, 63; PBO + ENZA, 62). At data cutoff (Sep 3, 2024; median follow-up, 33.2 mo in both arms) 35 pts (56%) in the TALA + ENZA arm and 41 pts (66%) in the PBO + ENZA arm had died. Clinically meaningful benefit in OS with TALA + ENZA vs PBO + ENZA was observed: HR=0.591 (95% CI, 0.369–0.944; $P=0.0262$); median OS (95% CI), 36.9 mo (21.7–42.4) vs 24.1 mo (16.8–30.5), respectively. Updated rPFS by BICR continued to favor TALA + ENZA vs PBO + ENZA (HR=0.312; 95% CI, 0.173–0.561; $P<0.0001$, median rPFS, 33.3 vs 10.5 mo, respectively). TALA + ENZA was favored vs PBO + ENZA in ORR by BICR (50% vs 32%, respectively; $P=0.2845$) and time to PSA progression (HR=0.540; 95% CI, 0.298–0.976; $P=0.0411$). Consistent with global and China cohort primary results, the most common grade ≥3 treatment-emergent adverse events (TEAEs) with TALA + ENZA were anemia (57%) and neutropenia (32%). TEAEs were generally manageable; 14 pts (22%) discontinued TALA due to TEAEs. No clinically meaningful between-arm differences were observed in global health status/quality of life (QoL) measured by EORTC QLQ-C30, except for role functioning, which favored TALA + ENZA. **Conclusions:** At extended follow-up, initial treatment with TALA + ENZA resulted in clinically meaningful improvement in OS, rPFS by BICR, and secondary efficacy endpoints vs PBO + ENZA in unselected pts with mCRPC in the TALAPRO-2 China cohort. No new safety signals were identified; QoL was maintained. Clinical trial information: NCT03395197. Research Sponsor: Pfizer.

Long-term safety of radium-223 (Ra-223) in metastatic castration-resistant prostate cancer (mCRPC): 7-year follow-up from the largest global prospective study.

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Background: Ra-223, an alpha-emitting radionuclide, is the first agent of its kind approved for the treatment of mCRPC. Although a pivotal phase 3 study evaluated its short-term safety, there is a need to investigate its long-term safety. The REASSURE study prospectively examined the long-term safety of Ra-223, including secondary primary malignancies (SPMs), in a large patient (pt) population enrolled across Europe, the United States, Israel, and Latin America. **Methods:** We report final analyses (data cut-off Oct 24, 2024) of REASSURE (NCT02141438), a global, noninterventional study (enrolment 2014–2017). Primary outcomes were the incidence of SPMs, short- (30 days) and long-term (7 years) safety events, and bone marrow suppression (BMS) management in pts who had ≥1 Ra-223 dose. Secondary outcomes included overall survival (OS). **Results:** Analyses included 1472 pts; median follow-up was 17 months (range 0.3–95.4). Median age was 73 years and 80% of pts had an ECOG PS of 0/1. In evaluable pts, median alkaline phosphatase, prostate-specific antigen, and lactate dehydrogenase levels were 133 U/L, 59 ng/mL, and 266 U/L, respectively. Overall, 81% of pts had bone-only metastases at baseline; 19% of pts had metastases in the bone plus other sites (mostly lymph nodes). Prior treatments included abiraterone (48% of pts), enzalutamide (39%), docetaxel (39%), and cabazitaxel (9%). Pts received a median of 6 Ra-223 doses; 67% received ≥5 doses. SPMs occurred in 2% of pts (25 SPMs in 24 pts). Of these pts, 16 (67%) and 1 (4%) had received prior or concomitant radiotherapy, respectively. Overall, 3% of pts had drug-related serious adverse events >30 days after completing Ra-223. Fractures were reported in 10% of pts and were less common in pts with (7% of 605) than without (12% of 867) concomitant BHA use. During Ra-223 and up to 30 days after the last dose, there was no notable difference in the incidence of abnormal platelet counts between pts with (3%) or without (2%) prior chemotherapy; similar findings were seen for abnormal neutrophil counts (5% and 5%, respectively). BMS treatments, assessed from the start of Ra-223, were more common in pts who had received prior taxanes (38%) than in those who had not (26%). The most common life-prolonging therapies received after Ra-223 were docetaxel (18%), enzalutamide (15%), abiraterone (11%), and cabazitaxel (11%). Median OS was 15.6 months (95% CI, 14.6, 16.4); pt subgroups that survived the longest will be characterized and presented. **Conclusions:** This real-world safety analysis of pts with mCRPC is the longest follow-up of a radiopharmaceutical reported to date and supports the well-established favorable safety profile of Ra-223. The incidence of SPMs was low. The rate of fracture was low, especially in the presence of BHAs. Prior taxane chemotherapy use had no impact on hematological toxicity. Clinical trial information: NCT02141438. Research Sponsor: Bayer.

Uptake of targeted therapy in a large cohort of patients with advanced prostate cancer and germline pathogenic variants.

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Background: Men with advanced prostate cancer (PrCa) and pathogenic germline variants (PGV) in homologous recombination repair (HRR) or mismatch repair (MMR) genes are eligible for targeted therapies, namely poly (ADP-ribose) polymerase inhibitors (PARPi), platinum chemotherapy, or immune checkpoint inhibitors (ICI). The influence of these PGV on uptake of targeted therapies is understudied and necessary to identify and intervene upon possible disparities. We describe PrCa targeted treatment patterns in men with advanced PrCa. **Methods:** Germline genetic testing (GGT) (Labcorp) and insurance claims data (Komodo Healthcare MapTM) were assembled for advanced PrCa (defined by ICD10/CPT codes) patients diagnosed from 2015-2024 with ≥ 1 year of claims pre-diagnosis. Treatment uptake by GGT result were compared with $X2$ tests (negative/variant of uncertain significance (VUS), vs HRR/MMR PGV) and multivariable logistic regression (negative/VUS vs *BRCA1/BRCA2*, other HRR/MMR PGV) (Table). **Results:** 11,545 men with advanced PrCa underwent GGT: 66% White, 50% commercial insurance, 27% PrCa family history, mean age at diagnosis: 65. 924 (8%) and 145 (1%) of men had ≥1 PGV in a HRR or MMR gene, respectively. 1,246 (11%) men received platinum chemotherapy, 332 (3%) received PARPi and 521 (5%) received ICI. Men with HRR PGV were more likely than men with VUS/negative results to receive platinum chemo (14% vs. 11%, p=0.001) and PARPi (16% HRR, 25% *BRCA1/2* vs. 2%, p<0.001 for both) and men with MMR PGV were more likely to receive ICI (19% vs. 4%, p<0.001). Black men had lower odds of platinum chemo and ICI than White men, but higher odds of PARPi . Among men with HRR PGV, Black men and those with *BRCA1/2* PGV were more likely to receive PARPi (Table). **Conclusions:** Less than 1 in 4 men with advanced PrCa and HRR/MMR PGV received appropriate targeted therapies. PARPi uptake among eligible patients was twice as high among Black men compared to White men, perhaps reflecting clinician perception of more aggressive disease; rates of platinum chemo and ICI were not similarly higher. These findings raise questions about appropriate receipt of targeted agents and future studies should qualitatively assess clinician prescribing patterns, including sequencing of therapies as approvals for first line PARPi expand.
Research Sponsor: None.

Multivariable analysis of factors associated (p<0.05) with targeted therapy uptake.

	Platinum chemo OR (CI)	ICI OR (CI)	PARPi OR (CI)	PARPi (HRR PGV only) OR (CI)
History of non-prostate cancer	12 (10-14)	12 (9-16)	1.4 (1-2)	NS
Positive GGT result		**(ref: negative/VUS)**		**(ref: other HRR)**
BRCA1/BRCA2	NS	NA	18 (14-24)	4 (3-6)
Other HRR	NS	NA	5 (3-7)	NA
MMR	NA	3 (2-5)	NA	NA
Black race/ethnicity (ref: White)	0.7 (0.6-0.9)	0.4 (0.3-0.7)	1.9 (1-3)	2 (1-4)

OR, odds ratio; CI, 95% confidence interval; NA, not applicable; NS, not significant.
NS factors not shown: insurance, age at diagnosis, age2, family history of PrCa, geographic region.

Molecular and clinical characterization of KLK2 mRNA expression in prostate cancer (PC).

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Background: KLK2 is an androgen-regulated gene that plays a critical role in PC biology. Given the development of KLK-2 targeted therapies, we sought to characterize the molecular and clinical features associated with KLK2 mRNA expression in PC. **Methods:** NextGen sequencing of DNA (592-gene/whole exome) and RNA (whole transcriptome) was performed on PC specimens (n=6,978) at Caris Life Sciences. KLK2-High/Low expression was defined as $>75^{th}$ /$<25^{th}$ quartile RNA transcripts per million (TPM). Castrate resistant PC (CRPC) and hormone sensitive PC (HSPC) were defined based on androgen deprivation therapy (ADT) duration prior to tissue collection: HSPC $<$ 3 and CRPC $\geq$ 3 months from ADT start. Overall survival (OS) was defined as the time of collection or first androgen receptor pathway inhibitor (ARPI) to death/last follow-up. **Results:** Specimens were derived from primary prostate (n=4,464, 64.0%), lymph nodes (n=828, 11.9%) or other metastatic sites (n=1,686, 24.2%). Higher KLK2 was observed in tumors from Black vs. White patients (8.88 vs. 8.75 $\log_2$[TPM+1], p$<$0.001). KLK2 was enriched in adenocarcinoma vs. mixed vs. NEPC (8.79 vs. 7.58 vs. 0.33 $\log_2$[TPM+1], p$<$0.001). Relative to primary tumors (8.93 $\log_2$[TPM+1]), KLK2 varied by metastatic site, with lowest expression in GI (7.46 Log_2[TPM+1], p$<$0.001), liver (7.88 $\log_2$[TPM+1], p$<$0.001), and CNS (8.25 $\log_2$[TPM+1], p$<$0.001). In primary tumors, high KLK2 associated positively with *SPOP* and negatively with *PI3K/PTEN*, *TP53*, and *RB1* alterations. Across primary, lymph node, and distant metastatic tumors, high KLK2 associated positively with AR signaling and negatively with NEPC signaling (all p$<$0.001). KLK2 strongly correlated with KLK3 (PSA) expression (R=0.87). KLK2 expression was higher in HSPC (n=1504) vs. CRPC (n=4519) tumors (1.78 Log_2[TPM+1], p$<$0.001). Among HSPC, KLK2-high tumors had decreased *TP53*, *RB1*, *AKT1*, *BRCA1* and increased *SPOP*, *CTNNB1*, *PTEN*, *BRCA2* mutations. CRPC tumors with high KLK2 had decreased *RB1*, *TP53*, *PIK3CA* and increased *RAD54L* and *ATM* mutations compared to low tumors. High KLK2 was associated with improved OS from collection time (median 69.7 vs. 35.9 months, p$<$0.001) and first ARPI initiation (median 48.9 vs. 39.5 months, p$<$0.001). KLK2-high HSPC and CRPC tumors had improved OS compared to low tumors (median 82.0 HSPC KLK2-high vs. 54.3 HSPC KLK2-low vs. 23.7 CRPC KLK2-high vs. 16.3 CRPC KLK2-low months, q$<$0.01). The combination of KLK2-high/AR-high was associated with increased OS compared to KLK2-high/AR-low, KLK2-low/AR-high, and KLK2-low/AR-low tumors (median 70.8 vs. 48.8 vs. 43.5 vs. 20.8 months, respectively, p$<$0.001). **Conclusions:** This large-scale clinic-genomic analysis reveals distinct patterns of KLK2 expression in PC. The correlation between high KLK2 expression, favorable genomic features, and improved OS supports its potential utility as a prognostic biomarker and may inform selection for KLK2-directed therapy. Research Sponsor: None.

5051 Poster Session

Promising early results of MHB088C (B7-H3 ADC) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) from a phase 1/2 multicenter study.

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Background: MHB088C is a novel B7-H3-targeted antibody-drug conjugate (ADC) incorporating the potent SuperTopoi payload, which is 5 to 10 times more potent than Dxd. Early data from an ongoing phase 1/2 study have shown that MHB088C is generally well tolerated, with early signs of clinical activity (ASCO 2024, abstract #3012). Here, we present preliminary findings from the subset of pts with mCRPC. **Methods:** This study consisted of 2 parts: dose-escalation (part 1) and expansion (part 2). Part 1 evaluated the safety and tolerability of MHB088C at doses ranging from 0.8 to 4.0 mg/kg, administered intravenously every 2 (Q2W) or 3 weeks (Q3W). Part 2 explored multiple doses to assess safety and prospective efficacy of MHB088C in selected tumor types, including mCRPC. **Results:** As of January 3, 2024, 36 pts with mCRPC were enrolled and received at least one dose of MHB088C (1.6~2.4 mg/kg, n=35; 3.0 mg/kg, n=1). The median age was 69 years (range: 51-83) and all pts had an ECOG performance status ≤1. These pts were heavily pretreated, with 100% having received novel androgen axis drugs (NAAD) and 80% having received docetaxel. The objective response rate (ORR) was 14.3%, and the disease control rate (DCR) was 95.2% in pts with measurable disease (n=21). At data cutoff, 19 pts (52.8%) remained on the treatment. Six-month radiographic progression-free survival (rPFS) was 87%. Preliminary data also indicate improvements in prostate-specific antigen (PSA) levels. Safety data were consistent with previous reports. The most common grade≥3 treatment-related adverse events were neutropenia (24.2%), platelet count decreased (11.1%) and anemia (15.2%). **Conclusions:** MHB088C demonstrated a manageable safety profile and promising anti-tumor activity in heavily pretreated pts with mCRPC. The preliminary safety and efficacy data are encouraging and warrant further investigation. Clinical trial information: CTR20231298. Research Sponsor: None.

Evaluating the prognostic utility of cell-free (cf)DNA tumor fraction (TF) in metastatic castration-resistant prostate cancer (mCRPC).

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Background: Accurate prognostication is essential for guiding treatment decisions. cfDNA TF provides a non-invasive quantitative assessment of tumor burden without the need for tissue biopsies, which are notoriously challenging to obtain in mCRPC patients. This study evaluates the utility of cfDNA TF as a prognostic biomarker in mCRPC. **Methods:** Patients treated for mCRPC at the Dana-Farber Cancer Institute with available plasma were identified. Plasma samples underwent (epi)genomic profiling using the Guardant360 platform. TF was estimated by normalizing cancer-specific differentially methylated regions with appropriately matched control regions within each sample. The association of TF with clinical prognostic biomarkers and overall survival (OS) from the time of plasma collection was assessed. Survival analysis was performed using cox proportional hazards methodology, continuous variables were compared using Mann-Whitney test, and linear correlations were calculated using Pearson correlation coefficient. Decision tree (DT) models were developed to evaluate the benefit of incorporating clinical prognostic biomarkers with TF in predicting OS at 12 months. A 70/30 split was used to separate the training and testing cohorts and hyper-parameters were optimized for the F1 score (harmonic mean of precision and recall). **Results:** A total of 103 patients with mCRPC were identified (median age at plasma collection: 72; median prior lines of therapy: 3; median mTF: 3.7%). 36%, 34%, and 30% of patients had TF <1%, 1-10%, and >=10% respectively. Compared to patients with TF <1% (median OS: 28 months), OS was significantly shorter among patients with TF 1-10% (median: 16 months; HR=2.6, p=.00032) and >=10% (median: 10 months; HR=7.8, p=6.0x10-12). TF was significantly correlated with max variant allele frequency (mVAF) (rho=0.79 ,p=2.1x10-23), a traditional genomic-based cfDNA measure of tumor burden; however, on multivariable analysis, only TF (HR=5.8,p=2.8x10-9), and not mVAF (HR=0.97,p=0.95), was independently associated with worse OS. Elevated TF was associated with known poor-risk disease features, including visceral metastases, higher ECOG scores, and elevated serum markers (alkaline phosphatase, PSA, LDH). Multivariable analysis identified TF > median as the strongest negatively prognostic marker for OS (HR=3.5,p=.00029). TF alone demonstrated comparable predictive accuracy for 12-month OS (F1: 0.72) to a model including all clinical prognostic markers plus TF (F1: 0.72). Decision tree models identified an optimal TF cutoff of 5.6%, with 88% (53/60) of patients with TF <5.6% alive at 12 months, compared to 36% (11/42) for those with TF ≥5.6%. **Conclusions:** Our findings suggest that methylated tumor fraction is a robust independent non-invasive prognostic biomarker in mCRPC, outperforming traditional clinical markers and genomic metrics. Future studies should explore the integration of TF into standard prognostic workflows and its potential to guide therapeutic decisions. Research Sponsor: None.

Real world outcomes for patients with metastatic castration resistant prostate cancer (mCRPC) and *AR* T878A alterations treated with enzalutamide.

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Background: Androgen receptor (AR) antagonists such as enzalutamide (enza) are standard therapy for mCRPC. *AR* alterations such as amplification (amp) and ligand binding domain (LBD) point mutations (PMs) can cause resistance to hormonal therapies such as enza. The most prevalent *AR* PMs are T878A and L702H. Preclinical evidence suggests that *AR* T878A retains sensitivity to enza compared to *AR* L702H which confers resistance by increasing activation by glucocorticoids. Clinical data evaluating the efficacy of enza in patients with these AR PMs is limited. Here, we analyzed real world data from patients with *AR* T878A compared to *AR* L702H, *AR* amp, or no detected *AR* mutations (*AR* no alt), as identified by circulating tumor DNA (ctDNA), to assess enza efficacy in patients with *AR* T878A versus *AR* L702H. **Methods:** We used GuardantINFORM, a real-world database that combines genomic data from deidentified patients tested via ctDNA with clinical data taken from commercial-payer health claims. Adult mCRPC patients treated with enza who had baseline ctDNA testing and at least 2 claims post ctDNA testing were included. Patients with ≥2 *AR* PMs were excluded. Matched cohorts were used to assess real-world overall survival (rwOS), time to treatment discontinuation (rwTTD), and time to next treatment (rwTTNT). Propensity score matching was conducted using age and NCI comorbidity index, race, ethnicity, testing location, and enzalutamide line-of-therapy, and was evaluated using Wilcoxon tests. **Results:** 1,316 mCRPC patients met inclusion criteria. 59 had *AR* T878A, 56 had *AR* L702H, 231 had *AR* amp, and 970 had *AR* no alt. T878A was compared to L702H, amp, and no alt. Patients with T878A demonstrated significantly improved rwTTD (median 8.0 vs 3.5 mo, P=0.001) and rwTTNT (median 15.8 vs 4.3 mo, P=0.003), but not significantly different rwOS (19.1 vs 13.6 mo, P=0.066) relative to L702H. Patients with T878A demonstrated significantly improved rwTTD (7.7 vs 4.8 mo, P=0.022), but not statistically improved rwTTNT (10.4 vs 6.4 mo, P=0.059) or rwOS (20.2 vs 14.9 mo, P=0.14) relative to *AR* amp. Patients with T878A demonstrated significantly shorter rwOS (median 19.2 vs 43.6 mo, P=0.03), but no difference in rwTTD (7.7 vs 7.8 mo, P=0.88) or rwTTNT (10.4 vs 14.4 mo, P=0.423) relative to *AR* no alt. **Conclusions:** To our knowledge, this is the largest study assessing outcomes of mCRPC patients with *AR* PMs subsequently treated with enza. Using real-world evidence, we show that *AR* T878A patients have longer time on therapy with enza relative to patients with *AR* L702H. rwOS following enza was numerically longer for T878A versus L702H. These findings suggests that *AR* T878A is relatively more sensitive to enza compared to other resistance mutations. Future work in larger prospective cohorts comparing hormonal treatments in *AR*-altered patients will help confirm the clinical significance of different *AR* alterations. Research Sponsor: None.

'One button push' fully automated PSMA PET quantification: Correlation with progression free and overall survival in patients undergoing [^{177}Lu] Lu PSMA therapy for metastatic castrate resistant prostate cancer.

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Background: [^{177}Lu]Lu-PSMA is an effective treatment in metastatic castrate-resistant prostate cancer (mCRPC). Whole body standardized uptake value (SUV)mean and total tumor volume (PSMA-TTV) are valuable screening biomarkers for ^{177}Lu-PSMA therapy but require labour intensive semi-quantitative software. This study aims to compare PSMA SUVmean, and PSMA-TTV from fully automated and semi-automated methods of PSMA-PET quantification for predictive and prognostic capability. **Methods:** Datasets of participants (pts) from ethics approved trials with mCRPC post androgen receptor signaling inhibition and post taxane (or unfit for taxane), treated with [^{177}Lu]Lu-PSMA with a prior screening ^{68}Ga-PSMA-11 PET/CT, and outcome data including PSA progression-free (PSA-PFS) and overall survival (OS) were included. Screening ^{68}Ga-PSMA-11 PET/CT of participants were quantified using MIM LesionID Pro to derive SUVmean and PSMA-TTV with a fully automated quantification process (Method A) and semi-automated quantification adjusted manually for error (Method B). Both methods utilised software that segmented all lesions above SUVmax 3 and a CT-based deep learning method to identify normal organs for automatic physiological uptake removal. SUVmean and PSMA-TTV were evaluated in quartiles. Associations between SUVmean and PSMA-TTV above and below the 75th percentile (Q4 vs Q1-3) were examined with Kaplan Meier estimates and log-rank tests. **Results:** Data from 139 pts were analysed, median age 72 years (IQR: 67–77) and median PSA 94 ng/ml (IQR: 34–325). The median time to PSA-PFS (120 events) 5.5 months (95%CI:4–6.0) and OS (82 events) 13.5 months (95%CI:11– 18). With method A (fully automated), SUVmean Q4 was 9.7 and PSMA -TTV Q4 was 1156ml. The corresponding results with method B (manually adjusted) were SUVmean Q4 9.9 and PSMA-TTV Q4 1203ml. Withmethod A, median PSA-PFS for SUVmean Q1-3 was 4.5 (95%CI:3–6) vs 7 months (mo) (95%CI:5–11) for SUVmean Q4 (p=0.003). Median OS for SUVmean Q1-3 was 12.0 (95%CI:10–6) vs 20 mo (95%CI:12.0–NE) for SUVmean Q4 (p=0.011). For PSMA-TTV Q4 vs Q1-3, median OS was 8.5 (95%CI:7 –12.0) vs 18 mo (95%CI: 13–20) (p<0.001). With method B, median PSA-PFS for SUVmean Q1-3 was 4.5 (95%CI:3– 6) vs 7.5 mo (95%CI:5–11) for SUVmean Q4 (p=0.002). Median OS for SUVmean Q1-3 was 13 (95%CI:10–17) vs 20 mo (95%CI:11 – NE) for SUVmean Q4 (p=0.03). For PSMA-TTV Q4 vs Q1-3, median OS was 8.5 (95%CI:7–12) vs 18 mo (95%CI:13 – 20) (p<0.001). **Conclusions:** PSMA SUVmean and PSMA-TTV with a fully automated quantification method predicted both PSA-PFS and OS in patients undergoing [^{177}Lu]Lu-PSMA therapy. Fully automated vs manually adjusted predictive capability was not different. This is an important step in moving PSMA-PET quantitative biomarkers from research tool to routine clinical care. Research Sponsor: None.

First-in-human study of ^{177}Lu-JH020002 in patients with metastatic castration-resistant prostate cancer.

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Background: ^{177}Lu-JH020002 is a novel radioligand therapy that delivers beta-particle radiation to PSMA-expressing tumor cells and the surrounding microenvironment, demonstrating high affinity and antitumor activity in preclinical studies. JH020002-01C is an ongoing, multicenter, open-label phase I/II study investigating the safety, tolerability, pharmacokinetics, dosimetry and preliminary antitumor activity of ^{177}Lu-JH020002 in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). Here, we reported the preliminary safety and efficacy results of phase I. **Methods:** Eligible pts for phase I had mCRPC, were refractory to or had progressed following at least one androgen receptor pathway inhibitor (ARPI) and chemotherapy, and had at least one PSMA-positive tumoral lesion (PET imaging). Pts received an intravenous dose of ^{177}Lu-JH020002 at the beginning of each 6-week cycle, up to a maximum of 6 cycles. Dose escalation and determination of the maximum tolerated dose (MTD) in phase I were based on an accelerated titration and 3+3 dose-escalation design, including 5 dose cohorts. The primary objective of phase I is to evaluate the safety and tolerability of ^{177}Lu-JH020002 and determine the recommended phase 2 dose. Secondary objectives are dosimetry, pharmacokinetics, efficacy and safety. Tumor response is assessed per PCWG3 criteria. **Results:** As of Jan 22, 2025, 12 pts received ^{177}Lu-JH020002 with a median cumulative dose of 18.06 GBq. 91.7% pts with bone, 33.3% nodal, 8.3% peritoneal metastases. 100% with ≥1 prior ARPI therapy, 50% ≥ 1 prior chemo regimen, 16.7% ^{223}Ra, 33.3% PARPi. No DLT was reported and MTD was not reached. The most common treatment related adverse events (TRAEs) were Grade1-2. No grade 4/5 AEs were reported. TRAEs of note were hematologic TRAEs, including lymphocyte count decreased (91.7%), platelet count decreased (50.0%), anaemia (66.7%) and white blood cell count decreased (16.7%). With follow-up ongoing, across cohorts 2-5, 63.6% with ≥ 50% PSA decline; 27.3% with ≥ 90% PSA decline. Seven pts were evaluated per PCWG3. None of them had progressive disease, and all of them remain under treatment follow-up. Among all pts, 1 was with measurable disease and had a partial response. **Conclusions:** ^{177}Lu-JH020002 exhibited excellent antitumor activity in heavily pre-treated pts with mCRPC. Toxicity was well tolerated and generally manageable. Further clinical trials are under planning. Clinical trial information: NCT06139575. Research Sponsor: Bivision Pharmaceuticals, Inc.

Exposure and clinical activity (cohorts 2~5, at doses ≥ 3.70 GBq).

Parameter, median (range) or n (%)	3.70 GBq	5.90 GBq	7.40 GBq	8.88 GBq	Total
No. of patients	2	3	3	3	11
Cumulative dose (GBq)	11.20 (4.2-18.2)	24.58 (5.4-35.2)	22.8 (22.1-29.1)	17.29 (17.28-17.9)	18.21 (4.2-35.2)
PSA decline	2 (100)	2 (66.7)	3 (100)	2 (66.7)	9 (81.8)
≥ 50% PSA decline	1 (50)	2 (66.7)	2 (66.7)	2 (66.7)	7 (63.6)

Substudy C of the Canadian cancer trials group (CCTG) IND.234: PC_BETS (Prostate Cancer Biomarker Enrichment and Treatment Selection)—A phase II study of darolutamide (DARO) selected by androgen-receptor (AR) circulating tumor DNA (ctDNA) in patients (PTS) with metastatic castration-resistant prostate cancer (mCRPC) after prior AR pathway inhibitors (ARPIs).

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Background: DARO is a unique AR antagonist, with preclinical studies suggesting activity in mCRPC models resistant to abiraterone or enzalutamide due to *AR* amplification (amp) or ligand binding domain mutations. In this substudy (SS) of the (PC-BETS) master protocol, we explored DARO in ARPI-resistant mCRPC stratified by ctDNA *AR* status. **Methods:** Pts had mCRPC, ECOG PS 0–1, evaluable disease, biochemical or radiographic progression, prior ARPI, and no cytotoxic chemotherapy in mCRPC. Genomic screening tested plasma cell-free DNA and matched leukocyte DNA via targeted sequencing with a prostate cancer panel including the *AR* exons, introns, and flank. Only patients with evidence of ctDNA ≥1% were eligible. Pts were assigned to SS by molecular tumor board if biomarker (BM)+; otherwise, BM- pts were randomized to BM- SS. SS-C tested DARO 600mg od in three cohorts—AR amp (C1), AR mutation (C2), or BM- (C3) in a 2-stage design. Primary endpoint was clinical benefit rate (CBR), defined by PSA50 response, RECIST CR/PR, or SD ≥12 weeks. **Results:** PC-BETS Arm C opened in Jan 2018 and closed Feb 2024; 72 pts were enrolled: 27, 26, and 19 in C1, C2, and C3, respectively. Median age was 74 y (53–88), 100% ECOG PS 0-1. Sixteen pts (22%) had docetaxel for hormone-sensitive disease and none for mCRPC. Prior ARPI were abiraterone (31/72, 43%), enzalutamide (37/72, 51%), or apalutamide (4/72, 6%). Pts had bone (67/72, 93%), lung (9/72, 13%), and/or liver (5/72, 7%) metastases. Baseline PSA was 2–20 in 13/72 (18%), 20–100 in 32/72 (44%) or >100 in 27/72 (38%). CBR was more frequent in AR amp or mutated cohorts than BM– (Table 1). DARO median exposure was 4 months (range 1–29). Common related AEs were fatigue (38%), diarrhea (18%), nausea (15%), and anorexia (11%). Median ctDNA fraction of CBR vs no CBR was: C1: 5 vs 16%, p=0.059; C2: 5 vs 19%, p=0.042; C3: 13 vs 13%, p=0.944. C1 CBR was higher with SPOP mutations (3/5, 60%) and all CBR pts had >10 AR copies. C2 CBR was seen with L702H (3/7, 43%) and T878A (4/7, 57%) but not F877L, W724C/L, or V716M. By data cutoff, all had discontinued therapy (radiographic ± biochemical 61%, biochemical only 22%, symptomatic 7%). DARO was well tolerated, with only 6% discontinuing for AEs. **Conclusions:** DARO demonstrates modest activity for unselected mCRPC following ARPIs. ctDNA analysis enriched for pts more likely to benefit from DARO including SPOP alterations, AR amp, and AR mutations L702H and T878A. Clinical trial information: NCT03385655. Research Sponsor: Bayer.

	C1: AR-amp	C2: AR-mutated	C3: BM negative
CBR	5/27 (19%)	7/26 (27%)	2/19 (11%)
PSA response	3/27 (11%)	4/26 (15%)	1/19 (5%)
TTP-PSA (mo)	2.8 (1.8–3.7)	2.8 (1.9–4.0)	1.9 (1.8–2.8)
OS (mo)	12.9 (6.6–19.9)	16.4 (12.9–29.0)	15.5 (12.2–NR)

Substudy F of the Canadian Cancer Trials Group (CCTG) IND.234: PC_BETS (Prostate Cancer Biomarker Enrichment and Treatment Selection)—A biomarker-selected phase II study of durvalumab and tremelilumab (DT) in patients (pts) with previously treated metastatic castration-resistant prostate cancer (mCRPC) resistant to AR pathway inhibitors (ARPI).

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Background: mCRPC with high neoantigen burden due to DNA mismatch repair deficiency (MMRd) and somatic hypermutation, or *CDK12* mutations, may respond best to immune checkpoint inhibition (ICI). CCTG IND.232 suggested that combination ICI with DT has efficacy in a subset of mCRPC but should be biomarker-directed. In this sub-study (SS) of the PC-BETS master protocol, we explored DT in ARPI-resistant mCRPC stratified by circulating tumor DNA (ctDNA) analysis. **Methods:** Pts had ECOG PS 0–1, evaluable disease, biochemical or radiographic progression, prior ARPI ± cytotoxic chemotherapy (max 1 in castrate resistant setting). Genomic screening tested plasma ctDNA and matched leukocyte DNA via deep targeted sequencing with a prostate cancer-specific panel including coding regions and introns of selected mismatch repair genes and estimating tumor mutational burden. Only pts with evidence of ctDNA ≥1% were eligible. Pts with a positive biomarker (BM+) on ctDNA were assigned to a specific SS by a molecular tumor board (MTB); BM- pts were randomized between SS. SS- F tested DT in 2 cohorts of pts: cohort 1: BM+ pts had either somatic hypermutation (HM) ± concomitant MMR gene alterations, or *CDK12* mutations, cohort 2: BM- pts without these alterations, in a 2-stage design. Primary endpoint was clinical benefit rate (CBR), defined by PSA50 response, RECIST CR/PR, or SD ≥12 weeks. Pts received T 225mg IV once on cycle 1, day 1 and D 1500mg IV day 1 every 4 weeks. **Results:** From January 2020 to February 2024, 25 pts were enrolled: 15 and 10 to cohort 1 and 2, respectively. Median age was 69y (63-84). Five pts had liver mets, 15 pts had had prior cytotoxics. 9 pts in cohort 1 had HM and the remainder had *CDK12* mutations only. Median N cycles given was 4 (1-45). 12 pts had a delayed or interruption of DT dosing. The most common related AEs were fatigue (36%), rash (36%), and diarrhea (32%). CBR was seen in 53% of BM+ pts: all also had PSA response and significantly higher median ctDNA% (34% vs 5%; 5-69%); no patient selected as BM+ due to *CDK12* mutations had CBR, while 8 of 9 pts selected based on HM had CBR. **Conclusions:** Liquid biopsy biomarker-informed treatment with DT demonstrated very promising efficacy in mCRPC pts with HM and merits further evaluation. *CDK12* mutations were not predictive of CBR. Toxicities experienced were characteristic of ICI. Clinical trial information: NCT03385655. Research Sponsor: AstraZeneca.

	BM +	BM -
CBR	8 (53%)	0
Median ctDNA%	25%	12.5%
TTP-PSA* (mo; 95% CI)	6.7 (1-NR)	1.9 (1.1-NR)
mOS (mo; 95% CI)**	15.2 (11.8-NR)	7.5 (2.1-NR)

*PSA time to progression; **median overall survival.

Substudy G of the Canadian cancer trials group (CCTG) IND.234: PC_BETS (V)—A circulating tumor DNA (ctDNA)–directed phase II study of carboplatin in patients (Pts) with previously treated metastatic castration-resistant prostate cancer (mCRPC).

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Background: PC-BETS registered pts with mCRPC for ctDNA-based genomic screening. A molecular tumor board (MTB) assigned pts to sub-studies (SS) based on prespecified biomarker (BM) criteria: BM-positive (BM+), or by randomization if BM-negative (BM-). IND.234G investigated carboplatin in 2 cohorts (C): C1 included BM+ pts with deleterious DNA damage response (DDR) gene alterations and C2 included BM- pts. **Methods:** Key inclusion criteria were: mCRPC, ECOG 0-1, evaluable disease, biochemical and/or radiological disease progression, received prior next-generation AR pathway inhibitor; prior chemotherapy allowed (max I regimen for mCRPC). The primary endpoint was clinical benefit rate (CBR: PSA50 response, RECIST CR/PR, or SD ≥12 weeks). Secondary endpoints included time to PSA progression (TTP-PSA), and overall survival (OS). Plasma ctDNA and matched leukocyte DNA underwent deep targeted sequencing with a prostate cancer specific panel that included ATM, BRCA1/2, and 22 other DDR genes. Patients with ctDNA <1% were not eligible unless they carried a germline DDR gene alteration. Pts received IV carboplatin (AUC5) on day 1 of 21-day cycles. **Results:** From 09/2020 to 02/2024, 36 pts were enrolled: 19 and 17 in C1 and 2, respectively. All pts were evaluable for safety while 1 pt was not evaluable for CBR (biochemical only disease). Median age was 69y (55-83) and 66y (54-77); 67%/82% had prior chemotherapy; 21%/6% had prior PARPi, and 6%/0% had liver metastases in C 1/2, respectively. In C1, qualifying gene alterations were: ATM (n=8 pts), BRCA2 (8), BRCA1 (1) and ATR (1). Median number of cycles was 4 (1-31). The most common adverse events (AEs) were anemia (97%), thrombocytopenia (89%), lymphopenia (69%), nausea (58%), neutropenia (42%), diarrhea (22%), vomiting (22%), and constipation (33%). Grade ≥3 non-hematologic AEs occurred in 28% of patients; 1 pt died from an unrelated myocardial infarction. 22 pts had dose delays and 15 pts had dose reductions for hematologic AEs. A summary of results is shown in Table 1. For C1, CBR was observed in 5/8 pts with BRCA2 alterations (4 pts had PSA response), 2/8 pts with ATM alterations (0 PSA responses), and 0/2 pts with ATR/BRCA1 alterations. CBR (with PSA response) was observed in 1 pt enrolled to C2 who did not have DDR gene alterations. **Conclusions:** Carboplatin was associated with meaningful clinical benefit in mCRPC pts with DDR alterations detected in ctDNA, but not in pts without DDR alterations. Carboplatin warrants further evaluation in mCRPC pts with DDR gene alterations. Clinical trial information: NCT03385655. Research Sponsor: Canadian Cancer Society.

	Cohort 1 (BM +) N=18	Cohort 2 (BM -) N=17
Median ctDNA% at baseline	16.5%	20%
Clinical Benefit (n, %)	7 (39%)	1 (6%)
TTP-PSA (mo; 95% CI)	2.0 (1.4-9.9)	1.7 (0.8-2.6)
mOS (mo; 95% CI)	21 (9.3-NR)	9.6 (6.5-NR)

5059 Poster Session

Phase 1b/2 KEYNOTE-365 cohort I: Pembrolizumab (pembro) plus carboplatin and etoposide chemotherapy (chemo) or chemo alone for metastatic neuroendocrine prostate cancer (NEPC).

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Background: Patients with NEPC are often treated with platinum-based chemotherapy but novel therapies with favorable efficacy and safety profiles are needed. Cohort I of the phase 1b/2 KEYNOTE-365 study (NCT02861573) was designed to evaluate the safety and efficacy of adding pembro to chemo in participants (pts) with NEPC. Preliminary data are presented. **Methods:** Adultpts with pathologically (morphology and immunohistochemistry) confirmed treatment-emergent (t-NE) or de novo metastatic NEPC (small cell, large cell, or mixed morphology per central review), disease progression ≤6 mo before screening, and ECOG PS of 0 or 1, with or without prior androgen deprivation therapy, are included. Enrollment is ongoing. Prior treatment (Tx) with ≤2 chemo regimens for metastatic castration-resistant prostate cancer and ≤2 next-generation hormonal agents are allowed. Prior Tx with platinum-containing regimens is not permitted. Pts are randomly assigned 1:1 to receive 4-6 cycles of carboplatin AUC 5 IV on day 1 Q3W + etoposide 100 mg/m^2 IV on days 1-3 Q3W with or without pembro 200 mg IV Q3W for ≤35 cycles. Primary end points are safety, ORR per RECIST v1.1 by blinded independent central review (BICR), and confirmed prostate-specific antigen (PSA) response rate (≥50% decrease from baseline [BL] measured twice ≥3 wk apart). Secondary end points include rPFS per PCWG3-modified RECIST v1.1 by BICR and OS. No formal hypothesis testing was performed. **Results:** As of August 26, 2024, 40 pts have been randomized; 19 pts received ≥1 dose of pembro + chemo and 18 pts ≥1 dose of chemo. Of treated pts, 29 (78%) had t-NE. Median follow-up was 11.7 mo (range, 0.5-28.7); 7 and 2 pts remain on Tx with pembro + chemo or chemo, respectively. For pts with RECIST-measurable disease, confirmed ORR was 33% (6/18; 95% CI, 13-59; 6 partial responses [PRs]) with pembro + chemo versus 6% (1/16; 0-30; 1 PR) with chemo. For pts with a BL PSA measurement, confirmed PSA response rate was 37% (7/19; 95% CI, 16-62) versus 18% (3/17; 4-43). In all treated pts, median rPFS was 5.1 mo (95% CI, 3.9-8.1) with pembro + chemo versus 4.0 mo (2.0-4.3) with chemo; 6-mo rPFS rate was 49% versus 21%. Median OS was 11.4 mo (95% CI, 5.1-not reached) versus 7.8 mo (3.6-8.5); 6-mo OS rate was 80% versus 65%. Grade 3 or 4 Tx-related AEs (TRAEs) occurred in 58% of pts with pembro + chemo versus 78% with chemo, most commonly anemia (32% vs 39%); no grade 5 TRAEs occurred. Immune-mediated AEs and infusion reactions occurred in 32% of pts with pembro + chemo versus 11% with chemo, most commonly hyperthyroidism (16% vs 6%) and infusion reactions (16% vs 6%). **Conclusions:** Based on these preliminary data in pts with NEPC, the addition of pembro to chemo is associated with promising efficacy outcomes compared with chemo alone and does not result in new or unexpected safety signals. Updated data from cohort I will be presented at the meeting. Clinical trial information: NCT02861573. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

5060 Poster Session

Impact of germline vs somatic BRCA mutation status on the efficacy of rucaparib vs physician's choice in the TRITON3 study of patients with metastatic castration-resistant prostate cancer.

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Background: Rucaparib significantly improved radiographic progression-free survival (rPFS) in men with BRCA-mutated chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) vs a control arm of physician's choice of therapy (docetaxel or androgen-receptor pathway inhibitor [ARPI] therapy: abiraterone acetate or enzalutamide) in the randomized, multicenter, open-label, phase 3 TRITON3 (NCT02975934) study. Herein, we conducted an analysis to determine the impact of germline vs somatic mutation status on the efficacy of rucaparib. **Methods:** Patients were randomized 2:1 to receive rucaparib 600 mg BID or physician's choice of docetaxel or ARPI following progression while on 1 prior second-generation ARPI in any setting. The primary endpoint was rPFS. Color Health did genetic testing. Treatment-emergent adverse events (TEAEs) were reported for the BRCA subgroup. **Results:** In the rucaparib arm, 201/270 patients had BRCA mutations, and in the physician's choice arm, 101/135 patients had BRCA mutations. Of patients with BRCA mutations: in the rucaparib arm, 80/201 (40%) were germline and 116/201 (58%) were somatic with 5/201 (2%) BRCA mutation status unknown, while in the physician's choice arm, 39/101 (39%) were germline and 48/101 (48%) were somatic with 14/101 (14%) BRCA mutation status unknown. rPFS was significantly improved with rucaparib treatment vs physician's choice in both the germline and somatic mutation groups (germline: HR, 0.52 [95% CI, 0.32–0.84]; somatic: HR, 0.38 [95% CI, 0.25–0.59]). Incidence rates of TEAEs were similar overall between patients with germline and somatic BRCA mutations in both arms. **Conclusions:** Rucaparib improves progression-free survival for patients with mCRPC with either germline or somatic BRCA mutations with a manageable safety profile. These data support the use of rucaparib as a beneficial treatment option for patients with BRCA-mutated mCRPC with germline or somatic mutations. Clinical trial information: NCT02975934. Research Sponsor: pharma& GmbH.

Prognostic relevance of Aurora kinase A (*AURKA*) expression in prostate cancer (PCa).

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Background: Amplification and overexpression of the *AURKA* gene characterize aggressive variants of prostate cancer, such as castration-resistant (CR) PCa and neuroendocrine PCa (NEPC), representing both a marker of progression and a promising therapeutic target. **Methods:** 7755 PCa specimens were sequenced for DNA and RNA at Caris Life Sciences and stratified into top (Q4) and bottom quartiles (Q1) based on *AURKA* expression. Castration status was defined as castrate (CS) if a specimen was androgen deprivation therapy (ADT)-naïve or collected within 90 days from the initiation of 1st generation ADTs. Additionally, specimens that received 2nd generation ADTs prior to collection were excluded from the CS cohort. All other ADT treated specimens (excluding the CS cohort) were considered CR. AR and NEPC scores were calculated as previously reported (Beltran, Nat Med 2016) and categorized into highest (H) and lowest (L) quartiles. Real-world survival was obtained from insurance claims data, and Kaplan–Meier estimates were calculated from specimen collection to last clinical contact for overall survival (OS) and from initiation to termination of specific ADTs to estimate time on treatment (TOT). Hazard ratios (HR) and p-values were calculated using the Cox model and log-rank test, with multiple testing corrections applied ($q<0.05$). **Results:** Compared to Q1, Q4 was associated with a higher median age (69 vs 67 years) and a higher proportion of non-Hispanic/Latinos (75 vs 70%), NEPC-H (42 vs 15%), metastatic (60 vs 22%), CR (46 vs 20%, all $q<0.05$) disease. Q4 was also associated with poor prognosis independent of race and ethnic backgrounds. Despite the significant enrichment of aggressive disease, Q4 was associated with poor prognosis independent of metastatic, NEPC-L or castration status. Further within NEPC-H specimens, Q4 was prognostic only among those that were also AR-L (Table 1). Relative to Q1, Q4 samples were enriched for mutations in *TP53* (48 vs 23%), *RB1* (10 vs 1%) and *PTEN* (11 vs 7%, all $q<0.05$). Interestingly, Q4 was associated with a longer Leuprolide-TOT (HR: 0.9(0.8-0.97), $p<0.01$) and a shorter Enzalutamide-TOT (HR: 1.2 (1-1.4), $p<0.05$). **Conclusions:** Analysis of a large dataset revealed that high *AURKA* expression correlates with poor prognosis across clinical and demographic subpopulations. *AURKA* inhibitors might enhance outcomes of metastatic PCa treated with AR pathway inhibitors by intensifying AR inhibition, increasing DNA-damage-related cell death, and/or preventing escape mechanisms like NEPC. Further studies are needed to identify contexts where *AURKA* inhibitors can improve metastatic PCa outcomes. Research Sponsor: None.

HR comparing OS in Q4 vs Q1 (all p<0.0001).

Conditions	HR (95% CI)
White	2.6 (2.3-2.9)
Black/AA	1.9 (1.5-2.5)
non-Hispanic/Latino	2.6 (2.3-2.9)
Hispanic/Latino	2.3 (1.7-3.2)
Primary	1.7 (1.5-2)
Metastatic	2 (1.7-2.4)
NEPC-L	2.3 (1.7-3.1)
NEPC-H/AR-L	2.1 (1.6-2.8)
CS	1.9 (1.6-2.2)
CR	2.4 (2-3)

PSA and alkaline phosphatase changes in the EORTC-1333 PEACE-3 study evaluating the addition of six cycles of radium 223 in metastatic castration-resistant prostate cancer (mCRPC) starting enzalutamide.

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Background: The EORTC/UNICANCER/CTI/CUOG/LACOG Peace 3 showed that adding Ra233 to enzalutamide significantly improves investigator-assessed progression-free survival (PFS) and overall survival (OS) in mCRPC with bone metastases. We examined the effect of the combination on the decline in prostate-specific antigen (PSA) and alkaline phosphatase (ALP). **Methods:** From 11/2015 to 03/2023, 446 men with mCRPC and bone metastasis were randomized 1:1 to enzalutamide alone (ENZ) or combined with 6 cycles of Ra223 (ENZ-RAD). The PSA/ALP response rate is estimated at 6/12 months based on the drop from baseline in all PSA/ALP evaluable patients. For PSA, any decline ≥ 50 or 90% from baseline is considered a PSA response. For ALP, any decline of ≥30% from baseline is regarded as a response. Each response needed to be confirmed by a second evaluation at least three weeks later. Time to response is from treatment start until the first date a response was observed. ALP normalization is a decline to ≤ 115 U/L in patients with baseline ALP >115 U/L. **Results:** PSA: The baseline median (Q1-Q3) for ENZ-RAD was 24.0 (7.8-68.8) ng/dl, and 21.4 (8.0-57.6) ng/ml for ENZ. The median time (95%CI) to a PSA response > 50% in months (mo.) was 2.79 (2.56-3.02) in the ENZ-RAD arm and 2.76 (2.63-2.79) in the ENZ arm (HR (95%CI) 1.00 (0.80-1.24)). PSA response rates ≥50% at 6 and 12 months were 77.1% (145/188) and 76.8% (109/142) in the ENZ-RAD arm, compared to 69.9% (127/182) and 66.2% (88/133) in the ENZ arm. The median time (95%CI) to a PSA response ≥ 90% in mo. was 1.87 (1.44-2.53) in the ENZ-RAD arm and 7.44 (3.67-NE) in the ENZ arm (HR (95%CI 1.48 (1.13-1.93)). PSA response rates ≥90% at 6 and 12 mo. were 50.5% (95/188) and 54.9% (78/142) in the ENZ-RAD arm, compared to 34.1% (62/182) and 37.6% (50/133) in the ENZ arm. ALP: The baseline median (Q1-Q3) ALP in the ENZ-RAD arm was 106 (78-183) UI/L, and in the ENZ arm, 124.5 (85-216). In the ENZ/RAD and ENZ arms, 45.6% (99/217) and 54.4% (122/224) of patients had ALP ≥ 115 UI/L at baseline. The ENZ-RAD arm had a median time (95%CI) to ALP response > 30% of 2.40 (1.97-2.79) mo., while the ENZ arm had a median of 3.71 (2.83-5.49) mo. (HR (95%CI) 1.42 (1.13-1.80)). ALP >30% response rates at 6 and 12 mo. were 56.5% (108/191) and 50.0% (71/142) in ENZ-RAD and 50.8% (93/183) and 47.4% (63/133) in ENZ. The median (95%CI) time to ALP normalization in the ENZ-RAD arm is 1.97 (1.87-2.50) mo. and 4.47 (2.99-14.06) mo. In the ENZ arm(HR 1.42 (1.13-1.80)). At 6 and 12 mo., the ENZ-RAD arm ALP normalization rates were 76.2 (64/84) and 77.4 (41/53), while 50.5% (47/93) and 61.3% (38/62) in the ENZ arm. **Conclusions:** The addition of six cycles of RA 223 to enzalutamide in the PEACE-3 trial improves PSA response time and rates (≥90%), ALP reduction time (≥30%), and ALP normalization time and rates at 6 and 12 months. Clinical trial information: NCT02194842. Research Sponsor: Bayer Healthcare, Astellas.

A novel prognostic model to optimize the timing of docetaxel (Doc) following an androgen receptor pathway inhibitor (ARPi) in metastasic castration-resistant prostate cancer (mCRPC).

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Background: ARPi has become a standard of care for advanced prostate cancer due to its activity and safety profile. DoC is a therapeutic alternative as first-line in unselected mCRPC patients (pts) after a first ARPi. Best timing to initiate Doc following an ARPi remains uncertain, with most predictive models based on baseline characteristics and without variables related to the disease evolution. We have developed and validated a tool to predict progression-free survival (PFS) and overall survival (OS) with Doc to capture individual tumor behavior and guide the optimal timing of Doc. **Methods:** mCRPC pts from PROREPAIR-B (NCT03075735) treated with an ARPi followed by Doc were selected for a derivation cohort (n=111). Those pts from PROSTAC (NCT02362620), PROSABI (NCT02787837) and/or PROSENZA (NCT02922218) not included in PROREPAIR-B treated with an ARPi followed by Doc were included in the validation cohort (n=243). Baseline characteristics at ARPi initiation, type and time of response/progression to ARPi and prognostic variables at initiation of Doc were collected. All variables underwent univariate Cox regression for PFS and OS from Doc in the derivation set. Only significant variables underwent the least absolute shrinkage and selection operator (LASSO) method to select the most relevant. Individual risk scores for PFS and OS were generated using Cox to classify patients into low- and high-risk groups and to construct a nomogram. Finally, an external validation was conducted in our second independent cohort. Predictive accuracy was assessed using Harrell's C-index. **Results:** The Lasso method identified 6 variables associated to PFS and OS: age at diagnosis, time to (t)mCRPC, development of new nodal and/or new visceral metastasis during ARPi, elevated LDH and ECOG at Doc initiation (Table). After bootstrap correction for internal validation the PFS and OS model showed a C-index of 0.71 (CI95% 0.66–0.77) and 0.74 (0.68–0.80), respectively. The model was validated in our second cohort with c-index of 0.62 (0.6-0.7) and 0.64 (0.6-0.7) for PFS and OS, respectively. **Conclusions:** Our validated model provides a pragmatic and widely accessible tool for physicians to estimate the potential benefit of Doc after an ARPi according to pts age and time to mCRPC, particularly in settings where targeted therapies at the time of progression to ARPi are not available. Research Sponsor: None.

Variable	PFS risk coefficient (rc)	PFS (HR CI95%)	OS rc	OS (HR CI95%)
Age (<60, 60-70, >70)	.35	1.5 (1.1-1.9)	.33	1.6 (1.2-2.3)
tmCRPC (>98, 98-23, <23)	-.17	0.7 (0.5-0.9)	-.49	0.4 (0.2-0.7)
Visceral MTS (never, persistent, new)	.48	1.2 (0.9-1.6)	.54	1.9 (0.9-3.9)
Nodal MTS (never, persistent, new)	.58	1.4 (1.0-1.9)	.66	2.0 (1.0-4.2)
LDH (xULN)	.10	1.2 (1-1.2)	.8	1.9 (1.0-2.4)
ECOG at Doc	.63	2.1 (1.4-2.9)	.74	4.1 (2.1-8.2)
Total Score (Low vs high)		**1.9 (1.2-3.1)**		**2.13 (1.3- 3.5)**

Additive clinical utility of tissue biomarkers of microsatellite instability (MSI) status and tumor mutational burden (TMB) to predict immune checkpoint inhibitor (ICI) effectiveness for real-world patients with metastatic castration-resistant prostate cancer (mCRPC).

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Background: FoundationOneCDx (F1CDx) supports two FDA-approved biomarkers to guide treatment decisions for ICI for patients with mCRPC: MSI status and TMB. MSI-H and TMB-H (10+ mut/MB) have strongly overlapping prevalence. We sought to better characterize ICI outcome associations of TMB-H / non-MSI-H population and relative effectiveness of taxanes & ICI among patients who received these agents in sequence. **Methods:** Following a prespecified analysis plan, this study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine mCRPC clinico-genomic database (FH-FMI CGDB), with data originating from ~280 US cancer clinics (~800 sites of care). Inclusion criteria included patients with mCRPC treated with single-agent anti-PD(L)1 therapy in the FH network between 1/1/2011 - 3/30/2024. This study used the MSI and TMB algorithms from the tissue based F1CDx. Time to next treatment (TTNT) and OS were assessed with Kaplan-Meier plots and in multivariable Cox models adjusted for ECOG performance score, socioeconomic status, prior treatment history, and baseline PSA. Among patients who received taxanes in a prior line of therapy, the effectiveness (TTNT1 vs. TTNT2) of taxane and ICI were compared. **Results:** Among 2995 prostate cancer tissue specimens in the database, 95 (3.1%) were MSI-H and 142 (4.7%) were TMB-H. 94 (3.1%) were MSI-H & TMB-H, 1 was MSI-H & TMB-L, and 48 (1.6%) were TMB-H & not MSI-H. Among these, 84 patients with mCRPC were treated with ICI and met inclusion criteria, including MSI-H & TMB-H (n = 30), non-MSI-H & TMB-H (n = 8), and non-MSI-H and TMB-L (n = 46). The respective median TTNT on ICI was 8.0 vs. 9.6 vs. 3 months. The respective median OS from initiation of ICI was 10.9 vs. not reached vs. 4.4 months. In multivariable models evaluating ICI only, compared to non-MSI-H & TMB-L, the MSI-H & TMB-H group had more favorable TTNT (HR: 0.20, 95%CI: 0.10 – 0.41, $p < 0.001$) and OS (HR: 0.33, 95%CI: 0.16 – 0.70, p = 0.004), and the non-MSI-H & TMB-H group also had more favorable TTNT (HR: 0.13, 95%CI: 0.04 – 0.45, p = 0.002) and OS (HR: 0.20, 95%CI: 0.05 – 0.75, p = 0.017). 50 of the 84 (60%) patients treated with ICI had prior mCRPC taxane treatment. Better TTNT2 on subsequent ICI vs. prior taxane was observed for MSI-H (HR: 0.49, 95%CI: 0.23 – 1.01, p = 0.051) and TMB-H (0.54, 95%CI: 0.30 – 0.98, p = 0.044), but the opposite was true for non-MSI-H and TMB-L subgroups, with significant treatment interactions for each (p = 0.0018, p = 0.00052). **Conclusions:** TMB-H (4.7%) is more prevalent than MSI-H (3.1%) by F1CDx in mCRPC. Non-MSI-H / TMB-H (1.6%) in the routine practice cohort have similar outcome associations on ICI to MSI-H. Both MSI-H and TMB-H by F1CDx are predictive of differential benefit for ICI vs. taxanes in later mCRPC treatment lines. Research Sponsor: None.

Suboptimal suppression of serum androgen levels among men treated with apalutamide and abiraterone acetate plus prednisone compared with abiraterone acetate plus prednisone alone.

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Background: Phase III studies of dual therapy with an androgen receptor (AR) antagonist, apalutamide (Apa) or enzalutamide (Enza) with abiraterone acetate (AA) plus (+) prednisone (P) in metastatic castration resistant prostate cancer (mCRPC) have not shown a survival benefit vs single agent therapy. Apa and Enza induce CYP3A4 activity, resulting in decreases in serum AA and P levels. The decrease in AA levels has not been considered clinically significant, but the potential impact of AR antagonist-mediated CYP3A4 induction on serum steroid levels, in context of clinical studies combining an AR antagonist with AA, has not been previously reported. **Methods:** We measured levels of AA, its metabolites and androgens using LC/MS-MS in available serum samples obtained at baseline and at 4 weeks of therapy in the PANTHER phase II study (n=86) of Apa (240 mg daily) and AA (1000mg daily) + P (10mg daily), and in the Abi Race phase II study (n=75) of AA (1000mg daily) + P (10mg daily) among men with mCRPC. Samples were batched and all sera assessed contemporaneously. Comparison of metabolite levels between studies used the Mann-Whitney test, and within study the Wilcoxon matched-pairs signed rank test. **Results:** At 4 weeks, median (med) levels of AA and its primary metabolites delta-4 and keto-Abi in PANTHER vs Abi Race were 13.1 vs 39.6 ng/ml, 0.49 vs 1.93 ng/ml, and 0.75 vs 8.98 ng/ml (p=<0.0001 for all), equating to 66%, 75%, and 92% lower levels with Apa and AA + P vs AA + P. Baseline steroid levels did not differ between the studies, but steroids downstream of CYP17A were suppressed markedly less effectively in the dual therapy PANTHER study: DHEAS was detectable in 80% vs 14% of samples (med 1.23 vs 0.49 ng/ml, p=<0.0001), DHEA in 90% vs 26% (med 0.44 vs 0.01 ng/ml, p=<0.0001), AED in 70% vs 11% (med 0.017 vs 0.010 ng/ml, p=<0.0001), and testosterone in 50% vs 17% (med 0.006 vs 0.005 ng/ml, p=0.0005). Despite the decrease in AA levels, steroids upstream of CYP17A in PANTHER were markedly elevated vs treatment with AA + P alone: pregnenolone (4.1 vs 0.79ng/ml, p=<0.0001), consistent with a suboptimal prednisone-mediated suppression of ACTH. **Conclusions:** Serum AA levels at week 4 are substantially lower, and androgen levels substantially higher, among men with mCRPC treated with Apa and AA + P vs AA + P. Our data suggest that Apa decreased P levels to the point that circulating ACTH remained sufficient to mediate ongoing basal adrenal androgen synthesis. Suboptimal suppression of steroids may explain why AA and AR antagonist combination studies have not been more effective. The clinical activity when both treatment strategies are at full efficacy remains to be fully tested, and will likely require use of dexamethasone or higher than standard dosing of prednisone. This may be particularly important for treatment of prostate cancers with greater dependence on AR signaling. Research Sponsor: Janssen Scientific Affairs, LLC.

Canadian Cancer Trials Group (CCTG) IND.234/223: PC_BETS (Prostate Cancer Biomarker Enrichment and Treatment Selection)—A molecularly selected co-operative group platform study.

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Background: PC-BETS registered patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) for circulating tumour (ct)DNA-based genomic screening to biomarker select and stratify pts for enrolment in a multi-arm platform trial testing clinical activity of investigational therapies. **Methods:** Pts (≥ 18 years old, ECOG PS 0-1, life expectancy ≥ 6 months) had mCRPC, disease progression (PD), no CNS involvement or serious illnesses and had received AR pathway inhibitor therapy +/- chemotherapy. Eligible pts were registered and screened using plasma ctDNA and enrolled to a substudy (SS) based on the presence (or absence) of a prespecified biomarker (BM), using a prespecified algorithm and a virtual web-based Molecular Tumour Board (MTB). ctDNA testing used an established targeted sequencing approach customised for mCRPC. Pts without BM positive genomic alteration(s) for an open SS were randomized to a BM negative SS cohort; pts who were never enrolled were followed for outcomes. Pts without detected ctDNA were not eligible for enrolment but could be rescreened after >8 weeks. Pts who discontinued a SS could be rescreened. Primary endpoint was clinical benefit rate (CBR; PSA50 response, RECIST CR/PR, or SD ≥12 weeks). Eight SS opened between 2017-2020. **Results:** From 2017-2024, 568 pts were screened from 11 centres across Canada. Pts: median age 71.5 (range 47.7-94.7), prior chemotherapy in 47.0%, and median ctDNA fraction was 7%. 216 pts were enrolled to 1 or more SS (3 pts enrolled to >1). See Table for summary of results. For all SS, toxicities were as expected. In SS-E, 1 pt had CBR and 1 pt received 25 cycles but did not meet CBR (both pts had AKT mutations). Clinical and genomic correlations will be presented. SS C, F and G are reported separately. **Conclusions:** Biomarker selected platform designs are an efficient way to screen potential new therapeutics, are well suited to multi-centre cooperative group settings and are strongly supported by patients advocates. CBRs were not reported for SS 223, B and D while modest clinical activity was seen for SS A (in the BM- cohort only) and E. Clinical trial information: NCT03385655. Research Sponsor: Pfizer; Canadian Cancer Society; AstraZeneca; F. Hoffmann-La Roche Ltd.; Treadwell Therapeutics; Bayer.

Total Screens / N pts				**606 / 565**				
ctDNA+ screen / pts				443 / 426				
N pts enrolled to SS				216				
SS	223	A	B	C	D	E	F	G
Drug/s	Palbociclib	Adavosertib	Savolitinib	Darolutamide	CFI-40095	Ipatasertib	Durvalumab / tremelimumab	Carboplatin
Target/pathway	CDK[1]	BRCA/ATM[2]	MET	AR	PTEN	PIK3CA/AKT	TMB high	BRCA/ATM[2]
Drug supplied by	Pfizer	AstraZeneca		Bayer[3]	Treadwell	Hoffman-La Roche[3]	AstraZeneca[3]	-
Enrolled to SS(BM+/-)	19 (9/10)	25 (11/14)	16 (6/10)	72 (53/19)	18 (9/9)	8 (BM+)	25 (15/10)	35 (18/17)
CBR (BM+)	0	0	0		0	1		
CBR (BM-)	0	3	0		0			

[1]CDK4/6/CCND1 amplification or CDK12 mutations; [2]or other HRR-related defects; [3]Plus partial funding to support SS.

5067 Poster Session

Phase 1 study of gotistobart (BNT316/ONC-392) in combination with lutetium Lu 177 vipivotide tetraxetan (Lu 177) in patients with metastatic castration-resistant prostate cancer (mCRPC).

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Background: When used in combination with physician's choice of care, Lu 177 showed significant PFS and OS improvements in mCRPC. Combinations with novel agents are being explored to extend the therapeutic benefit. Preclinical models have demonstrated that radiotherapy selectively expands and functionally activates regulatory T cells (Tregs) in the tumor microenvironment (TME). Given the role of gotistobart (a unique pH-sensitive anti-CTLA-4 antibody that preserves CTLA-4 recycling and avoids lysosomal degradation) in selective depletion of Tregs in the TME, this study will initially test the safety and toxicity of gotistobart plus Lu 177 in mCRPC. **Methods:** PRESERVE-006 (NCT05682443) is an open-label, randomized, active control, multi-center, phase 1/2 study of gotistobart in combination with Lu 177 in patients with mCRPC who have progressed after androgen receptor pathway inhibition. Patients were randomized to receive gotistobart at 3 mg/kg, Q4W, 6 mg/kg Q6W, or 10 mg/kg Q6W for up to 13 doses plus Lu 177 7.4 GBq (200 mCi) Q6W for up to 6 doses, or to the control arm to receive Lu 177 7.4 GBq (200 mCi), Q6W for up to 6 doses. Here we report results from the dose escalation phase (Phase 1) that aims to assess safety and select two dose regimens for the Phase 2 dose optimization study. **Results:** As of December 20, 2024, 24 patients received at least 1 drug dose with a median 6.21 (range 1.2–11.3) months on study. Median age was 70.5 (range 52–86) years, and 62.5%, 25.0% and 4.2% were White, Black, and Asian, respectively. Median follow-up was 10.9, 2.6 and 5.4 months for the 3 mg/kg Q4W (N = 6), 6 mg/kg Q6W (N = 5) and 10 mg/kg Q6W (N = 6) combination regimens, respectively, and 6.5 months for Arm B Lu 177 (N = 7). No deaths, dose-limiting toxicity, or Gr 4–5 treatment-related AEs (TRAEs) were observed at any gotistobart dose. TRAEs related to gotistobart or Lu 177 were Gr 1–2 at 3 mg/kg Q4W and 6 mg/kg Q6W; one patient (16.7%) in the 3 mg/kg regimen had Gr 2 colitis leading to treatment discontinuation. At 10 mg/kg Q6W, two patients (33%) had Gr 3 colitis (both of whom discontinued treatment) and one patient (16.7%) had Gr 3 fatigue. Infusion-related reactions (Gr 1–2) were seen in 6 mg/kg (40.0%) and 10 mg/kg (66.7%) regimens. In the efficacy-evaluable population, confirmed PSA50 (a key secondary endpoint for Phase 2) was observed in 4 of 6 patients and 3 of 6 patients in 3 and 10 mg/kg regimens, respectively versus 1 of 6 patients in the Lu 177 control group. **Conclusions:** With known limitations in sample size during dose escalation,gotistobart in combination with Lu 177 demonstrated a manageable safety profile and promising preliminary PSA50 rates in patients with mCRPC during the dose escalation phase. Overall findings support combination regimens with gotistobart doses less than 10 mg/kg in the ongoing Phase 2 randomized dose optimization study. Clinical trial information: NCT05682443. Research Sponsor: OncoC4 Inc; BioNTech SE.

Survival and hospitalizations with lutetium (Lu)-177 vipivotide tetraxetan in veterans with underlying genomic alterations.

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Background: Lutetium-Lu 177 vipivotide tetraxetan (^{177}Lu-PSMA-617) is a radioligand therapy used to treat metastatic castration resistant prostate cancer (mCRPC) with limited real-world survival data outside of large academic centers. Emerging data suggests outcomes are associated with somatic tumor genomic profiles, such as status of tumor suppressor gene (TSG) alterations, including TP53, PTEN, or RB1. We utilized a nationwide retrospective cohort within the Veterans Health Affairs (VHA) to evaluate overall survival of patients treated with ^{177}Lu-PSMA-617 and considered tumor suppressor gene alteration status, which could serve as a biomarker for personalized treatment. **Methods:** Veterans with mCRPC treated in the VHA who received at least one dose of ^{177}Lu-PSMA-617 through November 2024 were included. The National Precision Oncology Program (NPOP) was used to identify patients who underwent tumor sequencing and had TSG alterations. Age, Charlson comorbidity index (CCI), and number of hospitalizations were collected. The Kaplan-Meier method was used to estimate overall survival (OS), logistic regression for risk of hospitalization, and Cox proportional hazards models to estimate mortality. **Results:** A total of 228 Veterans who had received at least one dose of ^{177}Lu-PSMA-617 were identified. Mean age was 76.5 years (SD 7.6) with median CCI of 2 (IQR 1-4). Median OS was 11.4 months (95% CI 8.6-14.2) in the entire cohort and 29.8% of Veterans (68/228) were hospitalized in the year after first dose. Age was not associated with mortality or hospitalization, however CCI was associated with mortality (HR 1.12, 95% CI 1.01-1.24) and any hospitalization (OR 1.21, 95% CI 1.05-1.41). There were no differences in OS based on receipt of NPOP testing (HR 0.97, 95% CI 0.62-1.5). In 108 patients with NPOP testing, 44% (48/108) were found to have at least one TSG alteration. Median OS was shorter in patients with TSG alterations (5.8 vs. 18.0 months, p=0.001, HR 2.8, 95% CI 1.5-5.3) compared to patients without TSG alterations. When accounting for age and CCI, risk of death was increased in Veterans with TSG alterations (aHR 3.0, 95% CI 1.6-5.9). **Conclusions:** In US Veterans treated with ^{177}Lu-PSMA-617, median OS was 11.4 months, shorter than observed in other cohorts, although the mean age was higher. Comorbidities were prognostic for mortality and hospitalization while age was not. Veterans who had TSG alterations had significantly shorter OS in unadjusted and adjusted analyses, suggesting that patients with TSG alterations are less likely to benefit from ^{177}Lu-PSMA-617 and could consider different treatment modalities. Prospective studies are needed to identify additional clinical outcomes over time. Research Sponsor: Prostate Cancer Young Investigator Award to MWS; The Rate Elements Skewing Outcomes Linked to Veteran Equity in PCa (RESOLVE PCa) Consortium: Multilevel Modeling to Predict Prostate Cancer Incidence and Aggressiveness to Dr. Garraway and Dr. Maxwell; Department of Defense W81XWH-22-1-0602.

5069 Poster Session

A phase I and randomized phase II trial of radium-223 dichloride, peposertib, and avelumab in advanced metastatic castrate-resistant prostate cancer (mCRPC): Phase I results.

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Background: Ra-223 improves the overall survival in patients with mCRPC to the bone. We assessed the safety of standard-of-care Ra-223 in combination with peposertib, a DNA-dependent protein kinase inhibitor, with or without avelumab, an anti-PD-L1 antibody. **Methods:** Patients with mCRPC and two or more skeletal metastases identified by bone scintigraphy with or without lymph node metastases up to 3 cm in size, but no visceral metastases, were eligible. Progression after progression after at least one androgen receptor pathway inhibitor or taxane was required. Phase 1 consisted of a two-step sequential safety lead-in using a 3+3 design. Step 1 combined 6 standard cycles of Ra-223 (55 kBq/kg), with increasing doses of peposertib: 50, 100, and 200 mg PO bid on days 3-26 of each cycle. Step 2 combined Ra-223 with the maximum tolerated dose of peposertib and added standard avelumab 800 mg IV every 14 days, starting at cycle 2 of Ra-223. **Results:** A total of 9 patients participated in Step 1, where the maximum tolerated peposertib dose of 200 mg PO bid with Ra-223 was deemed tolerable. A total of 6 patients participated in Step 2 and the combination of Ra-223, peposertib at 200 mg PO bid, and standard avelumab was deemed tolerable. Of the 15 patients in Phase 1, none experienced grade 4 or higher treatment-related toxicities, while 7 experienced grade 3 toxicities, including neutropenia (1), anemia (1), cardiac chest pain (1), fall (1), maculopapular rash (2), and lymphopenia (2). The median (Q1, Q3) PSA velocity from the beginning to the end of treatment was lower for Step 2 versus Step 1: 2.1 (-0.1, 4.6) versus 23.5 (18.6, 77.1) ng/mL/month ($p = 0.0067$). OS and PFS were calculated with the limitation that the Phase 1 was non-randomized. Median OS was not reached for Step 2, as only 1 of 6 patients had died, versus 15.2 months for Step 1, where 8 out of 9 patients had died ($p = 0.0537$). The patient who died in Step 2 discontinued therapy prematurely after 3 cycles due to progression and survived 15.2 months (the 5 alive completed all 6 cycles). The median radiographic PFS was 7 months for Step 2 versus 12.7 months for Step 1 ($p = 0.8910$). **Conclusions:** The combination of Ra-223 and peposertib, with or without avelumab was well tolerated. The triplet combination showed the most promising results at this early evaluation. We continue to accrue in the randomized Phase II portion of the trial. Clinical trial information: NCT04071236. Research Sponsor: National Cancer Institute; EMD Serono; CrossRef Funder ID: 10.13039/100004755; Bayer.

5070 Poster Session

PSMA-targeted actinium-225 therapy in metastatic castration-resistant prostate cancer (mCRPC): Baseline and follow-up PSMA PET parameters associated with outcomes.

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Background: Prostate-specific membrane antigen (PSMA) is a validated therapeutic target in mCRPC. 225Ac-J591, an alpha-emitting radionuclide linked to an anti-PSMA antibody, has been studied in several early phase clinical trials. We evaluated baseline and follow-up (12 weeks post 225Ac-J591) PSMA PET metrics (SUVmax, SUVmean, and total tumor volume [TTV]) and their association with biochemical response (PSA50), overall survival (OS), and adverse events. **Methods:** Patients enrolled in phase I dose-escalation trials of 225Ac-J591, either as a single agent (NCT03276572, NCT04506567; n = 87) or in combination (with 177Lu-PSMA-I&T, NCT04886986, n = 18; or pembrolizumab and androgen receptor (AR) inhibitors, NCT04946370 n = 12), were included. 68Ga-PSMA-11 PET metrics were quantified using MIM Encore software. Outcomes assessed included PSA50, OS, and adverse events. Statistical analyses utilized univariate and multivariate logistic regression for PSA50, Cox regression for OS and Kruskal-Wallis and Wilcoxon rank sum tests for adverse events. **Results:** 117 patients were included with a median age of 71 yr and median baseline PSA of 58 ng/mL (range 0.67–9614). Prior therapies included chemotherapy (62%), >1 AR pathway inhibitor (53%), immunotherapy (42%), 177Lu-PSMA (28%), and radium-223 (17%). Metastatic sites included bone (88%), lymph nodes (63%), and visceral organs (29%). High CALGB (Halabi) risk in 56% of patients. Median baseline SUVmax, SUVmean, and TTV on PSMA-PET were 50 (31-85), 8.3 (5.7-11.8), and 308 (105-1066), respectively. Baseline SUVmean (OR 1.13, 95% CI 1.04–1.24, p = 0.006) and SUVmax (OR 1.01, 95% CI 1.00–1.02, p = 0.018) were associated with higher odds of PSA50, though only SUVmean remained significant on multivariable analysis (OR 1.11, p = 0.023). Baseline SUVmean and TTV were associated with OS (HR 0.95, p = 0.025; HR 1.000, p < 0.001), TTV remaining significant on multivariable analysis (HR 1.00, p = 0.007), along with prior chemotherapy (HR 1.45, p < 0.001) and CALGB high risk group (HR 1.84, p = 0.014). In multivariable analysis controlling for injected radioactivity, prior chemotherapy, and CALGB risk, TTV reduction was associated with PSA50 (OR 1.31, 95% CI 1.1–1.7, p = 0.015), but changes in SUVmean or SUVmax were not. Higher baseline TTV was more likely to have higher grade myelosuppression (anemia Gr 3/4 673 vs Gr 1/2 203, Gr0 284, p = 0.041), but less nausea and xerostomia. **Conclusions:** Higher baseline PSMA PET metrics, including SUVmean, SUVmax, and TTV are associated with PSA50 response and survival in patients receiving antibody-delivered alpha emitter 225Ac. Higher TTV, yielding more radionuclide delivery to tumor (most commonly bone) is associated with higher grade myelosuppression. However, the tumor antigen sink effect may decrease exposure to other PSMA+ organs leading to less xerostomia and nausea. Clinical trial information: NCT03276572, NCT04506567, NCT04886986, NCT04946370. Research Sponsor: Weill Cornell Medicine; Prostate Cancer Foundation; U.S. Department of Defense; POINT Biopharma; Merck; U.S. National Institutes of Health.

Preliminary phase 2 results of PT-112 monotherapy in late-line metastatic castration-resistant prostate cancer (mCRPC).

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Background: Late-line mCRPC has shown poor outcomes as a result of disease heterogeneity, metastases in bone and viscera including liver, and limited immunotherapeutic options. PT-112 is a novel therapy that inhibits ribosome biogenesis, induces robust immunogenic cell death, concentrates in bone and soft tissue, and previously exhibited clinical activity in patients (pts) with mCRPC. We report the results of a Phase 2 study of monotherapy PT-112 in the late-line mCRPC population. **Methods:** mCRPC pts with ≥3 prior standard of care treatments, including ≥1 androgen receptor pathway inhibitor (ARPI) and 1-2 taxanes with radiographic progression at entry were randomized to one of three dosing arms: Arm 1 (360 mg/m^2 Q2W), Arm 2 (250 mg/m^2 Q2W), and Arm 3 (360 mg/m^2 Q2W in cycle 1, then 250 mg/m^2 D15 of subsequent 28-day cycles). The primary endpoint was to determine the optimal dosing regimen based on safety and efficacy per FDA Project Optimus. **Results:** Pts on the study (N=111) had a median of 4 prior lines of therapy, 69% with ≥2 ARPis, 59% with 2 taxanes, and 24% with PSMA-Lu-177. At entry, pts had liver metastases (19%), bone-only metastases (28%), and evidence of bone progression (74%). The most common treatment-related adverse events (TRAEs) were fatigue (53%), nausea (42%), and anemia (41%); no G5 TRAEs. Discontinuation due to AEs was 12%. Due to superior balance of efficacy and tolerance at interim analysis, Arms 2 and 3 proceeded to full enrollment, while Arm 1 was discontinued. Safety and efficacy metrics are summarized in Table 1. In the more mature Arm 2, OS in pts without prior cabazitaxel (22 pts) was 16.4m and without cabazitaxel or PSMA-Lu-177 (17 pts) was 20.5m. 4% of pts had confirmed PCWG3 bone progression on study. A signal of immune response was observed via TCR sequencing with a statistically significant 20% increase in the percentage of TCR+ blood cells. **Conclusions:** PT-112 treatment resulted in a manageable and reasonably low rate of G3-4 TRAEs and was active in pts with very late-line mCRPC. The better balance of safety and efficacy in Arms 2 and 3 is indicative of an optimized RP3D. Biomarker responses (ALP, CTC and T cell) may reflect broad activity of PT-112. ctDNA analyses are ongoing. OS duration in these heavily pretreated patients, with low rates of bone progression and symptomatic skeletal events (SSEs) on study, are encouraging and supportive of a Phase 3 study of PT-112 vs standard of care. Clinical trial information: NCT02266745. Research Sponsor: Promontory Therapeutics Inc.

Study metrics.

Metric	Arm 1 (n=19)	Arm 2 (n=46)	Arm 3 (n=46)	All Pts (N=111)
G3-4 TRAEs (% of pts)	47	27	43	37
Adherence of dose regimen for first 2 cycles (% of pts)	42	59	67	59
Disease control rate (SD, PR, or CR) at 4 months (% of pts)	27	28	18	23
Median OS (m)	9.0	9.7	10.0	9.7
Median rPFS (m)	3.6	2.5	3.4	3.4
PSA50 (% of pts)	5	17	12	13
CTC0 (n, % of pts)	3/15 (20%)	5/22 (23%)	8/15 (53%)	16/52 (31%)
≥10% ALP decline (% of pts)	74	41	56	52
SSEs in first 4 months (% of pts)	16	4	2	5

Molecular characterization of STEAP1 and -2 in advanced prostate cancer.

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Background: *STEAP*1 and 2 (six-transmembrane epithelial antigen of prostate) are metalloreductase proteins involved in a variety of biologic processes. *STEAP1/2* are tumor-associated cell surface antigens highly expressed in prostate cancer (PC), although their role in cancer is poorly understood. *STEAP1/2* have emerged as successful targets for adoptive T-cell therapy trials for PC. We employed a multi-omics approach to investigate the molecular features associated with *STEAP1* and *STEAP2* expression in PC. **Methods:** NextGen Sequencing of DNA (592 genes or whole exome) and RNA (whole transcriptome) was performed for PC tumors (n = 7089) submitted to Caris Life Sciences (Phoenix, AZ). PC samples were stratified by *STEAP1/2* mRNA levels into top (high) and bottom quartile (low). Immune cell infiltration in the tumor microenvironment (TME) was inferred by quanTIseq. Transcriptomic signatures of androgen receptor signaling (AR), neuroendocrine classification (NEPC), and interferon gamma signaling (IFN) were calculated. Mann-Whitney U and X2/Fisher-Exact tests were applied where appropriate, with P-values adjusted for multiple comparisons ($q < .05$). **Results:** Of 7,089 samples, 63.2% were from the prostate; 11.7% from lymph node metastases (LNM); 7.3% from bone; and 17.8% from visceral/soft tissue metastases (V/STM). *STEAP*-1 and -2 were significantly correlated to each other ($R = 0.90$, $p<.001$), with significantly higher expression of *STEAP1* observed in primary prostate and LNMs, compared with reduced expression in V/STM (*STEAP1* TPM: 105.2 vs 140.6 vs 91.9 $p<.001$). Mutations in *AR* (3.8% v 1.9%), *KDM6A* (4.2% v 2.2%), *SPOP* (10.9% v 8.4%) and *AR*V7 (23.0% v 10.5%) were enriched in *STEAP1* high PC (each $q<.01$). Mutations in *KDM6A* (3.8% v 2.5%) and *AR*V7 (17.6% v 14.3%) were enriched in *STEAP*2 high PC (each $q<.05$). *STEAP1/2* expression negatively correlated with TMB count ($R = -0.03$, $p<.05$) and IFN score ($R = -0.26$, $p<.001$). Concordantly, fewer proinflammatory immune cell fractions (M1 Macrophages, NK cells, CD4+/CD8+ T cells, myeloid dendritic cells) were observed within the TME of *STEAP1/2* high PC ($p<.0001$). However, *STEAP1/2* expression correlated positively with the AR signature ($R = 0.39$, $p<.001$) and androgen response pathways, while correlating negatively with the NEPC signature ($R = -0.15$, $p<.001$). **Conclusions:** PC tumors expressing high *STEAP1/2* display distinct genomic and transcriptomic profiles compared to *STEAP1/2*-low PC, and *STEAP 1/2* expression varies across sites of metastases. Immune biomarkers and immune cell infiltration data suggest that STEAP1/2 may be associated with a cold TME. The recent success of STEAP1-targeting T-cell redirecting therapies mechanisms by which adoptive T-cell strategies may overcome immunosuppressive factors within the TME. Ongoing development of T-cell immunotherapeutics targeting STEAP1 may account for the differential expression profiles in guiding patient selection and combination strategies. Research Sponsor: None.

Characterization and impact of B7-H3 (*CD276*) expression across disease states and racial groups in prostate cancer.

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Background: B7-H3 (*CD276*) is an immunomodulatory protein overexpressed in prostate cancer (PC), representing a promising therapeutic target. However, expression of B7-H3 across PC disease states (hormone sensitive [HSPC], castration resistant [CRPC], neuroendocrine [NEPC]) and across races is poorly understood. We analyzed PC samples from a large clinico-genomic database to comprehensively characterize B7-H3 expression and elucidate its therapeutic potential in PC patients. **Methods:** We analyzed 7,682 PC samples with paired DNA/RNA profiling from Caris Life Sciences. Using *CD276* mRNA expression measured by transcripts per million (TPM), samples were stratified into B7-H3-high (>75% centile) or low (<25% centile) groups. Annotations of HSPCs and CRPCs were based on time of biopsy collection relative to first use of androgen deprivation therapies. NEPC was defined histologically (Epstein, AJSP 2014). Transcriptomic alterations were compared using Mann-Whitney U tests. Overall survival (OS) was obtained from insurance claims data and assessed by Kaplan-Meier and Cox proportional hazards analyses. **Results:** B7-H3 was expressed at similar levels across specimen sites (prostate, lymph node, bone, liver, lung). HSPCs and CRPCs had similar levels of B7-H3 expression, but was reduced in NEPCs (TPM = 5.07, 4.96, 4.48; q<0.0001). While B7-H3-high was associated with worse OS in HSPCs (HR 1.32, 95CI 1.14-1.53, p=0.0002), it was associated with better OS in CRPC (HR 0.82, 95CI 0.69-0.97, p=0.018). B7-H3 expression was comparable in white, African American (AA), and Asian patients. However, Asian patients with high B7-H3 had worse outcomes (HR 4.08, 95CI 2.10-7.93, p<0.0001) while AA patients had improved outcomes (HR 0.74, 95CI 0.57-0.97, p=0.027). In co-expression analyses, B7-H3 was positively correlated with AR transcriptional co-factors (*HOXB13*, *FOXA1*) (R=0.59, 0.47; q<0.0001) but had weaker correlations with lineage plastic factors (*EZH2*, *SOX2*, *ASCL1*) (R=0.26, 0.11, -0.02). Further, B7-H3-high correlated with high AR-score and low-NEPC. Given emergent bi-specific therapeutics in PC, we examined co-expression of B7-H3 with other cell surface targets. TROP2 (*TACSTD2*) and NECTIN-4 (*PVRL4*) exhibited the greatest correlation with B7-H3 (R=0.42, 0.40; q<0.0001); whereas PD-L1 (*CD274*), *CTLA4*, *DLL3*, and *CEACAM5* had weaker correlations (R=0.18, 0.08, 0.14, 0.09). **Conclusions:** High B7-H3 expression worsens prognosis in HSPC but improved prognosis in CRPC. Outcomes differed by race, with B7-H3-high Asian patients exhibiting worse OS while AA patients had better OS. The positive correlation between B7-H3 and AR co-factors suggests that B7-H3 is AR-regulated, at least in CRPC. Lastly, bi-specific approaches may be valuable against B7-H3-high tumors, with co-targeting of TROP2 and/or NECTIN-4. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; R37 1R37CA288972-01.

Plasma epigenomic profiling to reveal molecular correlates of response and resistance to 177Lu-PSMA-617 in metastatic castration-resistant prostate cancer (mCRPC).

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Background: The PSMA-directed radioligand therapy, 177Lu-PSMA-617, is the most recent FDA approved therapy in mCRPC. Despite prolonging progression-free survival (PFS) and overall survival (OS) at a population level, response to therapy is heterogeneous and resistance remains poorly understood. Benchmarking molecular correlates of clinical outcomes following 177Lu-PSMA-617 could provide critical insights into predicting response and resistance to therapy. We applied a multimodal epigenomic liquid biopsy platform to plasma samples from mCRPC patients treated with 177Lu-PSMA-617 to characterize molecular features associated with treatment response. **Methods:** Baseline plasma samples were collected from patients with mCRPC at the time of PSMA PET imaging and initiation of 177Lu-PSMA-617 therapy. Epigenomic profiling of genome-wide signals from promoters, enhancers, and DNA methylation was performed on 1 mL of plasma (N=85, ctDNA $\geq$ 0.5%). Plasma epigenomic signals were analyzed to evaluate pathway activity, their association with treatment response using Cox proportional hazards model and neuroendocrine transformation. Response to 177Lu-PSMA-617 was determined by investigator-assessed clinical-radiographic (CR)-PFS. **Results:** We observed a significant association between predicted PSMA PET SUV_{mean} from plasma epigenomic signals (using a previously derived model) and response to 177Lu-PSMA-617 (hazard ratio [HR] = 0.27, $P<0.05$). Further, unbiased analysis of plasma epigenomic signal across the genome identified *FOLH1* (the gene encoding PSMA) as being significantly associated with CR-PFS ($P<0.05$). Low circulating tumor fraction was also independently associated with favorable CR-PFS (HR = 0.42, $P<0.05$). Pathway analysis identified activation of estrogen signalling and cellular plasticity to be associated with shorter CR-PFS, and immune signalling gene signatures to be associated with longer CR-PFS (all FDR<0.1). A subset of patients (n=4) exhibited increased plasma epigenomic signal at neuroendocrine genes, such as *CHGA*, *DLL3* and *SEZ6*. While too small to draw statistical conclusions, elevated neuroendocrine gene activity in plasma was associated with numerically shorter OS. **Conclusions:** Epigenomic profiling of plasma cfDNA enabled minimally-invasive characterization of molecular correlates of response and resistance, identifying genes and pathways associated with favorable and poor outcomes to 177Lu-PSMA-617 in mCRPC. By providing real-time insights into tumor biology and therapeutic efficacy, this platform supports precision medicine approaches for optimizing outcomes in PSMA-targeted therapies. Research Sponsor: None.

Exploring PSMA heterogeneity and alternative targets expression in PSMA-negative prostate cancer.

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Background: This study aimed to systematically characterize the heterogeneity of PSMA expression in hormone-sensitive prostate cancer (HSPC) and metastatic castration-resistant prostate cancer (mCRPC), and to explore the expression profiles of alternative well-established tumor-associated antigens (TAAs) in PSMA-negative cases. **Methods:** Formalin-fixed paraffin-embedded (FFPE) real-world clinical samples were retrospectively collected from prostate biopsies and bone metastasis surgeries at Peking University First Hospital from 2013 to 2023. Standard immunohistochemistry (IHC) was performed to evaluate PSMA expression, quantified using membranous H-score (MHscore) and cytoplasmic H-score (CHscore).Intra-patient PSMA expression heterogeneity was assessed by Shannon diversity index (SDI) . The normalized membrane ratio (NMR) was defined as: MHscore / (MHscore + CHscore). PSMA-negative PCa was defined as PSMA MHscore $\leq$ 20. PSMA-negative samples were further assessed the expression of alternative TAAs: HER2, NECTIN4, TROP2, TF, B7H3 and STEAP1. **Results:** A total of 127 HSPC and 76 mCRPC cases were identified, including 27 pairs of matched samples. High PSMA expression heterogeneity (SDI >1) was observed in 86 (67.7%) HSPC and 23 (30.1%) mPCa, while moderate heterogeneity (0.5<SDI<1) was found in 20 (15.7%) HSPC and 25 (32.9%) mPCa. PSMA-negative cases were identified in 15.0% of HSPC and 36.8% of mCRPC. PSMA MHscore in HSPC was significantly higher than in mPCa ($p < 0.001$). The expression profiles of alternative TAAs in PSMA-negative cases are shown in Table 1. Additionally, the NMR of PSMA in HSPC was significantly higher than in mPCa ($p < 0.001$). STEAP1 and B7H3 exhibited consistently high NMR in PSMA-negative cases. No significant correlations were observed between PSMA alteration and novel anti-androgen therapy, chemotherapy, or radiation history in matched samples. **Conclusions:** PSMA expression exhibit notable inter- and intra-patient heterogeneity in both HSPC and mCRPC. B7H3 and TROP2 may have relatively more advantageous expression levels in PSMA-negative HSPC, while B7H3 and STEAP1 may potentially show better complementarity in PSMA-negative mCRPC. Research Sponsor: National High Level Hospital Clinical Research Funding (Interdepartmental Clinical Research Project of Peking University First Hospital), Beijing, China.

The expression profiles of alternative TAAs in PSMA-negative prostate cancer.

TAA	PSMA-negative HSPC (n=19) MHscore median(Q1-Q3)	PSMA-negative mCRPC (n=28) MHscore median(Q1-Q3)	p value					
			HER2	TROP2	NECTIN4	TF	B7H3	STEAP1
HER2	3.2(2.8-3.6)	29.3(11.6-70.3)	-	NS	#	###	NS	##
TROP2	84.8(51.2-137.1)	9.9(3.5-56.1)	***	-	NS	#	##	###
NECTIN4	7.1(6.2-12.9)	3.7(2.8-26.8)	***	***	-	NS	##	###
TF	12.5(9.0-72.0)	3.2(2.6-11.0)	***	NS	*	-	###	###
B7H3	110.0(98.9-133.0)	63.5(40.4-96.0)	***	NS	***	***	-	NS
STEAP1	25.7(9.4-103.1)	66.6(23.4-104.0)	***	NS	*	NS	**	-

*for HSPC #for mCRPC. */# p<0.05, **/## p<0.01,***/### p<0.001; NS: not significant.

Comparative effectiveness of cabazitaxel (C) vs. lutetium Lu-177 vipivotide tetraxetan (Lu) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).

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Background: C and Lu are both life-prolonging therapies for pts with mCRPC after progression on androgen receptor pathway inhibitor (ARPI) and docetaxel (D). Herein, our objective was to assess the comparative effectiveness of C vs. Lu in pts with mCRPC with prior progression on D and ARPI in real-world pts in the USA. **Methods:** A de-identified nationwide Flatiron Health electronic health record (EHR)-derived database was used to extract pt-level data. Eligibility: pts with mCRPC who progressed on D and ARPI and received for the first-time single-agent C or Lu. Pts who received alternative Lu or C in a later line of therapy (LOT) were excluded. Endpoints: real-world time to next therapy (rwTTNT) and real-world overall survival (rwOS). These were summarized via Kaplan-Meier survival estimates with a 95% confidence interval (CI) and compared in the context of propensity score (PS) matching weighted analysis using the Cox proportional hazard model. PS model included the following covariates: age, race-ethnicity, socioeconomic status, treatment year, Gleason score, ECOG performance status, log2PSA, alkaline phosphatase, hemoglobin, creatinine, LOT, insurance, and practice type. All the covariates achieved balance after PS matching weighting. **Results:** Among 24,105 pts with metastatic prostate cancer in the dataset, 1,445 met the eligibility criteria and were included (1,227 treated with C, 218 treated with Lu). In C cohort: median age was 73 (IQR 67 – 78), 66.9% had Gleason score $\geq$ 8, and median LOT was 4 (IQR 3-4). In Lu cohort: median age was 75 (IQR 67.25 – 80), 68.1% had Gleason score $\geq$ 8, and median LOT was 4 (IQR 3-5). In PS matching weighting analysis, there was evidence that pts receiving Lu had a significantly improved rwTTNT (median 8.3 months [mo], 95% CI 6.3 – 9.8) compared to those receiving C (median 4.7 mo, 95% CI 4.2 – 5.4) (HR 0.49, 95% CI 0.37 – 0.63, $p < 0.001$), which persisted after adjusting for covariates (HR 0.43, 95% CI 0.32 – 0.57, $p < 0.001$). Additionally, there was evidence that rwOS was longer in pts receiving Lu (median 10.3, 95% CI 8.9 – 12.8) compared to those receiving C (median 8.8 mo, 95% CI 6.6 – 10.8) (HR 0.69, 95% CI 0.51 – 0.92, $p = 0.01$). This improvement in rwOS with Lu compared to C persisted after adjusting for covariates (HR 0.61, 95% CI 0.44 – 0.84, $p < 0.001$). **Conclusions:** This is the largest real-world data to date assessing the comparative effectiveness of Lu vs. C, and it showed significantly longer rwTTNT and rwOS with Lu compared to C in pts with mCRPC pretreated with ARPI and D. Limitations: retrospective nature, selection bias, missingness, lack of randomization, etc. and residual confounding in real-world datasets. Upon external validation, these findings could guide treatment selection in the clinic and design of clinical trials. Research Sponsor: None.

Real-world prevalence of homologous recombination repair alterations (HRRa) and poly (ADP-ribose) polymerase inhibitor (PARPi) use/outcomes in patients (pts) with metastatic prostate cancer (mPC) by race and ethnicity.

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Background: Racial/ethnic (R/E) disparities in prostate cancer incidence and outcomes have long been noted. Increasing evidence points to underlying genetics/biology as potential drivers, which could influence response to targeted tx such as PARPi. Here, we used real-world evidence (RWE) to assess R/E variations in the prevalence of HRRa and outcomes of PARPi therapies in pts with mPC. **Methods:** This retrospective, RWE study used GuardantINFORM, a deidentified clinical genomic database combining claims and genomic data reported from the liquid biopsies, Guardant360 (G360) CDx (HRRa: *BRCA1/2, ATM, CDK12, MLH1*) and LDT (HRRa: *BRCA1/2, ATM, CDK12, CHECK2, FANCA, MLH1, PALB2, RAD51D*). Pts with mPC, age >18, and tested between July 2014 - Sep 2024 were included and grouped into non-Hispanic Black (NHB), non-Hispanic White (NHW), Asian/Other, and Hispanic (any race) cohorts. HRRa and frequency of PARPi treatment (tx) were assessed with two-sided Fisher's exact tests. Outcomes were assessed for PARPi tx overall, as monotherapy, or in combination with androgen receptor pathway inhibitor (ARPI) using pairwise comparisons and log-rank tests. **Results:** 30,913 pts with G360 liquid testing were identified. The rates of HRRa on the LDT panel were significantly higher for NHW (22.8%) when compared to NHB (18.1%, p<0.0001) and Hispanic (19.6%, p=0.017) cohorts. This was similarly seen on the CDx panel for NHW (16.7%) vs. NHB cohorts (15.0%, p=0.018). Similar *BRCA1/2* detection rates (range 5.2-5.8%) and frequencies of PARPi use were observed among R/E groups. No significant differences were observed in real world overall survival (rwOS), time to tx discontinuation, or time to next tx among R/E groups. While not significant, there was a numerical rwOS improvement for NHB when compared to NHW pts treated with PARPi/ARPI combinations (CDx panel, median NR vs. 20.5m, p=0.09), with no NHB pts known to be deceased at the end of follow up (median 10.5 months). **Conclusions:** Using a RWE dataset, we demonstrate distinct rates of HRRa between R/E groups identified using ctDNA analysis. Similar PARPi use among R/E groups suggest tx equity for pts receiving genomic sequencing. The numerically improved rwOS for NHB pts on combination PARPi/ARPI tx is hypothesis generating. This may support other studies demonstrating distinct outcomes in Black vs. White pts treated with ARPI, with potential added benefit in a combination paradigm. Research Sponsor: None.

Cohort	G360, n	LTD: HRRa, %	LTD: PARPi use in HRRa pts, %	CDx: HRRa, %	CDx: PARPi use in HRRa pts, %	LTD+CDx: BRCA1/2+, %	LTD+CDx: PARPi use in BRCA 1/2+ pts, %
All mPC	30,913	21.5	28.0	16.2	29.1	5.6	37.5
NHB	3,216	18.1	30.5	15.0	33.1	5.8	41.9
NHW	19,482	22.8	28.1	16.7	28.8	5.6	38.6
Asian/Other	1,150	20.3	28.9	15.7	28.0	5.7	36.1
Hispanic (any race)	2,152	19.6	30.0	15.3	32.1	5.2	37.5

LBA5078 **Poster Session**

Lower-dose versus standard-dose abiraterone in patients with metastatic castration resistant prostate cancer: A multicentric randomized phase III non-inferiority trial.

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5079 Poster Session

Assessment of PSMA PET/CT derived predictive markers for ^{177}Lu-PSMA-617 treatment outcomes: Results from the U.S. Expanded-Access program.

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Background: ^{177}Lu-PSMA-617 (Lu-PSMA) contributes to prolong progression-free survival (PFS) and overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) patients who progressed after chemotherapy. Pretherapeutic prostate-specific membrane antigen (PSMA) PET/CT information can be used to predict Lu-PSMA therapy response patterns and outcomes, with various quantitative and visual methods proposed. We aimed to test various proposed PSMA PET/CT-derived outcome predictors in the U.S. expanded-access program (EAP) cohort. **Methods:** Patients enrolled in the EAP (NCT04825652) for Lu-PSMA at 3 institutions with available pretherapeutic PSMA PET/CT and outcomes were included in this analysis. Quantitative analysis was performed for all tumor lesions on PSMA PET/CT with semi-automatically contouring. Total tumor volume (TV), total tumor SUVmean, total tumor SUVmax, total lesion uptake (TLU = TV * SUVmean), total lesion quotient (TLQ = TV / SUVmean), and quantitative PSMA PET tumor–to–salivary gland ratio (qPSG: high, $\geq$ 1.5; intermediate, 0.5–1.5; low, $\leq$ 0.5) were calculated for each patient. For visual analysis, visual PSG (vPSG: high, most of the lesions showed higher uptake than the parotid glands; intermediate, neither low nor high; low, most of the lesions showed lower uptake than the parotid glands) and heterogeneity and intensity of tumors (HIT: 1, SUVmax $<$ 15; 2, 15–79 with heterogeneous intensity; 3, 15–79 with homogeneous intensity; 4, $\geq$ 80) scores were used for assessment. Outcomes included a prostate-specific antigen (PSA) PFS, and OS. We evaluated the predictive performance of each model using Cox proportional hazards regression analysis and assessed their performance with the concordance index (c-index). **Results:** In total, 88 patients who received Lu-PSMA within the EAP between May 2021 and March 2022 were eligible and included in this analysis. For the PSA PFS, the total tumor SUVmean achieved the highest c-index of 0.678 (HR 0.91 [95% CI, 0.85–0.97], p = 0.004), followed by the total tumor SUVmax with a c-index of 0.640 (HR 0.99 [95% CI, 0.99–1.00], p = 0.034). For OS, the TLQ achieved the highest c-index of 0.658 (HR 1.01 [95% CI, 1.00–1.01], $p < 0.001$), followed by the total tumor SUVmean with a c-index of 0.634 (HR 0.89 [95% CI, 0.83–0.96], p = 0.004). The HIT score showed the third highest c-index of 0.632; however, when using score 1 as the reference, the HR did not exhibit a sequential trend across ordinal categories as anticipated. **Conclusions:** Quantitative analysis outperformed visual analysis in predicting the outcome of mCRPC with Lu-PSMA therapy in the EAP cohort. Total tumor SUVmean was identified as the most robust predictor for PSA PFS, while TLQ showed promise as a predictor for OS. Incorporating these predictors into clinical decision-making for pre-Lu-PSMA therapy could aid in patient selection and treatment planning. Clinical trial information: NCT04825652. Research Sponsor: None.

Molecular correlates of response in patients with metastatic castration-resistant prostate cancer treated with olaparib with or without cediranib (NCI9984).

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Background: The phase 2 NCI 9984 study (NCT02893917) randomized patients with progressive metastatic castration resistant prostate cancer (mCRPC) 1:1 to the PARP inhibitor (PARPi) olaparib (O) +/- the vascular endothelial growth factor receptor inhibitor (VEGFRi) cediranib (C+O). (C+O) improved radiographic progression free survival (rPFS) compared to (O). Though further development of this combination was precluded in part by toxicity, we hypothesized that defining molecular correlates of response in this study could suggest alternative combination strategies, including alternative VEGFRi, to improve the therapeutic efficacy of PARPi in prostate cancer. **Methods:** Tumor biopsies were reviewed by a pathologist to ensure adequate tumor content. Whole exome DNA sequencing (WES) was performed on pre-treatment biopsies and germline DNA from blood, and RNA sequencing (RNA-seq) was performed on both pre- and on-treatment biopsies. Sequencing data was analyzed using standard computational pipelines to determine tumor-specific DNA variants and gene expression. Mutational signatures were inferred using SigMA, and clonal architecture was inferred using PhylogicNDT. Transcriptome changes were inferred using gene set enrichment analysis and DESeq2. Molecular features were associated with rPFS using descriptive statistics. **Results:** 23 pre-treatment biopsies– 11 (O) and 12 (C+O) – yielded WES data that passed quality control (QC). 62 RNA-seq samples passed QC – 28 (O) and 34 (C+O) – with 30 pair pre-post samples. After stratifying patients with WES data by response above or below the median rPFS for each treatment arm, no genomic alteration was significantly associated with response. We detected evidence of COSMIC mutational signature 3 (Sig3), indicative of HRR deficiency, in 9 pre-treatment samples – 4 (O) and 5 (C+O), only 2 of which contained a *BRCA2* alteration. The presence of Sig3 was not associated with improved rPFS in either treatment arm. RNA-seq demonstrated decreased in HRR and double strand DNA break repair gene sets as well as an increase in interferon signaling with (C+O) treatment. **Conclusions:** Molecular profiling of pre- and on-treatment tumor biopsies confirms prior preclinical observations that the addition of cediranib suppresses the expression of genes associated with HRR, which may explain the improved rPFS of (C+O) treatment relative to (O). No DNA alterations were significantly associated with therapeutic response in this more limited genomic cohort, but we confirm findings from other studies that mCRPC tumors possess mutational signatures of HRR deficiency in the absence of *BRCA2* alterations, which has implications for PARPi deployment in mCRPC. Additionally, our work broadly demonstrates the both the feasibility and sample attrition rate of correlative studies on clinical trials. Research Sponsor: National Cancer Institute.

5081 Poster Session

Clinical implications of HER3 overexpression in a diverse patient cohort with prostate cancer.

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Background: Prostate cancer (PCa) contributes to almost 15% of US cancer cases annually with significant racial disparities, where black men are more likely to develop and die from prostate cancer than any other cohort. Previously, we reported that *HER3/ERBB3* overexpression (OE) was enriched in the tumors of Black/ African American patients and was correlated with a unique androgen receptor signature as well as worse clinical outcomes. Here, we evaluate an expanded and more mature patient cohort to understand the effect of HER3 OE on clinical outcomes. In vitro experiments further support the targeting of HER3 in prostate cancer disease. **Methods:** Chart review was performed on a diverse cohort of PCa patients from the University of Illinois Health (n=106). Tempus laboratories performed whole transcriptome RNA sequencing, and HER3/*ERBB3* OE status was determined by Tempus as compared to a reference database. Patients were grouped into HER3 OE and wild-type groups, and clinical outcomes were analyzed between groups using students' t-test and Kaplan Meier plots with the Gehan-Breslow-Wilcoxon test. LNCaP cells were virally transduced with HER3 overexpression and non-targeting control vectors and validated via Western blot. Cell growth was quantified via nuclear fluorescence object count using Incucyte instruments and software. Drug treatment efficacy was validated via Western blot. **Results:** The final cohort (n= 71 Black/AA, 19 white, and 5 other) demonstrated 42% of patients presenting with HER3 OE. A majority of patients presented with de novo metastases (55% of HER3 OE, 45% of HER3 WT). Of patients who initially presented with localized disease, time to metastasis was significantly faster in the HER3 OE group (p=0.04). HER3 OE was also associated with faster time to the development of castration resistance (p=0.02). In preclinical PCa models, HER3 OE cells grew significantly faster than control($p \leq 0.01$), and were less sensitive to enzalutamide($p \leq 0.01$). Additionally, we found that by inhibiting HER3 signaling (patritumab, erlotinib, trastuzumab, capivasertib) PCa cells become more sensitized to enzalutamide($p \leq 0.01$), suggesting a role for dual AR and HER3 targeting in PCa treatment. **Conclusions:** Our clinical and translational data supports the role of HER3 overexpression as a novel and targetable prognostic marker in diverse patients with PCa. Future studies should further evaluate HER3 inhibition in combination with AR targeted therapies to improve therapy sensitivity and reduce development of resistant disease. Research Sponsor: None.

Ceramides and response to dual secondary hormonal therapy in metastatic castration-resistant prostate cancer (mCRPC) among Black men.

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Background: Multiple reports suggest that Black patients with mCRPC have different responses to radiation, immunotherapy, chemotherapy, and secondary hormonal therapy compared with White patients with mCRPC. In our prospective trial of combination therapy with apalutamide (Apa) and abiraterone acetate (AA) plus prednisone (P) among Black and White men with mCRPC (PANTHER, ClinicalTrials.gov identifier NCT03098836), we previously reported the 24-month radiographic progression-free survival (rPFS) for Black and White men were 61% (95% CI 49, 78) and 38% (95% CI 27, 54), while the 36-month overall survival (OS) rates were 68% (95% CI 55, 83) and 50% (95% CI 37, 66), respectively. Our previously reported exploratory genome-wide analysis identified genetic ancestry-related single nucleotide polymorphisms in genes that were known to play a role in ceramide metabolism that associated with time to prostate specific antigen (PSA) progression on AA + P therapy in mCRPC. Ceramides are associated with cancer biology and therapeutic outcomes, with ceramide Cer(d18:1/20:0), in particular, having been reported as a biomarker for colon cancer. Ceramide Synthase 4 (CerS4), which produces Cer(d18:1/20:0), has been reported to be associated with worse prognosis in colorectal cancer. We therefore hypothesized that expression of distinct ceramide species may be associated with rPFS or OS among Black and White patients with mCRPC treated with combination Apa and AA + P in the PANTHER study. **Methods:** Serum from 37 White and 28 Black patients enrolled in the PANTHER study who had fasted for 8-12 hours was collected and evaluable at baseline. Metabolomic profiling was done using the Biocrates MxP Quant 500 Kit. Median levels for each of 26 ceramides were calculated using the study population and used as a cut point. Cox proportional hazard models were used to calculate the hazard ratio for rPFS and OS associated with above or below median ceramide expression. Models were stratified by race. **Results:** In the PANTHER study, among Black patients, expression of Cer(d18:1/20:0) was associated with rPFS (HR 4.02; 95% CI 1.06, 15.2; p value = 0.041), but there was no significant association found among White patients. Expression of Cer(d18:1/20:0) was also associated with improved OS among Black patients (HR 4.82; 95% CI 1.51, 15.4; p = 0.008), but there was no significant association found among White patients. No significant associations were found with any other ceramides. **Conclusions:** Our study showed that Cer(d18:1/20:0) associated with prolonged rPFS and OS among Black patients with mCRPC treated with the combination of Apa and AA + P therapy. Pending validation, this distinct ceramide species has potential to serve as a predictive indicator of response to combination Apa and AA + P therapy among Black mCRPC patients. Drug and funding for Abi Race and PANTHER provided by Janssen Scientific Affairs, LLC. Research Sponsor: Janssen Scientific Affairs, LLC; Department of Defense Prostate Cancer Research Program; W81XWH1910458.

Integrated CTC- and EV-based detection of PSMA protein and efficacy of ^{177}Lu-PSMA-617 radioligand therapy.

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Background: Blood-based predictive biomarkers of sensitivity to ^{177}Lu-PSMA-617 are lacking, and may facilitate clinical decisions. Here, we studied whether integrated PSMA protein detection in circulating tumor cells (CTCs) and extracellular vesicles (EVs) is associated with outcomes in patients receiving ^{177}Lu-PSMA therapy. **Methods:** We enrolled 100 metastatic castrate-resistant prostate cancer (mCRPC) pts who were candidates for ^{177}Lu-PSMA into a prospective biomarker trial. Blood samples were collected for CTC and EV analysis at baseline, at the time of response, and at progression. Baseline characteristics included serum PSA, alkaline phosphatase (ALP), hemoglobin, albumin, and radiographic tumor burden. PSMA+ CTCs were enumerated using an AI-empowered holographic imaging platform combined with in-flow protein marker analysis (Astrin Biosciences, St. Paul, MN); PSMA protein was quantified in plasma EVs using shotgun proteomics via mass spectrometry (Arafa et al., *Cancers* 2024; 16: 4261). We assessed the impact of PSMA+ CTCs and EV-derived PSMA protein on PSA_{50} responses, PFS, and OS. Multivariable Cox regressions were used to adjust for baseline PSA, ALP, and hemoglobin. Exploratory analyses of other EV-derived proteins were also conducted. **Results:** Of 100 enrolled pts, 47% had Gleason sum 9-10, 62% had >10 bone mets, 12% had visceral mets, 72% had received ≥3 prior systemic therapies, and median PSA was 57 (range 1.5–5,000) ng/mL. High PSMA+ CTC counts (> median) were associated with shorter overall survival (OS) (HR 2.71, 95%CI 1.18–6.21, p=0.02). PSA_{50} response rates were similar for those with high and low PSMA+ CTC counts (39% vs 42%, p=0.8). Shotgun proteomics from plasma EV samples identified >11 000 unique proteins, of which 12% represented the cell surfaceome. EV-PSMA protein correlated with baseline PSA, ALP, and tumor burden (all $p<0.05$). High EV-PSMA protein (> median) was associated with worse OS (1.81, 95%CI 0.97–3.35, p=0.06). PSA_{50} response rates were similar for those with high and low EV-PSMA protein (48% vs 42%, p=0.5). After multivariate adjustment, nonsignificant trends for shorter OS persisted for pts with high PSMA+ CTCs (HR 1.71, 95%CI 0.72–4.05) and high EV-PSMA levels (HR 1.49, 95%CI 0.78–2.84). Worse OS was also observed in pts with high EV levels of B7-H3 (HR 2.85, 95% CI 1.58–5.14, p=0.002), Trop-2 (HR 2.23, 95%CI 1.22–4.05, p=0.008), and STEAP1 (HR 1.69, 95%CI 0.93–3.06, p=0.08) proteins. **Conclusions:** In mCRPC pts receiving ^{177}Lu-PSMA, high PSMA+ CTC counts and high EV-derived PSMA levels portended poor survival. PSMA protein may be a novel blood-based biomarker of ^{177}Lu-PSMA sensitivity, facilitating treatment decisions, with relevance for other PSMA-targeting strategies. The robust detection and prognostic impact of additional cell-surface proteins (*e.g.* B7-H3, Trop-2, STEAP1) may fuel the development of alternative novel therapeutics. Research Sponsor: The American Cancer Society; Novartis; University of Minnesota Translational Working Group.

Transcriptional profiling to identify a program of enzalutamide extreme non-response in lethal prostate cancer.

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Background: The androgen receptor pathway inhibitor (ARPI) enzalutamide is one of the principal treatments for metastatic hormone-naïve and castration-resistant prostate cancer (CRPC). Most patients respond to enzalutamide. However, tumors from a subset of patients exhibit extreme non-response and are primary refractory to treatment. We sought to understand the gene expression program of enzalutamide extreme non-response (ENR) and identify alternate therapeutic approaches for tumors driven by this program. **Methods:** We analyzed gene expression by RNA-sequencing in pre-treatment metastatic biopsies from men with CRPC treated on a prospective enzalutamide clinical trial (NCT02099864). We focused on those with ENR (progression within 3 months) vs. long-term response (progression after 24 months) and identified a gene program linked to enzalutamide ENR. We validated the utility of this program in additional patient cohorts using a multivariable analysis and in preclinical models. **Results:** Unsupervised clustering correctly classified ENR patients whose tumors harbored proliferative, epithelial-to-mesenchymal transition, and stemness genes sets. Using a supervised approach, we developed a gene signature to measure the ENR program. High expression of this program in CRPC patient validation cohorts was independently associated with poor tumor control with AR targeting in multivariable analysis. Conversely, high expression of the program was independently associated with benefit with docetaxel chemotherapy, suggesting the ENR program is predictive and not merely prognostic. In support of our findings, high expression of the ENR program was strongly linked to docetaxel sensitivity in a large panel of CRPC models. Finally, we identified putative regulators of the ENR program—several of which can be targeted pharmacologically with agents that are FDA-approved or in clinical trials. **Conclusions:** The enza ENR program we identified is independently predictive of ENR to AR targeting. However, patients whose tumors harbor this program may be good candidates for docetaxel chemotherapy or clinical trials testing agents that block putative regulators of this program. Research Sponsor: Stand Up to Cancer-Prostate Cancer Foundation (PCF) Prostate Dream Team; SU2C-AACR-DT0409; National Cancer Institute; R01CA251245, R01CA282005, R01GM147365, T90 DE030859, P50 CA186786; National Comprehensive Cancer Network (NCCN)/Astellas Pharma Global Development, Inc./Pfizer, Inc.; National Comprehensive Cancer Network (NCCN)/Astellas Pharma Global Development, Inc./Pfizer, Inc. Award; U.S. Department of Defense; W81XWH-21-1-0539,W81XWH-22-1-0833, HT94252410252.

Integrated analysis of tissue genomic sequencing and high purity circulating tumor cell RNA sequencing for prostate cancer lineage states as a prognostic factor for survival and resistance to 177Lu-PSMA-617 in patients with metastatic castrate resistant prostate cancer.

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Background: Genomic mutations, including *RB1*, *PTEN*, and HRR genes, associate with poor prognosis and treatment resistance in metastatic prostate cancer (mPC). mPC lineage states such as neuroendocrine prostate cancer (NEPC) also drive resistance and poor survival. Identifying the timing and association of genomic mutations with lineage states has been limited by the challenges of obtaining serial tumor biopsies. We report an integrated analysis of clinical next-generation sequencing (NGS) data, ctDNA, and mPC lineage state phenotypes with a novel high purity circulating tumor cell (CTC) RNA sequencing method. **Methods:** We collected 273 CTC samples from 117 patients with mPC in a prospective biomarker trial. 69 patients had clinical NGS from a recent tissue biopsy and 60 patients treated with $PSMA^{LU}$. CTCs were purified via immunomagnetic capture on a microfluidic platform and analyzed via RNA-seq. We compared CTC lineage states, somatic mutation status and median overall survival (mOS). **Results:** Gene expression analysis of high CTC purity samples identified four CTC phenotypes: luminal A-like (LumA), luminal B-like (LumB), low proliferation (LP), and neuroendocrine (NE). Compared to patients with low CTC burden/purity (mOS NR), patients with LumA and LP phenotypes had similar survival ((LumA: mOS 13mo, p=ns, LP: mOS: 11.8mo, p=ns), while patients with LumB and NE phenotypes had shorter survival (LumB: mOS 6mo, HR 9.1[3.8-21.8], p<0.0001, NE: mOS 3.7mo, HR 11.8[2.4-57.2]), p=0.0019). mOS for patients with high-risk genomic mutations (*RB1*, *PTEN*, *TP53*) and a LumA or LP lineage state was 12.7mo versus 4mo for patients with high-risk mutations and a LumB or NE lineage state (HR 3.59 [1.51-8.51], p=0.004). mOS was not reached for patients without high-risk mutations and a LumA or LP lineage state vs 8mo for patients without high-risk mutations but a LumB or NE lineage state (HR 19.7 [1.99-1.95], p<0.0001). Among patients treated with 177Lu-PSMA-617 in a prospective substudy (n=37), no patients had pretreatment CTC NE phenotype, but pre-treatment CTC LumB phenotype was associated with decreased rPFS (3.5mo vs 11.7mo, HR 4.8 [95% CI 1.4-16.1], p<0.005) and OS (7.6mo vs NR, HR 9.3 [95% CI 2.3-37.8], p<0.0005) compared to pretreatment LumA/LP/Low CTC burden phenotypes. **Conclusions:** Lineage states detected by high purity CTC RNAseq are prognostic for poor OS and decreased benefit from 177Lu-PSMA-617. The presence of high-risk genetic mutations including *RB1* is prognostic for poor OS and combined evaluation of high-risk genetic mutation status with lineage state phenotype identifies patients with the worst clinical outcomes that would benefit from treatment intensification and early disease monitoring for these more aggressive subtypes of mCRPC. Research Sponsor: None.

Association between epigenomic biomarkers and baseline clinical characteristics in patients with mCRPC treated with rucaparib in TRITON2.

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Background: TRITON2 is a phase 2 study evaluating rucaparib in 277 patients with metastatic castration resistant prostate cancer (mCRPC). PSA has been used to predict radiographic progression free survival (rPFS), overall survival (OS) and monitor response, however, new approaches are needed to improve performance. Recently, it has been demonstrated that hypermethylated tumor DNA in the peripheral blood can be used to detect and monitor response and as a prognostic marker. Here, we evaluate the association between baseline methylation-based tumor fraction (TF) and clinical outcomes in patients with mCRPC. **Methods:** Pre-treatment plasma samples from patients participating in TRITON2 were sequenced using Guardant Infinity, a next-generation sequencing platform that evaluates genomics and epigenomics with ~15Mb of coverage for methylation-profiling and quantification. TF is calculated from thousands of cancer-type specific differentially hypermethylated regions. Patient outcomes were evaluated using the median-split baseline values for TF and PSA vs rPFS and OS by Cox proportional hazard model. **Results:** Two hundred thirty of 277 patients were eligible for baseline analysis and were successfully sequenced. Methylation-based TF was detected in 229/230 patients (99.6%). TF ranged from 0.02% to 99%, with a median of 25.1%. Baseline methylation-based TF was associated with Gleason score (p=0.012) but was only very weakly correlated with PSA levels (R^2=0.09). Patients with baseline TF $\leq$ median demonstrated superior rPFS and OS vs those $>$ median (HR=0.54, p=0.013; HR=0.42, p= 3.72e-07), respectively. In contrast, baseline PSA was only associated with superior OS (HR=0.52, p=1.31e-04), but not rPFS (HR=0.71, p=0.186). **Conclusions:** In patients from TRITON2, methylation-based TF appeared superior to PSA for tracking disease activity, both in terms of rPFS and OS. This suggests that methylation-based TF is a candidate disease monitoring tool that should be further investigated as a potential replacement for both radiological and PSA-based disease monitoring. Clinical trial information: NCT02952534. Research Sponsor: None.

Genomic landscape and clinical characteristics of patients (pts) with neuroendocrine prostate cancer (NEPC) with or without aggressive variant prostate cancer characterized by molecular signature (AVPC-MS).

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Background: NEPC is a rare, aggressive subtype that can arise *de novo* or after treatment with androgen receptor inhibitors. Recent NEPC clinical trials have also included pts who have AVPC-MS (Aggarwal *et al*, ASCO 2024). However, the prevalence and clinical characteristics of NEPC with or without AVPC-MS need further investigation. **Methods:** The de-identified Tempus Lens dataset was used to retrieve records of pts diagnosed with NEPC. Pts were classified as having AVPC-MS if they had ≥2 alterations in *TP53*, *RB1*, and/or *PTEN*. Demographic and clinical characteristics were summarized using descriptive statistics and compared between individuals with and without AVPC-MS using chi-square and Fisher's exact tests. The prevalence of genomic alterations between pts with and without AVPC-MS was compared using a two-proportions Z-test with False Discovery Rate (FDR) correction to account for multiple comparisons. **Results:** A total of 308 pts diagnosed with NEPC were identified and included in this analysis. Among them, 124 (40.3%) had *RB1*, 141 (45.8%) had *TP53*, and 64 (20.8%) had *PTEN* alterations. A total of 109 (35.4%) pts met the criteria for AVPC-MS whereas 81 (26.2%) pts harbored only a single alteration in either *TP53*, *RB1*, or *PTEN* and thus did not meet the criteria. The proportion of individuals aged >60 years was similar between those with and without AVPC-MS (56.0% vs. 58.8%, p=0.70). Additionally, 48.6% of pts with AVPC-MS were white, compared to 60.8% of those without AVPC-MS (p=0.03). Mortality rates did not significantly differ between the groups (66.1% in AVPC-MS vs. 61.8% in non-AVPC-MS, p=0.40). Individuals with AVPC-MS had significantly higher alterations of *TMPRSS2* (38.5% vs. 18.1%) and *PIK3CA* (8.3% vs. 2.5%) compared to those without AVPC-MS (FDR-adjusted $p < 0.05$). However, no significant difference was observed for alterations in *FOXA1* and *BRCA2* in the AVPC-MS group compared to non-AVPC-MS (10.1% vs. 10.1% and 8.3% vs. 11.1%, respectively). Among pts with available data, high tumor mutational burden (TMB) was observed in 7.8% (8 of 103) of pts with AVPC-MS compared to 2.1% (2 of 97) of those without AVPC-MS (p=0.10). Similarly, microsatellite instability-high (MSI-high) was detected in 6.6% (7 of 106) of pts with AVPC-MS and 1.9% (2 of 106) of those without AVPC-MS (p=0.17). **Conclusions:** Approximately one in three patients with NEPC also meet the criteria for AVPC-MS. Our findings suggest that the biological drivers for NEPC are mutually exclusive from AVPC-MS in most patients, and highlight the importance of utilizing pathologic confirmation of NEPC rather than relying on genomic surrogates. Further research is warranted to explore the clinical implications of these genomic differences and to develop personalized treatment approaches for pts with AVPC-MS. Research Sponsor: None.

Triplet versus doublet therapy in older patients with metastatic hormone-sensitive prostate cancer: A network meta-analysis.

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Background: Multiple treatment options are now available for metastatic hormone-sensitive prostate cancer (mHSPC) with the expanded approval of androgen receptor axis-targeted (ARAT) agents. Comparing the therapeutic benefits of these treatments in older patients would contribute to selecting the optimal treatment for this population. **Methods:** We performed a systematic search of PubMed, Embase, Web of Science and Cochrane library for randomized controlled trials (RCTs) evaluating the efficacy of androgen deprivation therapy (ADT) in combination with ARAT agents and/or docetaxel in older patients (aged ≥70 or ≥75 years) with mHSPC. A network meta-analysis (NMA) was conducted to compare and rank the efficacy of the available treatment options. The first NMA compared four treatment classes, grouping ARATs as a single class: ARAT + ADT + docetaxel, ARAT + ADT, ADT + docetaxel, and ADT alone. The second NMA analyzed seven treatment options, treating different ARAT agents as independent regimens: two triplets (abiraterone or darolutamide) + ADT + docetaxel, three doublets (abiraterone, enzalutamide, or apalutamide) + ADT, ADT + docetaxel, and ADT alone. A random effects model was used to estimate hazard ratio (HR) for overall survival (OS) for each treatment. **Results:** 10 RCTs comprising 3,496 patients were analyzed. In the first NMA (grouping ARAT agents as a single class), triplet therapy was associated with a significant 30% lower risk of death compared to ADT + docetaxel (HR 0.70, 95% CI 0.50-0.96), and a non-significant 31% lower risk of death compared to ARAT + ADT (HR 0.69, 95% CI 0.43-1.11). In the second NMA (treating different ARAT agents as independent treatments), darolutamide + ADT + docetaxel was associated with a significant improvement in OS with HRs of 0.47 (95% CI: 0.28-0.78) and 0.61 (95% CI: 0.40-0.94) compared to ADT alone and doublet (ADT + docetaxel), respectively. However, the triplet of abiraterone + ADT + docetaxel was associated with a non-significant OS benefit, with HRs of 0.61 (95% CI 0.36-1.04) and 0.80 (95% CI 0.51-1.25) compared to ADT alone and ADT + docetaxel, respectively. The triplet therapies with darolutamide and abiraterone ranked first and second, with P score of 0.92 and 0.69, respectively, followed by apalutamide + ADT (0.62), enzalutamide + ADT (0.59), ADT + docetaxel (0.42), abiraterone + ADT (0.21) and ADT alone (0.05). Further, our data suggest a clear additional benefit from adding docetaxel as a component of doublet and triplet therapies, as shown by the superiority of ADT + docetaxel over ADT alone (P score 0.42 vs 0.05) and abiraterone + ADT + docetaxel over abiraterone + ADT (P score 0.69 vs 0.21). **Conclusions:** Triplet therapy of darolutamide + ADT + docetaxel should be prioritized over other treatment options for fit older patients with mHSPC. Further research utilizing real-world effectiveness data is essential to validate this recommendation. Research Sponsor: None.

Prognostic validation of six androgen production, uptake, and conversion genes (APUC-6) in the CHAARTED prostate cancer trial.

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Background: Metastatic prostate cancer (mPC), whether synchronous or metachronous, remains incurable. Persistent androgen receptor (AR) activation promotes tumor progression and metastasis and impacts patient survival. A group of six genes (*HSD3B1*, *HSD3B2*, *CYP3A43*, *CYP11A1*, *CYP11B1*, *CYP17A1*) involved in androgen production, uptake, and conversion (APUC-6) has been identified, exhibiting cohesive behavior that may define a subset of mPC with distinct clinical outcomes. Our study investigates the association of APUC-6 genes with clinical outcomes in metastatic hormone-sensitive prostate cancer (mHSPC) and their potential to predict differential therapeutic responses. **Methods:** We analyzed APUC-6 and *AR* expression in microarray data from the phase 3 ECOG-ACRIN E3805 CHAARTED trial (n=160). Synchronous high-volume disease patients (n=113 or 70%) composed the majority of profiled cases. Patients were stratified into four subgroups based on APUC-6 and *AR* gene expression: APUC-6 high/*AR* low (n=34), APUC-6 high/*AR* high (n=6), APUC-6 low/*AR* low (n=86) and APUC-6 low/*AR* high (n=34). Key clinical outcomes included progression-free survival (PFS), time-to-castration resistance (ttCR) and overall survival (OS), with subgroup analyses based on the timing of metastasis. **Results:** Standard clinicopathologic factors were balanced between subgroups except lower proportion of patients with Gleason score ≥8 in APUC-6 high/*AR* low subgroup (68.8% versus 81.0%-100% other subgroups).APUC-6 expression was significantly negatively correlated with *AR* expression (R= -0.26, p=0.001). Patients with APUC-6 high/*AR* low expression represented a distinct subgroup that showed significantly improved PFS (median PFS 47.3 months, $p<0.0001$), ttCR (median ttCR 17.3 months, p=0.0011) and OS (median OS 58.1 months, $p<0.0001$) compared to other subgroups, including APUC-6 low/*AR* high (PFS: median PFS 17.7 months, hazard ratio (HR) 0.43, CI 0.22-0.82, p=0.0092; ttCR: median ttCR 12.0 months, HR=0.56, CI 0.32-1, p=0.049; OS: median OS 29.4 months, HR 0.31, CI 0.16-0.61, p=0.00032). Similar survival benefits of APUC-6 high/*AR* low subgroup were observed within patients with synchronous high-volume disease (median PFS 23.1 months, p=0.0022; median ttCR 14.9 months, p=0.021; median OS 57.6 months, p=0.00038). **Conclusions:** In the CHAARTED mHSPC cohort, APUC-6 expression was inversely correlated with *AR* expression. The APUC-6 high/*AR* low subgroup exhibited favorable PFS, ttCR and OS outcomes and maintained the survival benefits in synchronous high-volume disease. These findings suggest that high APUC-6 expression with low *AR* expression may define a favorable-risk mHSPC subgroup with distinct therapeutic implications. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U54CA273956; The Movember Foundation; The Distinguished Gentlemen's Ride; The Prostate Cancer Foundation; The Department of Defense; W81XWH-21-1-0296; From an anonymous donor.

8-year outcomes of enzalutamide (ENZA) versus a non-steroidal anti-androgen (NSAA) for metastatic, hormone-sensitive prostate cancer (ENZAMET; ANZUP 1304).

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Background: We previously reported that ENZA improved overall survival (OS) after median follow-up times of 34 and 68 months, in comparison with a NSAA, when added to testosterone suppression, with or without concurrent early docetaxel, for mHSPC. We now report outcomes after median follow-up of 98 months. **Methods:** Participants (pts) with mHSPC were randomly assigned (1:1) from 31MAR2014-24MAR2017 to treatment with ENZA 160 mg or NSAA, in addition to testosterone suppression. Concurrent early docetaxel was used in 45%. OS was the primary endpoint and analysed with the Kaplan-Meier method, log-rank test for p-values, and Cox regression for hazard ratios (HR). Secondary outcomes included deaths due to prostate cancer (PC) versus (vs) other causes. The numbers of pts experiencing specified adverse events (AE) of grade 3-5 are expressed per 100 person-years of study treatment exposure to account for differing treatment durations. **Results:** After a median follow-up of 98 months, data cut-off 30JUN2024, death was reported in 285/563 (51%) pts assigned ENZA vs 337/562 (60%) assigned NSAA. OS was longer among those assigned ENZA than NSAA (medians 95 vs 70 months; OS at 96 months 50% vs 40%; HR 0.73, 95% CI 0.63 to 0.86; p=0.0001). Clinical PFS also continued to favour ENZA over NSAA (HR 0.49; 95% CI 0.42 to 0.57; p<0.0001). PC accounted for 468 of all 622 deaths, and were less frequent among those assigned ENZA than NSAA (207 vs 261). Deaths due to other causes accounted for a total of 154 deaths, and were similarly frequent among those assigned ENZA vs NSAA (78 vs 76). Mean duration of study treatment was longer for ENZA than NSAA (58 vs 36 months). 185/562 (33%) remain on ENZA with 88% on full dose. G3-5 AE of interest were reported in the following numbers of pts per 100 years of study treatment with ENZA vs NSAA: cardiac disorder 2.2 vs 2.2, nervous system disorder 2.3 vs 2.0, fall 0.70 vs 0.24. Causes of death according to PSA at 7 months are tabulated below. Among those with PSA at 7 months ≤0.2, deaths were due to PC in 29%, and other causes in 13%. Among those with PSA at 7 months >0.2, deaths were due to PC in 60%, and other causes in 13%. **Conclusions:** Treatment with enzalutamide continues to confer substantial OS benefits at 8 years. These findings highlight long-term safety, toxicities, non-PC causes of death, and survival outcomes of those with and without PSA ≤0.2 at 7 months. ClinicalTrials.gov Identifier NCT02446405. Clinical trial information: NCT02446405. Research Sponsor: Astellas; Cancer Council Australia; The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).

Landmark analysis by PSA at 7 months	ENZA (N=555)	NSAA (N=549)	ALL (N=1104)
Deaths due to prostate cancer, PSA ≤0.2	100/375 (27%)	87/270 (32%)	187/645 (29%)
Deaths due to other causes, PSA ≤0.2	54/375 (14%)	33/270 (12%)	87/645 (13%)
Deaths due to prostate cancer, PSA >0.2	104/180 (58%)	170/279 (61%)	274/459 (60%)
Deaths due to other causes, PSA >0.2	22/180 (12%)	39/279 (14%)	61/459 (13%)

5091 Poster Session

Prognostic value of PSMA PET against CHAARTED criteria in an ENZAMET sub-cohort.

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Background: CHAARTED criteria using CT and bone scan are widely recognized as prognostic in metastatic, hormone-sensitive prostate cancer (mHSPC) and can guide decisions about treatment, including intensification. However, clinicians are increasingly using PSMA PET/CT (PSMA-PET) instead of conventional imaging. Currently, PSMA-PET criteria for identifying poor prognostic mHSPC has limited evidence. The aim of this study is to identify features on PSMA PET/CT that correlate to progression free survival (PFS) and overall survival (OS) in the context of CHAARTED criteria in an ENZAMET sub-cohort. **Methods:** ENZAMET (ANZUP 1304, NCT02446405) is an international, open-label, randomized, phase 3 trial. Eligible participants had mHSPC evident on CT and/or bone scan. Participants (pts) were randomly assigned (1:1) to receive testosterone suppression plus enzalutamide or a non-steroidal antiandrogen (NSAA). Pts who underwent PSMA-PET prior to study enrolment were identified for this sub-study. Imaging (PSMA-PET, CT, bone scan) were de-identified, and centrally evaluated by three imaging experts blinded to clinical outcomes for number, site, and intensity of metastatic deposits. Additional correlative findings on bone scan and PSMA-PET/CT were determined. A semi-automated quantitative imaging analysis was undertaken to derive PSMA-total tumor volume (PSMA-TTV). The analysis evaluated the association between PSMA-TTV (analysed continuously and as quartiles Q1-3 vs Q4), site (lymph node, bone, viscera) with PFS, OS, and CHAARTED criteria. Kaplan-Meier survival estimates, log-rank tests, and Cox regression after adjusting for treatment arm were used for analysis. **Results:** 100 pts (51 enzalutamide, 49 control NSAA) had a PSMA-PET/CT prior to enrolment. In this sub-cohort, median age was 69 years, 36 were synchronous, 74 patients were low volume on CHAARTED criteria. On PSMA-PET 19 pts had bone only disease, 37 had lymph node (LN) only, 33 bone and LN and 9 visceral involvement. In 54 pts with bone involvement on PSMA-PET, 53 had concordant findings on bone scan. Median PSMA TTV in the study cohort was 28 mL (61 mL vs 22 mL in CHAARTED high vs low volume) with the highest PSMA TTV quartile (Q4) >71mL. 5-year PFS for PSMA TTV Q4 vs Q1-3 was 36% vs 61% (p=0.011), with HR per doubling of TTV = 1.19 (95%CI: 1.03 – 1.38). In the pts with CHAARTED criteria low volume mHSPC, 5-year PFS for PSMA TTV Q4 vs Q1-3 was 21% vs 57% (p<0.001). 5-year OS for PSMA TTV Q4 vs Q1-3 was 60% vs 74% (p=0.18) with HR per doubling of TTV = 1.10 (95%CI: 0.91 – 1.32). **Conclusions:** PSMA-TTV is associated with PFS in mHSPC in this ENZAMET sub-cohort with the highest volume quartile (>71mls) showing significantly shorter PFS, including within the CHAARTED criteria low volume cohort. Further validation of PSMA-TTV as a prognostic biomarker with potential to identify patients for intensification is warranted in larger mHSPC cohorts. Clinical trial information: NCT02446405. Research Sponsor: Astellas; Cancer Council Australia; The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).

How low do you need to go? Association between various prostate-specific antigen (PSA) response measures and clinical outcomes in metastatic castration-sensitive prostate cancer (mCSPC) in the Veteran Health Administration (VHA) data.

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Background: Clinical trials show that combined treatment (tx) with androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPIs) improves PSA response and overall survival (OS) in patients (pts) with mCSPC. Our real-world study assessed the impact of PSA response on OS and progression in pts receiving ADT ± other tx. **Methods:** VHA data (2017–2024) were analyzed for adults with mCSPC who initiated index tx, ie, ADT ± other tx (ARPI, nonsteroidal antiandrogen [NSAA], docetaxel), and had PSA values at baseline (365 days prior to ADT initiation [index date]) and during index tx. PSA response was examined as: 1) ≥90% decline from baseline PSA; 2) PSA <0.2 ng/mL during index tx. Progression was defined as PSA progression (≥25% rise and ≥2 ng/mL increase from nadir PSA during PSA follow-up [index date to 8/31/2024]), initiation of a new tx, hormone resistance or death. Landmark analyses with Cox proportional hazards regressions assessed the association of PSA response (by 9 months [mo] post index date) with OS and time to progression after 9 mo post index date. **Results:** Overall, 4890 pts started first line mCSPC tx: ADT alone, 47%; ADT + ARPI, 40%; ADT + NSAA, 7%; ADT + docetaxel (± ARPI ± NSAA), 6%. Median follow-up was 24.7 mo, with a median PSA follow-up of 14.6 mo. During PSA follow-up, 44% of pts reached PSA <0.2 ng/mL and 74% had ≥90% PSA decline from baseline. PSA decline of ≥90% was related to a 22% reduced risk of death but was unrelated to progression (Table). In contrast, PSA <0.2 ng/mL was associated with greater reduction in the risk of death (54%) and progression (55%). **Conclusions:** In a real-world mCSPC setting, pts who achieved PSA <0.2 ng/mL within 9 mo of initiating ADT ± other tx had lower risk of death and progression than pts who did not. Reaching ≥90% PSA decline was modestly associated with improved OS but not progression, suggesting a PSA nadir of <0.2 ng/mL is needed for optimal outcomes. Disclosure: A genAI tool (01/09/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. Research Sponsor: The study was sponsored by Pfizer Inc. and Astellas Pharma Inc., the co-developers of enzalutamide. Medical writing support was provided by Roham Sadeghimakki and Rosie Henderson of Onyx (a division of Prime, London, UK), funded by the sponsors.

	≥90% PSA decline		PSA <0.2 ng/mL	
	Achieved	Not achieved†	Achieved	Not achieved†
OS‡§				
Pts at risk, n	2609	683	1512	1780
Events, n (%)	672 (26)	224 (33)	236 (16)	660 (37)
Median (95% CI), mo	NR (53, NE)	50 (39, NE)	NR (NE, NE)	37 (33, 42)
HR (95% CI); *P* value	0.78 (0.66, 0.91); <0.001	–	0.46 (0.40, 0.54); <0.001	–
Time to progression§‖				
Pts at risk, n	2395	569	1444	1520
Events, n (%)	1060 (44)	271 (48)	440 (31)	891 (59)
Median (95% CI), mo	27 (24, 29)	26 (20, 32)	51 (44, 57)	15 (13, 16)
HR (95% CI); *P* value	0.93 (0.81, 1.06); 0.28	–	0.45 (0.40, 0.50); <0.001	–

†Comparator group.
‡Time from post-index day 270 to death.
§Adjusted for age, race, region, index year, log of time from metastasis to index date, site of metastasis and comorbidities.
‖Time from post-index day 270 to first evidence of disease progression.

Association of circulating immune and metabolic markers with clinical outcomes in the ENZAMET trial (ANZUP 1304).

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Background: ENZAMET showed that enzalutamide (ENZ) significantly improves overall survival (OS) of metastatic hormone-sensitive prostate cancer (mHSPC) compared to conventional non-steroidal anti-androgen (NSAA). However, intrinsic and acquired resistance to ENZ are ongoing problems. In the CHAARTED mHSPC cohort, elevated circulating IL8 and IGFBP1, and a low IGF1:IGFBP1 ratio, were associated with shorter OS and shorter time to castration-resistance. The aim of this study was to confirm the prognostic association of IL8, IGFBP1, and IGF1:IGFBP1 in mHSPC, and also explore the relationship of a set of immune markers with ENZ treatment by post-hoc analysis of ENZAMET. **Methods:** Baseline plasma levels of IL8, IGF1, IGFBP1, C-reactive protein (CRP), and 14 other cytokines were profiled in 852 participants of ENZAMET (ENZ n=420; NSAA n=432) using Milliplex antibody assays (Merck). The association of these markers with OS and clinical progression-free survival (cPFS) was assessed by Cox regression. **Results:** In the whole study cohort, we confirmed that high IGFBP1 and IL8, and low IGF1:IGFBP1 were significantly associated with shorter OS and shorter cPFS ($p \leq 0.029$). High CRP, CXCL16, IL6, MIC1 and YKL40, and low IL28A were also associated with shorter OS ($p \leq 0.015$). These markers were independently associated with OS in multivariable analysis with treatment arm, volume of disease, concurrent docetaxel, and presence of visceral metastases ($p \leq 0.047$, Table). None of these markers were predictive of ENZ response. In subgroup analyses by treatment arm, IGFBP1 and IGF1:IGFBP1 were prognostic in the ENZ arm (OS $p \leq 0.042$, cPFS $p \leq 0.02$) but not in NSAA (OS p=0.08, cPFS $p \geq 0.2$). IL8 was prognostic in the NSAA arm (OS p=0.02, cPFS p=0.006) but not in ENZ (OS p=0.5, cPFS p=0.5). MIC1 was the only marker that was prognostic in both treatment arms (OS & cPFS $p \leq 0.002$). **Conclusions:** These data validate IL8, IGFBP1, and IGF1:IGFBP1 as prognostic biomarkers in mHSPC. Furthermore, pro-inflammatory and macrophage-associated cytokines are associated with poorer clinical outcomes. Clinical trial information: NCT02446405. Research Sponsor: Astellas; Cancer Council Australia; The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).

Hazard ratio (HR) for OS from univariable analyses and multivariable analyses with clinical variables.

Variable (log2)	HR (95% CI) from univariable analysis	P-value	HR (95% CI) from multivariable analysis with clinical variables	P-value
IL8	1.10 (1.01-1.19)	0.029	1.09 (1.00-1.18)	0.047
IGFBP1	1.12 (1.04-1.21)	0.004	1.10 (1.02-1.18)	0.018
IGF1/IGFBP1	0.94 (0.90-0.98)	0.008	0.94 (0.90-0.98)	0.004
CXCL16	1.43 (1.10-1.84)	0.007	1.31 (1.04-1.65)	0.020
CRP	1.10 (1.05-1.16)	<0.001	1.08 (1.03-1.14)	0.002
IL6	1.13 (1.07-1.20)	<0.001	1.10 (1.04-1.17)	0.001
MIC1	1.39 (1.23-1.58)	<0.001	1.23 (1.08-1.40)	0.002
YKL40	1.19 (1.08-1.32)	<0.001	1.17 (1.06-1.29)	0.001
IL28A	0.93 (0.88-0.99)	0.015	0.91 (0.86-0.97)	0.002

Impact of somatic/germline homologous recombination repair (HRR) alterations on metastatic hormone-sensitive prostate cancer (mHSPC) outcomes by disease volume.

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Background: The impact of HRR mutations in castration-resistant prostate cancer has previously been reported, but their role in mHSPC patients (pts) contemporaneously treated has not been established. Here we report the prevalence of somatic/germline HRR mutations, and their effect on the outcomes in mHSPC pts stratified by CHAARTED disease volume and BRCA/HRR alterations. **Methods:** Eligible mHPSC pts diagnosed between Jan. 2018 and Dec. 2023 underwent paired somatic/germline DNA sequencing. Cases with alterations in ≥1 HRR gene were hierarchically classified as BRCA, non-BRCA, HRR non-BRCA, or non-HRR. Radiographic progression free survival (rPFS), time to castration resistance (TTCR), and overall survival (OS) were reported for all subgroups; associations between mutations and outcomes were assessed using inverse probability of treatment weighting (IPTW) models, which were controlled for treatment modality and other baseline characteristics. **Results:** Of 556 pts, 69 (12.4%) harbored alterations in *BRCA1* and/or *BRCA2* genes (BRCA) and 90 (16%) had alterations in HRR non-BRCA genes. mHSPC was synchronous in 451 pts (81.1%) and was classified by conventional imaging as high-volume (HV) in 306 (55%) and low-volume (LV) in 250 (45%) pts as per CHAARTED criteria. Most pts (44.8%) were treated with androgen deprivation therapy (ADT)+androgen-receptor-pathway inhibitor (ARPi), 30.4% received docetaxel (Doc)+ADT, and 11.3% were treated with ADT+ARPi+Doc. Only 13.5% received ADT alone. Baseline pt characteristics and treatments administered were similar across all subgroups after adjustment. BRCA pts had significantly shorter rPFS, TTCR, and OS compared with non-BRCA in all groups (Table) using IPTW models. Similar significant differences were observed when BRCA pts were compared with HRR non-BRCA pts, but no clinically relevant differences were observed between HRR non-BRCA and non-HRR pts. **Conclusions:** Presence of BRCA mutations significantly worsened survival outcomes in HV and LV mHSPC treated with doublet or triplet therapy or ADT alone. Research Sponsor: Janssen; Fundación CRIS; 19-26; Instituto de Salud Carlos III; PI22/01593, PI19/01380.

Outcomes	ALL BRCA (n=69) vs non-BRCA (n=487)	HV BRCA (n=42) vs non-BRCA (n=264)	LV BRCA (n=27) vs non-BRCA (n=223)
rPFS			
Median (95% CI)[a]	14.6 (12.4–16.8) vs 30.6 (27.8–36.6)	13.0 (11.2–16.4) vs 21.5 (19.0–28.6)	16.0 (12.5–28.8) vs 43.0 (35.0–54.7)
HR (95% CI)	2.4 (1.8–3.3)**	2.1 (1.4–3.0)*	3.7 (2.3–5.8)**
TTCR			
Median (95% CI)[a]	11.5 (10.1–14.6) vs 22.9 (20.4–26.9)	10.9 (9.6–12.4) vs 17.0 (14.5–20.2)	13.8 (9.8–18) vs 35.9 (26.9–43.0)
HR (95% CI)	2.2 (1.7–3.0)**	1.9 (1.3–2.7)*	3.6 (2.3–5.5)**
OS			
Median (95% CI)[a]	26.4 (24.0–34.6) vs 55.2 (50.2–62.5)	25.0 (17.8–33.1) vs 41.4 (33.4–52.8)	34.6 (24.0–50.0) vs 71.6 (62.5–78.5)
HR (95% CI)	2.7 (2.0–3.6)**	2.5 (1.7–3.5)**	3.4 (1.8–6.5)*

*$p<0.05$; **$p<0.0001$.
[a]Observed, in months.
CI, confidence interval; HR, hazard ratio.

^{177}Lu-PSMA-617 consolidation therapy post docetaxel in patients with de-novo high-volume metastatic hormone-sensitive prostate cancer: A randomized, phase 2 trial.

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Background: De-novo high-volume metastatic hormone-sensitive prostate cancer (mHSPC) presents a therapeutic challenge with a dismal five-year survival rate. Till recently, androgen deprivation therapy (ADT) with docetaxel had been the standard-of-care for such patients. Nevertheless, a substantial proportion of patients continue to harbour residual disease after completion of docetaxel. ^{177}Lu-PSMA-617 has shown positive survival outcomes in the metastatic castrate-resistant setting. Here, we intended to evaluate the role of upfront ^{177}Lu-PSMA-617 as consolidation therapy for residual disease following docetaxel in de-novo high-volume mHSPC patients. **Methods:** This was an investigator-initiated randomized, parallel-group, open-label, phase 2 trial. Patients with de-novo high-volume mHSPC who were initiated on ADT plus docetaxel (75 mg/m^2/cycle x 6) and had residual non-progressive disease after completion of six cycles of docetaxel (defined as serum PSA >0.2 ng/mL with PSMA-positive disease on ^{68}Ga-PSMA-11 PET/CT) were randomized in 1:1 ratio to the experimental arm (^{177}Lu-PSMA-617, 7.4 GBq/cycle x 2, 6 weeks apart with continued ADT) or control arm (continued ADT only). The primary end-point was the proportion of patients achieving a serum PSA of ≤0.2 ng/mL at 6 months from randomization. Major secondary end-points included radiographic progression-free survival (rPFS), PSA-PFS, and treatment-emergent adverse events (TEAEs). A total sample size of 78 patients was estimated to be recruited assuming a 30% improvement in the primary end-point in the experimental arm with two-sided alpha of 5% and power of 80%. **Results:** The trial was terminated early due to poor accrual COVID-19 pandemic and following the change in standard of care from doublet to triplet therapy incorporating an androgen-receptor pathway inhibitor along with ADT plus docetaxel. Thirty high-volume mHSPC patients (15 in each arm) were recruited between January 2021 and May 2024. The primary end-point was achieved in 9/15 (60%) patients in the experimental arm versus 2/15 (13.3%) patients in the control arm (risk ratio: 4.5, 95% CI: 1.2-17.4, p=0.008). The median rPFS was 18 months in the experimental arm versus 9 months in the control arm, while the median PSA-PFS were 15 months and 9 months, respectively. No major grade 3/4 TEAEs were seen in the experimental arm. **Conclusions:** In de-novo high-volume mHSPC patients treated with docetaxel and having residual disease, ^{177}Lu-PSMA-617 consolidation therapy demonstrated remarkable efficacy in terms of biochemical response. Larger phase 3 trials are needed to definitively establish its survival benefits. Clinical trial information: CTRI/2021/01/030267. Research Sponsor: None.

Real-world patient (pt) characteristics, treatment patterns, and overall survival (OS) in metastatic hormone-sensitive prostate cancer (mHSPC): Insights by *PTEN* status.

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Background: The loss of function of the tumor suppressor gene *PTEN* is associated with an increased risk of recurrence and poor clinical outcomes in advanced prostate cancer (PC). Current understanding of *PTEN* prevalence and pt characteristics, treatment patterns, and survival outcomes by *PTEN* status in mHSPC is limited. **Methods:** This cohort study used retrospective longitudinal data from the US-based deidentified Flatiron Health–Foundation Medicine mPC clinicogenomic database. Male pts diagnosed (dx) with mHSPC between January 1, 2018, and March 31, 2024, who underwent comprehensive genomic profiling of a solid tumor specimen were included. Pts with *PTEN* alterations were classified as *PTEN*-homs del (homozygous deletion, defined as a copy number variant [CNV]=0) or *PTEN*-mut (CNV=1, pathological short variant alterations or rearrangements). Pts without *PTEN* alterations identified were classified as *PTEN*-nonaltered. Pt characteristics and treatment patterns were descriptively analyzed. Kaplan-Meier survival probabilities for real-world overall survival (rwOS; unadjusted) were estimated by *PTEN* status (*PTEN*-homs del, *PTEN*-mut, and *PTEN*-nonaltered). **Results:** Of 1630 included pts, 39.8% had tumors with *PTEN* alterations (*PTEN*-homs del, 23.2%; *PTEN*-mut, 16.6%). Overall, pts were predominantly non-Hispanic White with a mean (SD) age of 69 (9.1) years at mHSPC dx. At initial dx, 66.7% presented with a Gleason score of 8 to 10, and 68.1% had de novo metastatic disease. Median (IQR) prostate-specific antigen level (ng/mL) at metastatic diagnosis was lower in *PTEN*-homs del (47 [9-193]) and *PTEN*-mut (42 [11-157]) mHSPC relative to *PTEN*-nonaltered (68 [15-337]) mHSPC. *BRCA* mutations were less frequent in *PTEN*-homs del (6.1%) tumors relative to *PTEN*-mut (9.6%) and *PTEN*-nonaltered (10.3%) tumors. All other pt characteristics were generally similar across *PTEN* groups. The most common first-line treatments across all *PTEN* groups were ADT alone and ARPI ± ADT. Median (95% CI) rwOS (months) was 29.0 (24.1-33.6) in *PTEN*-homs del, 32.7 (27.8-37.9) in *PTEN*-mut, and 42.3 (38.7-46.0) in *PTEN*-nonaltered mHSPC groups. Pts with *PTEN* alterations tended to have lower landmark survival probabilities than pts without *PTEN* alterations (Table). **Conclusions:** Among pts with mHSPC, worse survival was observed in pts with tumors harboring *PTEN* alterations relative to pts without *PTEN* tumor alterations, despite similar pt characteristics and treatment patterns across *PTEN* groups. Research Sponsor: AstraZeneca.

rwOS probability, % (95% CI)	*PTEN*-homs del (n=378)	*PTEN*-mut (n=271)	*PTEN*-nonaltered (n=981)
12 month	81.6 (76.0-87.6)	83.9 (77.9-90.4)	90.7 (88.2-93.4)
24 month	56.8 (50.6-63.7)	64.4 (57.5-72.0)	73.8 (70.3-77.4)

Outcomes of initial vs delayed docetaxel therapy in veterans with metastatic hormone sensitive prostate cancer and high volume of disease.

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Background: Docetaxel (DOC) continues to demonstrate efficacy in metastatic hormone sensitive prostate cancer (mHSPC), particularly in combination with androgen deprivation therapy (ADT) ± androgen receptor pathway inhibitors (ARPI). However, a paucity of data exists evaluating treatment sequencing with DOC for patients with high volume disease. We assessed overall survival (OS) of patients with mHSPC treated with either DOC followed by ARPIs or ARPIs followed by DOC. **Methods:** A nationwide retrospective study of 696 US Veterans with de novo (synchronous) mHSPC who received both DOC and an ARPI in combination with ADT in the Veterans Health Administration between 2015-2023. Of these, 581 (83.5%) had high-volume disease. Patients either received DOC (1) within 4 months of and (2) greater than 4 months after ADT. The early DOC group received an ARPI after the initial 4 months while the late DOC group received an ARPI within 4 months of ADT. Age, baseline PSA, Charlson comorbidity index (CCI) and BMI values were acquired for each patient. Survival analysis was performed using the Kaplan-Meier method. **Results:** Of the 581 Veterans with high-volume disease, 400 received DOC early (68.8%) and 181 received DOC later (31.2%). Patients who received DOC early had a significantly longer OS than those who received it later (median 36.3 vs 29.3 months, $p<0.001$, HR 0.65, 95% CI 0.53-0.80). Findings were similar when adjusted for age, baseline PSA, and CCI (aHR 0.69, 95% CI 0.56-0.85). Additionally, patients who received DOC early had a significantly longer rwPFS than those who received it later (median 17.0 vs 12.5 months, $p<0.001$, HR 0.63, 95% CI 0.52-0.76). Findings were similar when adjusted for age, baseline PSA, and CCI (aHR 0.64, 95% CI 0.53-0.78). Evaluation of baseline characteristics between DOC vs ARPI combination therapy showed that the early DOC group was younger (mean 66.4 vs 69.6 years, $p<0.001$). However, no other statistically significant differences were found between the two groups when comparing baseline PSA, BMI, and CCI. **Conclusions:** Initial DOC in Veterans with de novo high volume mHSPC was associated with longer survival. While all patients were candidates for chemotherapy, the Veterans who were treated early with DOC were younger. These finding support early docetaxel in patients with aggressive disease that are likely to develop castration-resistance and require subsequent therapies. Research Sponsor: None.

Patient characteristics.

	Docetaxel Early (n=400)	Docetaxel Late (n=181)	p-value
Age (mean)	66.4	69.6	< 0.001
Baseline PSA (median)	174	217	0.23
Creatinine Value (median)	1.00	1.02	0.1
BMI (mean)	28.7	28.0	0.06
Charlson Comorbidity Index (mean)	1.66	1.90	0.36

Prospective monitoring of prostate specific membrane antigen–positive biochemically recurrent prostate cancer (PSMA+ BCR): Preliminary data from 6-month PSMA follow-up.

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Background: PSMA imaging can identify recurrent prostate cancer after definitive surgery/radiation prior to detection on computed tomography (CT) or bone scan. Radiation to PSMA+ findings is common but lacks clear data demonstrating long term benefit. PSMA+ biochemically recurrent prostate cancer (PSMA+ BCR) is often defined and treated as metastatic castration sensitive prostate cancer (mCSPC), yet PSMA imaging alone as an eligibility criteria was never studied in the mCSPC trials. PSA+ BCR requires better understanding to define at-risk patients (pts). **Methods:** NCT05588128 enrolls pts after definitive and possibly salvage therapies. Pts are required to be 1 year removed from definitive therapy with a PSA>0.5 ng/ml, testosterone>100 ng/dL, and negative CT/bone scans. Lymph nodes (LNs) up to 1.5 cm and prior therapies are permitted. At enrollment pts have a baseline PSMA, which is repeated every 6 months (mos) if positive. If negative PSMA is done annually. CT and bone scan are also repeated annually. Pts are allowed to have radiation therapy or systemic therapies for ≤6 mos and remain on-study. Up to 350 pts will be enrolled and followed for up to 5 years. **Results:** Over 120 pts have enrolled since 3/2023 and 86 pts are evaluable after the 6-month PSMA scan/follow-up. The pts have a median age of 71 years, PSA=3.05, PSA doubling time=11.1 mos (29% less than 6 mos). In an overlapping descriptive analysis 10 pts were PSMA- and 17 pts had only local disease. For PSMA+ LNs, 17 pts had 1 LN, 9 pts had 2-3 LNs+, 5 pts had 4 LNs+, and 18 pts had 5+ LNs. 7 pts had bone findings, but negative bone scan. 4 pts had PSMA+ serosal nodules. 4 pts had radiation to solitary LNs. 1 pt elected androgen deprivation and 1 pt had salvage radiation. 4 pts enrolled on a clinical study at the NCI without androgen deprivation. At 6 mos PSMA scan only 1 pt had metastatic disease (bone scan findings). No pts had LNs beyond eligibility size criteria. No pts had new visceral findings. **Conclusions:** These preliminary data from an ongoing study suggest PSMA+ BCR is an indolent disease process and pts are at limited risk for clinically relevant progression within 6 mos. This study continues to accrue at the NCI and will seek to better define high risk PSMA+ BCR. These preliminary data may better inform the risk/benefits of aggressive treatment of PSMA+ BCR and clinical studies in PSMA+ BCR. Clinical trial information: NCT05588128. Research Sponsor: NCI Intramural Porgram.

Evaluation of de novo oligometastatic, oligorecurrent, and oligoprogressive prostate cancer patients managed with radiation therapy: A multi-institution, real-world dataset.

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Background: Oligometastatic prostate cancer (omPCa) is historically defined as ≤5 metastases, with non-standard treatment approaches and unknown prevalence in the molecular diagnostic imaging (MDI) era. Clinical trials in advanced PCa based on conventional imaging modalities (CIM) complicate extrapolation of findings to omPCa detected by MDI. We evaluated outcomes of omPCa patients (pts) treated with radiotherapy (RT) in a multi-institutional cohort. **Methods:** Pts presenting with de novo (synchronous), oligorecurrent (OR, metachronous), or oligoprogressive (OP, progressive) omPCa (<5 non-visceral lesions), detected by CIM and/or MDI and treated with RT across 7 institutions were identified. RT was metastasis-directed (MDT) only (or in the case of de novo pts, prostate-only or prostate + MDT) using conventional, hypofractionated or stereotactic body RT (SBRT) regimens. Clinical outcomes, including disease (dz) progression (any biochemical recurrence or distant metastasis, DM) and survival were assessed. Progression-free survival (PFS), DMFS, and overall survival (OS) were determined using the Kaplan-Meier method; univariable analyses were performed with Cox proportional hazard regression. **Results:** 625 omPCa pts (193 de novo, 342 OR, 90 OP) received RT between 2014-2024. Most pts (415/625, 66%) were diagnosed using MDI. 25% presented with pelvic lymph nodes (LNs) only, 7% non-regional LNs only, 56% bone-only dz, and 12% with a combination. Most pts (551/625) received systemic therapy with RT: 51% androgen deprivation therapy (ADT) alone, 43% ADT + androgen receptor signaling inhibitor (ARSI, n=239), and 6% ADT + ARSI + docetaxel. Median FU post-omPCa diagnosis was 26 months (range, 1-225) for 613 pts with details available. 153 pts developed new DM (outside of documented OM). Five-year OS post-diagnosis was 87% (95%CI 81,91). 5-year PFS post-RT was 34% (95%CI 24,44), with median PFS of 43 months. Concurrent ARSI use improved PFS (HR 0.67, 95%CI 0.50,0.91, p=0.01) on Cox proportional hazard regression. Use of any systemic therapy improved DMFS (HR 0.46, 95%CI 0.29,0.72, p<0.001). Both OR and OP dz were associated with worse DMFS (HR 2.2, 95%CI 1.4,3.5; HR 6.3, 95%CI 3.7,10.6, respectively, p<0.001 for both) and OP dz was associated with poor OS (HR 5.8, 95%CI 2.7,12.7). There was no impact by RT approach on outcomes. **Conclusions:** In this multi-institutional omPCa cohort reflecting real-world practice patterns of detection and treatment, the addition of ARSI to RT improved PFS, and use of any systemic therapy with RT improved DMFS. De novo omPCa had more favorable clinical outcomes compared to OP/OR presentations. Research Sponsor: None.

Characteristic	Age	Gleason score		Number of lesions	
	Median (range)	Score	n (%)	#	n (%)
	70 (44-92)	6	43 (7%)	1	351 (56%)
		7	206 (33%)	2-3	229 (37%)
		8	163 (26%)	4-5	45 (7%)
		9	166 (27%)		
		10	20 (3%)		
		n/a	27 (4%)		

Assessment of the impact of delays to radiotherapy on prostate cancer mortality in localized prostate cancer.

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Background: Resource constraints and patient preferences may lead to delays in the treatment of localized prostate cancer, but the implications of such delays remain unclear. We aimed to investigate the impact of time from diagnosis to treatment initiation (TTI, including neo-adjuvant ADT) on prostate cancer-specific mortality (PCSM) in patients receiving radiotherapy for localized prostate cancer. **Methods:** Patients diagnosed with localized prostate cancer from 2004 to 2020 who received radiotherapy as part of their first course of treatment were identified from the SEER 17 database. Those who initially underwent active surveillance or surgery, as well as those whose TTI exceeded 24 months, were excluded. The remaining patients were divided into cohorts with prespecified TTI intervals of 0-3 months, 4-6 months, and >6 months. Covariates were age, race, county median income, county remoteness, diagnosis year, T stage, PSA, Gleason grade, and treatment modality (external beam radiotherapy, brachytherapy, or a combination). Missing covariates were imputed 50 times using multiple imputations with chained equations, after which propensity score weighting using Bayesian additive regression trees was performed for each imputed dataset. Pooled marginal Cox models, in accordance with Rubin's rules, were used to compare the PCSM of the three TTI cohorts. Additionally, a prespecified subgroup analysis based on NCCN risk classification was completed. **Results:** A total of 230,278 patients with a median follow-up of 7.8 years were eligible for analysis, of whom 168,432 (73.1%) had a TTI of 0-3 months, 46,738 (20.3%) had a TTI of 4-6 months, and 15,108 (6.6%) had a TTI of >6 months. After propensity score weighting, the maximal standardized mean difference across all covariates and imputations was less than 0.03. Weighted 10-year PCSMs were 5.9%, 5.6%, and 7.1% for patients with TTIs of 0-3 months, 4-6 months, and >6 months, respectively. The PCSM of patients with a TTI of 4-6 months did not differ from that of patients with a TTI of 0-3 months (HR 0.95, 95% CI 0.89-1.01; P=0.09). However, patients with a TTI of >6 months had a higher risk of PCSM than those with TTIs of 0-3 months (HR 1.22, 95% CI 1.09-1.36; P<0.001) or 4-6 months (HR 1.28, 95% CI 1.13-1.45; P<0.001). There was no significant interaction between TTI and NCCN risk group (P=0.49). **Conclusions:** A TTI exceeding 6 months was associated with an increased risk of prostate cancer mortality. These findings support the timely initiation of treatment for patients undergoing radiotherapy for localized prostate cancer. Research Sponsor: None.

PCSM by NCCN risk subgroup.

Subgroup	4-6 months vs. 0-3 months HR (95% CI)	>6 months vs. 0-3 months HR (95% CI)	>6 months vs. 4-6 months HR (95% CI)
Overall	0.95 (0.89-1.01)	1.22 (1.09-1.36)	1.28 (1.13-1.45)
Low risk	1.02 (0.89-1.17)	1.05 (0.86-1.29)	1.04 (0.83-1.30)
Intermediate risk	0.94 (0.86-1.03)	1.19 (1.02-1.38)	1.27 (1.07-1.50)
High risk	0.94 (0.85-1.03)	1.28 (1.06-1.54)	1.37 (1.11-1.68)

5101 Poster Session

Five-year outcomes of SABR in intermediate- and high-risk prostate cancer without ADT.

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Background: Stereotactic ablative body radiotherapy (SABR) is emerging as a prominent treatment option for localized prostate cancer (PCa). Most existing studies have primarily focused on low- and intermediate-risk PCa patients, who typically have favorable prognoses regardless of treatment. Additionally, the necessity of adding androgen deprivation therapy (ADT) remains a subject of ongoing debate, given its associated side effects and limited impact on overall survival (OS). In this study, we present the long-term outcomes of patients predominantly with intermediate- and high-risk PCa who were treated with SABR without ADT. **Methods:** This was a single-center prospective study of 87 patients with localized PCa who underwent SABR without subsequent ADT. SABR was delivered in an ultra-hypofractionation regimen (36.0 – 42.7 Gy) using Varian TrueBeam/EDGE linear accelerators between July 2015 and June 2024. The primary endpoint was biochemical recurrence-free survival (bRFS), with secondary endpoints including toxicity and overall survival (OS). **Results:** A total of 87 patients, with a median age of 68.8 years (range: 50–86 years), were included. The median follow-up period was 31 months (range: 3–105 months). The distribution of patients by risk group was as follows: low-risk (21.8%), intermediate-risk (55.1%), and high-risk (17.9%). The 1-, 3-, and 5-year bRFS rates were 97.6%, 92.2%, and 90.0%, respectively. Importantly, no patient died as a result of PCa progression during the observation period. No clinically significant toxicity was reported. **Conclusions:** The findings of this study suggest that SABR as a standalone treatment modality is a safe and effective approach for localized PCa, providing durable biochemical control without significant toxicity. However, further investigations involving larger patient cohorts and longer follow-up periods are needed to confirm these results and enhance their reliability. Research Sponsor: None.

COBRA: Assessment of the efficacy of ^{64}Cu-SAR-bisPSMA using histopathology and standard of care imaging as reference standard in patients with biochemical recurrence of prostate cancer following definitive therapy.

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Background: Accurate staging of recurrent prostate cancer (PC) is essential to inform the best treatment strategy. ^{64}Cu-SAR-bisPSMA may offer several advantages over the currently approved PSMA positron emission tomography (PET) agents due to its bivalent structure (SAR-bisPSMA) and longer half-life of ^{64}Cu (12.7h vs. $<$2h for ^{18}F and ^{68}Ga), as previously reported (2-3x higher tumor uptake and detection of additional PC lesions vs. approved PSMA PET agents). **Methods:** This was a Phase 1/2 study assessing the safety/efficacy of ^{64}Cu-SAR-bisPSMA (200 MBq) in PC patients with biochemical recurrence (BCR) and negative/equivocal standard of care (SOC) imaging (NCT05249127). PET/computed tomography (CT) imaging was performed on Day 0 and Day 1 (1-4h and 24$\pm$6h post-dose, respectively) and interpreted by 3 blinded central readers. PET/CT results were assessed against a composite Reference Standard (histopathology, SOC imaging [interpreted by 2 readers], prostate specific antigen response post-focal therapy). Efficacy endpoints included detection rate (DR; % participants with a positive scan out of all scanned participants) and correct detection rate (CDR; % participants with a true positive scan out of all scanned participants with at least one evaluable Reference Standard). **Results:** Fifty-two participants were enrolled (50 had ^{64}Cu-SAR-bisPSMA PET results); 39 and 30 had follow-up SOC imaging by Day 90 and by Day 180, respectively, and 9 had histopathology. ^{64}Cu-SAR-bisPSMA DR range across readers on Day 0 was 44–58% (95% confidence interval [CI]: 30–71.8), increasing on Day 1 to 58–80% (95% CI: 43.2–90). DR on follow-up SOC imaging by Day 90 ranged from 15-31% and 7-10% by Day 180. CDR as assessed against the composite Reference Standard on Day 0 was 19.0–26.2% (95% CI: 8.6; 42.0), increasing to 26.2–33.3% (95% CI: 13.9; 49.5) on Day 1. CDR was considerably higher when using histopathology as the Reference Standard (44.4–55.6% and 55.6–77.8% for Day 0 and Day 1, respectively), than SOC imaging (10.3–20.5% and 23.1%–25.6% for Day 0 and Day 1, respectively). **Conclusions:** ^{64}Cu-SAR-bisPSMA is effective in detecting PC in BCR of PC, with lesions identified in up to 80% of participants with negative/equivocal baseline SOC imaging. CDR was considerably higher when using the gold standard of histopathology to verify ^{64}Cu-SAR-bisPSMA PET lesions vs SOC imaging, which highlights the limitations of using less sensitive methods to verify the ^{64}Cu-SAR-bisPSMA PET findings. These results have important clinical implications, as the identification of lesions in BCR patients can inform different treatment pathways. Clinical trial information: NCT05249127. Research Sponsor: Clarity Pharmaceuticals.

Secondary outcomes by prior definitive treatment (tx) in patients (pts) with high-risk biochemically recurrent prostate cancer (hrBCR) treated with enzalutamide (enza) monotherapy (mono): EMBARK post hoc analysis.

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Background: The phase 3 EMBARK trial demonstrated clinically meaningful improvement in metastasis-free survival and secondary efficacy endpoints with enza mono vs leuprolide alone. Herein, we descriptively report secondary endpoints for enza mono vs leuprolide alone across prior definitive tx subgroups. **Methods:** Eligible pts had hrBCR, with a prostate-specific antigen (PSA) doubling time of ≤9 months. Pts were randomized 1:1:1 to enza + leuprolide, leuprolide alone, or enza mono. Secondary endpoints included time to PSA progression, first use of new antineoplastic tx, distant metastasis, resumption of any hormonal therapy after tx suspension, and symptomatic progression. Post hoc subgroup analyses descriptively compared secondary endpoints for enza mono vs leuprolide alone in pts with radical prostatectomy (RP) only, radiotherapy (RT) only, or RP + RT. **Results:** In both tx groups (enza mono and leuprolide alone), nearly half of pts had prior RP + RT (Table). Enza mono vs leuprolide alone numerically reduced the risk of PSA progression, first use of new antineoplastic tx, distant metastasis, and symptomatic progression in all prior definitive tx subgroups (Table). Time to resumption of any hormonal therapy favored leuprolide alone vs enza mono across all prior definitive tx subgroups. **Conclusions:** Tx with enza mono showed improvements in all secondary endpoints except time to resumption of any hormonal therapy vs leuprolide alone, regardless of prior definitive tx. The small sample sizes of the nonrandomized prior tx subgroups and low event numbers should be considered when interpreting the results. Interaction analyses of secondary endpoints across prior definitive tx subgroups will be reported in the presentation. Disclosure: A genAI tool (10/01/24; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. 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 Roham Sadeghimakki and Rosie Henderson of Onyx (a division of Prime, London, UK), funded by the sponsors.

Secondary endpoints	Mono (n=355)						Leuprolide alone (n=358)†		
	RP only (n=99)		RT only (n=90)		RP + RT (n=166)		RP only (n=75)	RT only (n=104)	RP + RT (n=179)
Time to:	Event, n	HR (95% CI)	Event, n	HR (95% CI)	Event, n	HR (95% CI)	Event, n	Event, n	Event, n
PSA progression	12	0.62 (0.28, 1.34)	18	0.53 (0.30, 0.95)	7	0.14 (0.06, 0.33)	17	37	39
First use of new antineoplastic tx	23	0.68 (0.38, 1.22)	33	0.76 (0.48, 1.20)	28	0.37 (0.23, 0.58)	25	48	67
Distant metastasis	10	0.81 (0.32, 2.08)	14	0.65 (0.31, 1.34)	16	0.45 (0.24, 0.85)	9	20	30
Resumption of any hormonal therapy	77	1.68 (1.14, 2.46)	60	2.23 (1.46, 3.39)	142	1.58 (1.22, 2.03)	54	47	116
Symptomatic progression	28	0.61 (0.36, 1.03)	38	0.79 (0.52, 1.22)	51	0.56 (0.39, 0.80)	32	52	85

†Leuprolide alone was the comparator.
CI, confidence interval; HR, hazard ratio.

Neoadjuvant niraparib in men with DNA repair gene deficient clinically localized prostate cancer: Clinical and molecular results from a phase 2 investigator-initiated trial.

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Background: Many men with clinically localized prostate cancer experience disease progression and recurrence despite curative local therapy. Neoadjuvant treatments may reduce recurrence risk and the need for salvage therapy. Primary prostate cancer is genomically diverse and PARP inhibitors (PARPi) represent a novel class of targeted cancer therapy with known activity in advanced prostate cancers, particularly in the setting of DNA damage repair (DDR) gene alterations. **Methods:** Men with National Comprehensive Cancer Network unfavorable intermediate to high-risk prostate cancer were screened for somatic or germline DDR gene alterations. Consenting men were enrolled into a single arm phase II pilot study (NCT04030559) of neoadjuvant niraparib 200mg per day for 90 days prior to planned radical prostatectomy (RP). The primary endpoint was complete or partial pathologic response [minimal residual disease (MRD) defined as $<$0.5 cc of residual tumor]. Secondary endpoints were toxicity and biochemical progression free survival (bPFS). Raw tissue and ctDNA sequencing data was obtained by the clinical NGS vendor and analyzed. **Results:** Eleven (of planned 30) men were enrolled with a median age of 68 years and median PSA at diagnosis of 10.7 ng/mL. Germline-mutations were noted in *BRCA2* (n=3 patients with loss-of-function, 2 with additional loss-of heterozygosity detected), *MSH6* (n=1), *CHEK2* (n=1); somatic mutations were noted in *ATM* (n=3), *SPOP* (n=4), *PPP2R1A* (n=1), *ZFHX3* (n=1), and *ZMYM3* (n=2). No complete or partial pathologic responses were observed. PSA responses were variable on niraparib. There was one grade 3+ adverse event (thrombocytopenia) requiring a dose reduction. After a median follow up of 27 months, bPFS is 56% for the overall cohort. One patient with bi-allelic loss of *BRCA2* (germline and somatic) and a coincident *ATM* mutation had the most dramatic change in PSA (-76%) with notable radiographic regression on MRI. We detected a decline in ctDNA for the somatic mutations seen in the pre-niraparib prostate biopsy NGS (*ATM* and PIK3R1) within 7 weeks of niraparib treatment. A new reversion mutation in *BRCA2* was detected in the serum of this patient by 12 weeks which disappeared after stopping niraparib. This BRCA2 reversion mutation was also detected in the prostatectomy tissue. **Conclusions:** In this small study, neoadjuvant niraparib did not result in substantial pathologic response after RP in a group of men with prostate cancer and heterogeneous mutations in genes involved in DDR. Variable responses even in the face of bi-allelic BRCA2 loss suggest that additional biomarkers including ctDNA analysis to identify patients who may benefit are needed. Early reversion mutations may contribute to PARPi resistance in hormone sensitive prostate cancer. Clinical trial information: NCT04030559. Research Sponsor: Janssen.

5105 Poster Session

A randomised clinical trial to improve healthy lifestyle adherence in prostate cancer patients undergoing radiotherapy (Microstyle study).

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Background: The standard non-surgical approach for localized Prostate Cancer (PCa) is radiotherapy (RT) but PCa patients may experience worsening of bowel disorders affecting quality of life and attributable to RT. The main aim of the study was to examine whether personalized dietary and physical activity counselling, provided at the start of RT, improves adherence to a healthy lifestyle, according to the standardised WCRF/AICR score[1] that assists clinicians in providing evidence-based recommendations to reduce risk of morbidity and improve quality of life in cancer patients. **Methods:** We designed a randomized controlled cross-over trial with two arms – MicroStyle[2]: an intervention (IG) and a control (CG) group, which were enrolled at the start of RT and followed for six months (T6) and 12 months (T12) respectively. Clinical data, questionnaires and circulating biomarkers were collected at two Italian Cancer Centres (Milan and Naples) on different time points. Linear regression models and logistic models were applied to estimate differences by arms in the WCRF/AICR score and its association with toxicity and circulating biomarkers. **Results:** Of the 308 patients enrolled, 299 completed the baseline evaluation, and 286 completed the six-month follow-up. The intervention showed at T6 a greater WCRF adherence compared to the CG: change from baseline 0.2 95%CI: 0.03, 0.36, p =0.02 IG vs CG) adjusting for baseline. The proportion of adherent subjects significantly increase at T6 with IG (26% vs 19%, P=0.04) and at T12 (28% vs 13%, P=0.01) more than CG. A high WCRF score at T6 was found to be associated with a significantly reduced rectal toxicity (P=0.03). IG at T12 was associated with lower Testosterone (P=0.04) and lower Estradiol (P=0.02) adjusting for hormonal therapy and baseline values. Patients with WCRF improvement were associated with lower IL6 and higher adiponectin Improvement of WCRF adherence is significantly associated with improvement in quality of life (P=0.04, IPSS) and prostate symptom (p=0.05, IPSS), sexual function (P=0.01, IIEF) and in particular erectile dysfunction (P=0.03, IIEF) and functional assessment of cancer therapy (P=0.01, FACT-P), adjusting for baseline values. **Conclusions:** This innovative trial showed that that a personalized dietary and physical activity counselling during RT significantly improves adherence to a healthy lifestyle, influencing rectal toxicity and circulating biomarkers. Future analyses will explore the toxicity associated with RT, changes in microbiome and its potential interactions with lifestyle factors. Funding: This study is funded by Italian Ministry of Health, Ricerca Finalizzata 2019 (RF-2019-12368771). ClincalTrial.gov registration number: NCT05155618. 1) https://epi.grants.cancer.gov/wcrf-aicr-score/details.html. 2) Gnagnarella, BMC Cancer (2022) doi s12885-022-09521-4. Clinical trial information: NCT05155618. Research Sponsor: Italian Ministry of Health, Ricerca Finalizzata 2019.

External validation of a pathology-based multimodal artificial intelligence biomarker for predicting prostate cancer outcomes after prostatectomy.

Chien-Kuang Cornelia Ding, Kevin Shee, Janet E. Cowan, Yi Ren, Siyi Tang, Xiaoxuan Yang, Tamara Todorovic, Imelda Tenggara, Robert Krumm, Huei-Chung Rebecca Huang, Rikiya Yamashita, Danielle C. Croucher, Meghan Tierney, Felix Y. Feng, Timothy Showalter, Matthew R. Cooperberg, Peter Carroll; University of California, San Francisco, San Francisco, CA; Department of Urology, University of California, San Francisco, San Francisco, CA; Artera, Los Altos, CA; Artera, Inc., Vancouver, BC, Canada; Radiology School of Medicine, University of California, San Francisco, San Francisco, CA

Background: Radical prostatectomy (RP) improves survival and delays metastasis in localized prostate cancer (PCa) patients (pts), yet 20-40% of men experience biochemical recurrence (BCR) within 10 years, with one-third of these progressing to metastatic disease. Predictive tools for risk stratification and treatment-decision making in this population remain limited. We previously developed and validated an RP digital pathology-based multimodal AI (MMAI) model using RP H&E images and select clinical variables to predict post-surgical outcomes in BCR pts (RP MMAI v1.1). We present the first external validation of this model in both BCR and non-BCR post-RP pts. **Methods:** Surgical pts with localized disease, clinical data, and long-term follow-up we re identified at UCSF (n=738). MMAI scores were generated from RP H&E images and clinical data (age, Gleason grade group (GG), pT-stage, surgical margins (SM), post-RP PSA). Fine & Gray regression with other-cause mortality as a competing risk was performed to determine the ability of MMAI score to predict any metastasis (primary analysis), bone metastasis (BM), and disease progression (DP: 2 consecutive PSA $\geq$0.2 ng/ml or salvage treatment) after RP. Hazard ratios, 95% confidence intervals, and p-values (for primary analysis) are reported. **Results:** MMAI scores were returned for 640 (87%) cases with images and clinical data. Median (IQR) post-RP follow-up was 11.5 (7.7-24.8) years. Post-RP Cancer of the Prostate Risk Assessment (CAPRA-S, range 0-12) scores were 56% low (0-2), 31% intermediate (3-5) and 13% high ($\geq$6) risk. Characteristics at RP were 71% GG1/2, 64% pT2, and 79% negative SM. The majority of pts had undetectable PSA$<$0.05 after RP (87%). Cumulative incidence of DP and metastasis were 27% and 7% at 10 years, respectively. After adjusting for CAPRA-S, MMAI was independently associated with any metastasis (HR 1.76, [95% CI 1.23-2.53], p$<$0.001) and BM (HR 2.72, [95% CI 1.71-4.32]) in post-RP pts, as well as with DP in 561 pts with undetectable PSA after RP (HR 1.51, [95% CI 1.27-1.80]). Using a cutoff previously defined in BCR pts, 10-yr risk of any metastasis or BM after RP was higher in RP MMAI high risk (18% and 16%) vs. low risk pts (3% and 1%). In a subgroup of 211 salvage-eligible pts (detectable PSA and/or salvage treatment), MMAI remained independently associated with any metastasis (HR 1.71, [1.18-2.47]) and BM (HR 2.71, [1.74-4.23]) after CAPRA-S adjustment. **Conclusions:** This study validates the RP MMAI model, originally developed in BCR pts, as an independent prognostic tool in both BCR and general post-RP settings, even when controlling for a validated clinical risk model. These findings support its potential to guide personalized management strategies for post-RP pts, while offering advantages in accessibility, efficiency, and cost compared to existing platforms. Research Sponsor: None.

Utility of the PROSTest, a novel blood-based molecular assay, versus PSA for prostate cancer stratification and detection of higher grade disease.

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Background: Prostate cancer (PCa) is the most common solid organ cancer in men and the fifth leading cause of cancer-related deaths globally. PSA has utility for identifying men at risk but has low specificity and is associated with significant biopsy-related morbidities through over-investigation and over-diagnosis of disease. The PROSTest is a novel 27-gene mRNA expression machine learning-based liquid biopsy assay that was developed to help detect PCa. We evaluated the utility of this assay to predict prostate cancers in symptomatic men undergoing biopsy or surgery for PSA >2ng/mL. **Methods:** One hundred and twenty-three men were evaluated, 105 (85%) met eligibility criteria (age >55 years, PSA >2ng/ml, symptomatic) and underwent image-guided biopsy or surgery. Samples for PSA and PROSTest were collected prior to biopsy. PROSTest was measured following RNA isolation and cDNA production from RNA stabilized blood samples. The PCR results were fed into a machine learning algorithm that reports a score on a scale 0-100, and with the use of cutoff 50, the score is transformed into a binary readout; positive or negative. In addition to the 2x2 table below, the diagnostic value of the PROSTest was demonstrated by ROC curve. Separately, we examined whether scores could be used to differentiate Gleason Grade 1 vs Gleason Grade 2-5 patients. **Results:** The median age of the cohort was 68 years (55-86 years). Baseline PSA median was 8.2ng/mL (IQR: 7.2-92ng/mL). Sixty-five (62%) had a PCa diagnosis (27 GG1; 38 GG2-5) as confirmed by biopsy or after surgery. Baseline PROSTest results were >50 in 65 (62%). The distribution of PROSTest versus outcomes is included in Table 1. PROSTest sensitivity was 97% and specificity of 96% for detecting PCa. The AUROC for PROSTest was 0.39 higher than PSA (PROSTest: 0.99 vs. PSA: 0.61, $p<0.0001$). GG2-5 exhibited significantly higher ($p<0.0001$) PROSTest scores (92±3.8) than GG1 and BPH (41±41). PROSTest scores >93 were 79.1% accurate and 92.5% specific for detecting higher risk disease. **Conclusions:** In this head-to-head comparison, baseline PROSTest was a more sensitive and more specific biomarker than PSA in the diagnosis of all Gleason's grades and may have value for differentiating GG1 from GG2-5. This requires validation in a larger, prospectively collected cohort. Research Sponsor: None.

2x2 table identifying PROSTest score relationship with PCa detection (tissue diagnosis).

	Biopsy/Surgery	
	Prostate cancer detected (n=65)	**No Prostate cancer (including 5 prostatitis, 35 BPH) (n=40)**
PROSTest +ve (score ≥50)	63 (96.9%)	2 (5.0%)
PROSTest -ve (score <50)	2 (3.1%)	38 (95%)

A large language model (LLM)-based multi-agent framework for risk stratification and treatment recommendations in localized prostate cancer (locPCa).

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Background: We previously proposed a hybrid framework combining LLMs and rule based algorithm (RBA) for automating risk stratification in locPCa. Herein, we aim to validate the risk stratification agent (RSA) in a prospective cohort, develop & evaluate the treatment recommendation agent (TRA) based on NCCN guidelines, and develop an interactive interface to facilitate clinicians for accurate risk stratification and treatment recommendations at the point of care. **Methods:** This study included pts with locPCa (2004-2024) presenting at Mayo Clinic with at least 1 positive prostate biopsy and MRI report available. For RSA prospective validation, GPT4 extracted key phenotypic variables (PSA, T stage, prostate volume, number of cores, Gleason patterns, grade group) from unstructured MRI and biopsy reports using a zeroshot prompt. An RBA then classified pts into NCCN risk groups. The agent performance was compared with the treating clinician's documentation and evaluated against gold-standard labels manually annotated by two independent clinicians. For development of TRA, two experiments were performed using GPT4 with and without retrieval-augmented generation (RAG) to generate treatment plans. Generated treatment plans were evaluated using NCCN guideline-informed treatment decision tree based algorithm (DTA). Evaluation metrics, weighted – accuracy (acc) and F1, were computed. A clinician facing interface (lisr.org/risk) was developed to provide accurate risk stratification and treatment plans. **Results:** A total of 858 pts were included (500 for prospective validation, 358 for treatment recommendations). Prospective validation for RSA demonstrated a higher F1 score of 0.89 compared to the treating clinician (F1: 0.58). Treatment recommendation experiments showed that GPT4 with RAG achieved higher acc (64% full – all correct treatment options and 36% partial – at least 1 correct treatment option) compared to GPT4 alone (35% and 65%, respectively). Sensitivity analysis using DTA-informed GPT4 note generation achieved 94% full acc and 6% partial acc. GPT4 alone generated hallucinated treatment options in 71% of cases, while GPT4 with RAG reduced this to 32%. **Conclusions:** The multi-agent framework based on LLM and RBA achieves high accuracy in risk stratification and treatment recommendation for locPCa. A multi-agent framework with an interactive interface holds high promise to enable efficient, accurate decision-making, and improve locPCa management at the point of care Research Sponsor: None.

Performance evaluation.

	RSA (acc; F1) %		TRA (full acc; partial acc) %		
	Clinician	RSA*	GPT4	RAG+GPT4	DTA+GPT4
Overall	**60; 58**	**89; 89**	**29; 71**	**64; 36**	**94; 6**
V. High	94; 33	96; 96	55; 45	69; 31	93; 7
High	46; 52	92; 89	-	-	-
Int. Unf	80; 61	91; 90	5; 95	38; 62	93; 7
Int. Fav	57; 64	84; 87	0; 100	98; 2	100; 0
Low	57; 65	87; 80	100; 0	95; 5	90; 10
V. Low	8; 13	50; 67^	-	-	-

*Statistical significance ($p<0.01$) except for ^V. Low.

Insight into the global mortality trends due to prostate cancer among the under-55 population: An analysis of the Global Burden of Disease-2021.

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Background: Prostate cancer (PC) is the most prevalent non-skin cancer among males, and it is increasingly diagnosed in those under 55. This younger demographic often faces more aggressive disease progression and a higher risk of metastasis, driven by genetic predispositions, family history, and racial factors. **Methods:** Data were systematically collected from the GBD-2021 covering key metrics such as incidence, prevalence, death rates, Disability-Adjusted Life Years (DALY), Years of Life Lost (YLL), and Years Lived with Disability (YLD) across the age group of 20-54 years. Global estimated and stratified data based on 204 regions were further analyzed to assess average annual percentage changes (AAPC) and 95% confidence interval (CI) from 1990 to 2021. **Results:** There were 2,06,612 deaths due to prostate cancer among those aged 20-54 from 1990-2021. Between 1990 and 2021, the global PC incidence in individuals aged 20-54 increased from 0.82 to 1.55 per 100,000, with an AAPC of 2.03 (CI: 1.65-2.41, $p<0.0001$). The highest incidence was recorded in Lithuania, Bermuda, and Australia, while Vietnam, Bhutan, and Algeria reported the lowest. Notable AAPC increases were observed in Cabo Verde (7.26, CI: 6.80-7.72, $p<0.0001$), followed by the Republic of Korea and Vietnam. Conversely, Somalia experienced a significant decline (-1.73, CI: -2.04 to -1.43, $p<0.0001$). During the same period, the global prevalence of PC rose from 7.18 to 13.94 per 100,000, with an AAPC of 2.13 (CI: 1.75-2.54, $p<0.0001$). Prevalence trends across countries were similar to incidence trends. Between 1990 and 2021, the global mortality rate for prostate cancer in individuals aged 20-54 rose slightly from 0.37 to 0.41 per 100,000, with an AAPC of 0.20 (CI: 0.07-0.32, $p=0.003$). Significant increases were observed in Cabo Verde (AAPC 4.24, CI: 3.89-4.58, $p<0.0001$) and the Northern Mariana Islands. Conversely, Sweden and Luxembourg showed declines, with AAPCs of -2.55 (CI: -3.11 to -1.98) and -2.28 (CI: -2.49 to -2.06), respectively. The highest increases across DALY, YLD, and YLL were observed in Cabo Verde, Zambia, and the Republic of Korea, while Somalia, Sweden, and Luxembourg observed significant declines. **Conclusions:** There has been a rise in mortality rates among young prostate cancer patients aged 20-54, along with increasing morbidity indicators such as YLD, DALY, and YLL. African countries have consistently noted significant rises in both incidence and mortality rates, while a decline was noted in European countries. This could be attributed to the lack of screening protocols and the inadequacy of treatment. The global incidence and prevalence of prostate cancer in this age group have nearly doubled over the past 30 years. Future research should focus on regional disparities and develop strategies to reduce the impact of this disease on younger populations. Research Sponsor: None.

TPS5110 Poster Session

Study protocol: Phase 2 trial of re-treatment with 177Lu-PSMA-617 molecular radiotherapy for metastatic castration resistant prostate cancer (RE-LuPSMA trial).

John Nikitas, Stephanie Lira, Zachary Ells, Shaojun Zhu, Tristan Grogan, David Elashoff, Adrien Holzgreve, Lena Unterrainer, Magnus Dahlbom, Martin S. Allen-Auerbach, Johannes Czernin, Jeremie Calais; University of California, Department of Radiation Oncology, Los Angeles, CA; Ahmanson Translational Theranostics Division, University of California, Los Angeles, Los Angeles, CA; Department of Medicine Statistics Core, UCLA, Los Angeles, CA

Background: The phase III VISION trial demonstrated that ^{177}Lu-PSMA-617 radioligand therapy (RLT) improved overall survival (OS) in patients with metastatic castration-resistant prostate cancer (mCRPC) who previously received taxane-based chemotherapy and at least one androgen receptor pathway inhibitor (ARPI). As a result, ^{177}Lu-PSMA-617 therapy has been approved in this patient population by the U.S. Food and Drug Administration for up to six cycles (7.4 GBq per cycle) every 6 weeks. Unfortunately, this treatment is not curative and patients relapse even after initially favorable responses. When this occurs, patients have limited treatment options given they have had prior chemotherapy and ARPI regimens. Re-administration of ^{177}Lu-PSMA-617 in patients who previously benefited from therapy and had limited toxicity seems to be a promising option. Small retrospective studies have reported favorable outcomes. Further prospective data with larger sample sizes are needed to confirm these findings. **Methods:** RE-LuPSMA is an investigator-initiated, single-arm, single-center, open-label, phase 2 clinical trial (NCT06288113). This study plans to enroll 40 patients with progressive mCRPC who previously completed 4-6 cycles of ^{177}Lu-PSMA-617 therapy with a favorable response. Favorable response is defined as a prostate-specific antigen (PSA) decline ≥50% during the first regimen. Progression following the first regimen is defined using imaging or PSA (two consecutive PSA increases ≥3 weeks apart). Patients who received another line of prostate cancer therapy within two months of completing the first regimen of ^{177}Lu-PSMA-617 are excluded. Patients must meet PSMA PET/CT VISION criteria. PSMA PET/CT must have been completed within 8 weeks of the planned first cycle of re-challenge therapy. Upon enrollment, participants will receive up to 6 additional cycles of ^{177}Lu-PSMA-617 (7.4GBq every 6 weeks). Patients will follow-up every 6 months until 2 years from the end of re-challenge therapy. The primary endpoint is 12-month OS measured from the start of re-challenge therapy. The study will have 80% power to detect a difference between the null hypothesis of 50% and the study hypothesis of 71%. Secondary endpoints include adverse event rates, PSA response rates (proportion of patients with a PSA decrease of ≥50%), biochemical progression-free survival (time until PSA level increases 25% and 2 ng/mL above the nadir), radiographic progression-free survival, and health-related quality of life changes (measured using Functional Assessment of Cancer Therapy - Radionuclide Therapy [FACT-RNT] and Brief Pain Inventory [Short Form]). Enrollment has started with a planned study duration of 4 years of which subject accrual occurs in the first 12 months. Clinical trial information: NCT06288113. Research Sponsor: UCLA Ahmanson Translational Theranostics Division; Novartis.

TPS5111 Poster Session

Phase 1, open-label, first-in-human study of ABBV-969, a dual variable antibody-drug conjugate, in patients with metastatic castration-resistant prostate cancer.

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Background: Metastatic castration-resistant prostate cancer (mCRPC) is an incurable disease with high unmet need. Six-transmembrane epithelial antigen of prostate 1 (STEAP1) is highly enriched in > 85% of prostate cancer (PC),[1] and prostate-specific membrane antigen (PSMA) expression is > 100-fold higher in patients (pts) with mCRPC.[2] These are well-established and actionable targets in mCRPC. ABBV-969, a dual variable domain IgG1 drug conjugate, targets STEAP1 and PSMA and includes a topoisomerase-1 inhibitor (Top1i) payload. Based on preclinical data, ABBV-969 is expected to have greater efficacy and wider activity than targeting either antigen alone. We describe a first-in-human study of ABBV-969 in pts with mCRPC. **Methods:** This phase 1 open-label study (NCT06318273) of ABBV-969 monotherapy evaluates safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy. Eligible pts, ≥ 18 years of age, have mCRPC treated with and progressed on ≥ 1 prior novel hormonal agent for mPC/CRPC and ≥ 1 taxane for PC (or have refused, are intolerant to, or unable to access taxanes). Pts must have a life expectancy > 6 months, serum testosterone levels ≤ 50 ng/dL, ≥ 1 metastatic lesion at baseline, and serum prostate-specific antigen (PSA) levels ≥ 1.0 ng/mL. Part 1 (dose escalation) of the study will enroll up to ~80 pts and is guided by the Bayesian optimal interval design primarily based on the dose-limiting toxicity rate. Part 2 (dose expansion) will randomize up to 60 pts in 2 (1:1) or 3 (1:1:1) dose levels (determined in part 1). Part 1 will enroll pts in US, Israel, Japan, and Australia with Canada, France, and Spain added in part 2. Optimal (recommended phase 2) dose will be determined by the totality of PK, PD, safety, and efficacy data. Pts will receive intravenous ABBV-969 until disease progression, intolerable toxicity, or other study discontinuation criteria are met. The study objectives and endpoints are shown in the Table. 1. Xu M, et al. Cancers 2022;14:4034. 2. Sweat SD, et al. Urology 1998;52:637–40. Clinical trial information: NCT06318273. Research Sponsor: AbbVie Inc.

Objectives and endpoints.

Objective	Endpoint
Primary	
Safety and tolerability	Adverse events and dose-limiting toxicities Clinical laboratory parameters, vital signs, ECG
Secondary	
Preliminary efficacy	**Primary** ≥ 50% prostate-specific antigen (PSA) decrease from baseline **Secondary** Confirmed complete response(CR)/partial response (PR) per RECIST v1.1 PSA response duration Duration of response for pts with CR or PR Overall survival Progression-free survival
Pharmacokinetic (PK) characterization	PK parameters including C_{max}, T_{max}, $t_{1/2}$, and area under the curve using noncompartmental methods Determination of antidrug antibodies
Dose optimization	Recommended phase 2 dose determined using all available information

Previously presented at ESMO 2024, FPN: 1660TiP, Raanan Berger et al - reused with permission.

TPS5112 Poster Session

VALOR study: A phase II trial of vorinostat to augment response to 177Lutetium-PSMA-617 in the treatment of patients with PSMA-low metastatic castration resistant prostate cancer.

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Background: ^{177}Lu-PSMA-617 (LuPSMA), a prostate specific membrane antigen (PSMA) targeting radioligand therapy, is approved for men with mCRPC. However, responses are only observed in ~50% of patients, with pre-clinical and clinical data indicating that those with high, homogenous PSMA expression experience the greatest benefit. Therefore, therapeutic strategies to increase PSMA expression may improve outcomes to LuPSMA and potentially other PSMA targeting therapeutics. Our group recently showed that epigenetic repression of the *FOLH1* (PSMA gene) promoter was associated with decreased PSMA expression and that treatment with a histone de-acetylase inhibitor (HDACi) consistently resulted in increased PSMA protein expression both in vitro and in vivo. Based on these results, we are conducting a proof-of-concept clinical trial testing whether the HDACi vorinostat can increase PSMA expression in patients and prime them for improved response to subsequent therapy with LuPSMA. **Methods:** This single-arm, single-center, open label pilot trial seeks to enroll 15 patients with PSMA-low mCRPC who are otherwise eligible for LuPSMA. PSMA-low is defined as baseline total tumor PSMA SUVmean <10, a threshold that has been correlated with inferior outcomes with LuPSMA compared to those with higher SUVmean (PSMA-high). patients receive a 28-day treatment cycle of vorinostat (400mg PO daily) followed by repeat ^{68}Ga-PSMA-11 PET. Patients will then proceed to receive subsequent treatment with LuPSMA per investigator's discretion. The primary endpoint is to determine the conversion rate of PSMA-low to PSMA-high expression as determined by ^{68}Ga-PSMA-11 PET. The target enrollment provides 86% power to detect a conversion rate of 33% with vorinostat- a rate believed to be clinically meaningful and would justify a future randomized trial- relative to an assumed null conversion rate of 5% based on a 1-sample test of binomial proportions with 2-sided α=5. Key secondary endpoints include clinical efficacy of LuPSMA (e.g., radiographic and PSA response rates, PFS, OS) following vorinostat and safety and tolerability of the proposed sequential therapy. Patients enrolled on the trial undergo serial blood collection and metastatic tissue (if safe and feasible) at baseline, post-vorinostat treatment, and following progression on LuPSMA. Blood samples will be processed for analysis of circulating tumor cells (CTC) and (ct)DNA. Detailed analyses of these biospecimens will include orthogonal assessments of PSMA expression (including IHC, CTC staining), RNA sequencing, and methylation profiling. These molecular studies will be correlated with the pre/post vorinostat PSMA PET images and clinical outcomes with LuPSMA. Clinical trial information: NCT06145633. Research Sponsor: Novartis.

TPS5113 **Poster Session**

Mevrometostat in combination with enzalutamide in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with abiraterone acetate: The phase 3, randomized MEVPRO-1 study.

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Background: Resistance to androgen receptor (AR) pathway inhibitors (ARPI; e.g., abiraterone, enzalutamide) in mCRPC may be driven by preservation of AR signaling through various mechanisms. Enhancer of zeste homolog 2 (EZH2) is implicated in the pathogenesis of prostate cancer and ARPI resistance. Combining ARPI with therapies that modulate alternative signaling pathways, including epigenetic modifiers such as EZH2, could be a promising treatment approach to overcome resistance. Mevrometostat is a potent and selective small molecule EZH2 inhibitor. The optimal treatment sequence for patients with mCRPC who progress after first-line treatment with ARPI is not defined; a second ARPI or docetaxel are options used in real-world settings. Results from the dose-escalation period of a phase 1 study (NCT03460977) showed promising activity for mevrometostat combined with enzalutamide, with a manageable adverse-event profile in abiraterone-exposed patients with mCRPC (Schweizer MT, et al. *J Clin Oncol*. 2024;42(16_suppl):5061). Diarrhea, dysgeusia, and anemia were the most common adverse events considered to be related to mevrometostat. The current trial aims to evaluate radiographic progression-free survival (rPFS), overall survival (OS), and safety of mevrometostat plus enzalutamide compared with standard of care in patients with mCRPC previously treated with abiraterone. **Methods:** MEVPRO-1 (NCT06551324) is a global, open-label, phase 3 trial in patients with mCRPC aged ≥18 years with progression on ≥12 weeks of abiraterone, castration testosterone levels ≤50 ng/dL, ECOG performance status 0–2, and life expectancy ≥6 months. Approximately 600 patients will be randomized 1:1 to receive mevrometostat (875mg twice daily with food) with enzalutamide (160 mg once daily [QD]), or physician's choice of enzalutamide (160 mg QD) or docetaxel (75 mg/m^2 intravenously every 21 days). Randomization will be stratified by previous docetaxel in the metastatic castration-sensitive setting, physician's choice of comparator (enzalutamide/docetaxel) prior to randomization, and presence of hepatic metastases. The primary endpoint is blinded independent central review-assessed rPFS per RECIST 1.1 (soft tissue) and PCWG3 (bone) assessed by blinded central radiology review. Key secondary endpoint is OS. Secondary endpoints include antitumor activity by objective response rate and duration of response, safety, pharmacokinetics, ctDNA, and patient-reported outcomes. Time to event endpoints will be compared between treatment arms using a stratified log-test. HRs and 95% CIs will be estimated using a stratified Cox proportional hazard model, and Kaplan–Meier analysis will summarize time-to-event endpoints. Clinical trial information: NCT06551324. Research Sponsor: This study is sponsored by Pfizer Inc. Enzalutamide for the study is provided by Astellas Pharma Inc. Medical writing support was provided by Michelle Mancher, Allison TerBush, and Rosie Henderson of Onyx (a division of Prime), funded by Pfizer Inc.

TPS5114 **Poster Session**

Precision diagnostics in prostate cancer treatment (PREDICT): A phase 2 multi-arm biomarker based study (Alliance A032102).

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Background: Advances in genomic sequencing have allowed for a deeper understanding of the molecular complexity of metastatic castration-resistant prostate cancer (mCRPC) with several actionable alterations now identified, fueling new biomarker-based treatment strategies. For this reason, it is recommended that all patients with mCRPC undergo germline and somatic tumor profiling. In addition to DNA aberrations, gene expression changes can capture actionable targets and activated pathways. The phase 2 PREDICT trial is using both DNA and RNA aberrations to select patients with mCRPC for rationally designed biomarker-based therapeutic strategies. **Methods:** This is a multi-center, multi-arm, biomarker-driven phase 2 umbrella study with a primary objective of objective response rate for patients with mCRPC and measurable disease. Secondary objectives include radiographic progression-free survival, PSA response, time to first symptomatic skeletal event, overall survival, safety, and correlative studies. Eligible patients must have progressive mCRPC of any histology, received a prior androgen receptor pathway inhibitor (ARPI), and received or refused taxane chemotherapy. Patients with measurable and non-measurable disease are eligible. Patients must have standard of care next generation DNA sequencing via any CLIA-certified tissue or circulating tumor DNA assay for initial trial enrollment. For arm allocation based on RNA alterations, testing will be via the CLIA-certified Caris MI Tumor Seek assay, which includes whole exome and whole transcriptome sequencing, derived from tissue obtained within 12 months of enrollment. A real-time molecular tumor board will convene to review genomic reports and confirm arm allocation on a rolling basis as biomarker results become available. Patients with Rb loss (DNA), Rb functional loss signature (RNA), NEPC signature (RNA) will be allocated to treatment with the EZH1/2 inhibitor valemetostat. Patients with at least 2 of 3 tumor suppressor gene DNA alterations (TP53, RB1, PTEN), FANC alteration (DNA), or SLFN11 overexpression (RNA) will be allocated to cabazitaxel plus carboplatin. Patients without any study-defined alterations will be allocated to physician choice treatment with either cabazitaxel, ARPI, or ^{177}Lu-PSMA-617. The study is designed to accommodate future biomarker arms. A maximum of 64 patients with measurable disease and 94 patients with non-measurable disease for a total of 158 patients will be accrued to each treatment arm. A Simon two-stage minimax design per arm was used to determine whether the response rate for measurable disease patients was greater than 0.20. This design has a type 1 error equal to 0.05 and has power equal to 0.90 if the probability of response is 0.37. Clinical trial information: NCT06632977. Research Sponsor: https://acknowledgments.alliancefound.org; Daiichi Sankyo; U10CA180882.

TPS5115 **Poster Session**

An oral prostate cancer RIPTAC therapeutic in phase 1 for metastatic castrate resistant prostate cancer (mCRPC).

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Background: New therapies are urgently needed to treat prostate cancer, especially for patients progressing on existing drugs that inhibit the activity of the Androgen Receptor (AR) (e.g. Androgen Receptor Pathway Inhibitors (ARPIs)). Metastatic Castration-Resistant Prostate Cancer (mCRPC) is a more aggressive stage of the disease, characterized by increased AR expression and signaling. To address this unmet medical need, we have developed a Regulated Induced Proximity Targeting Chimera (RIPTAC™) Therapeutic HLD-0915. HLD-0915 is a heterobifunctional small molecule that leverages full length AR (FL-AR) expression in tumor cells to form a trimeric complex with an Essential Protein (EP) needed for cell survival. This results in EP loss of function in prostate cancer cells and a selective antitumor effect. HLD-0915 activity requires only the presence of FL-AR and retains activity regardless of whether there are AR or non-AR aberrations that may otherwise serve as drivers of disease. Preclinically, HLD-0915 treatment results in tumor shrinkage and PSA declines following oral dosing in murine models of castration-resistant and ARPI-resistant forms of the disease, while delivering a favorable therapeutic index. The Phase 1 trial in mCRPC will investigate safety and early signs of efficacy in the intended patient population. **Methods:** This first-in-human, multicenter, open label Phase 1/2 study evaluates the safety, tolerability, and clinical activity of HLD-0915 in patients with mCRPC. Phase 1 consists of monotherapy dose levels employing a Bayesian Optimal Interval (BOIN) design with each dose level starting with a minimum of 3 patients per cohort with the primary objectives of defining the maximal tolerated dose and/or recommended dose for expansion and characterizing safety and tolerability of HLD-0915. This study also aims to characterize the PK profile and assess clinical activity by PSA declines and objective response rate per RECIST and will explore ctDNA, tumor cell genetics, and PD biomarkers. Patients with progressive mCRPC who may or may not have received prior novel antiandrogen therapy, a taxane, or PSMA targeted radioligand will be enrolled. Cohort 1 enrollment begins in January 2025. The Phase 2 portion of the study will confirm the RP2D and clinical activity in up to 3 cohorts which will be decided in the future based on emerging data. Clinical trial information: NCT06800313. Research Sponsor: None.

TPS5116 Poster Session

Mevrometostat in combination with enzalutamide for androgen receptor pathway inhibitor (ARPI)-naïve patients with metastatic castration-resistant prostate cancer (mCRPC): The phase 3, randomized MEVPRO-2 study.

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Background: Mevrometostat is a potent, selective inhibitor of the histone methyltransferase enhancer of zeste 2 (EZH2), which is canonically involved in epigenetic repression of target genes. In prostate cancer, EZH2 overexpression is associated with poor prognosis, contributing to disease progression through transcriptional repression of tumor suppressor genes and androgen receptor (AR) activation, co-regulation of AR-mediated transcriptional programs, and cell cycle deregulation through methylation of non-histone targets. Given the associations between EZH2 and the AR, the addition of an EZH2 inhibitor to ARPI is hypothesized to extend the duration of clinical response and delay antiandrogen resistance compared with ARPI alone. In a nonrandomized, phase 1 dose-escalation study, objective responses to mevrometostat with enzalutamide were observed in patients with CRPC and prior abiraterone or enzalutamide treatment (NCT03460977; Schweizer MT, et al. *J Clin Oncol.* 2024;42(16_suppl):5061). The most common adverse events considered to be related to mevrometostat were diarrhea, dysgeusia, and anemia. Despite guideline recommendations for treatment intensification with ARPIs or chemotherapy for metastatic castration-sensitive prostate cancer (mCSPC), many patients do not receive ARPIs at the mCSPC stage. MEVPRO-2 (NCT06629779) will evaluate mevrometostat plus enzalutamide compared with enzalutamide alone in ARPI-naïve patients with mCRPC. **Methods:** MEVPRO-2 is a global, double-blind, randomized, phase 3 trial. Key inclusion criteria are males, ≥18 years, with progressive mCRPC, castrate testosterone of ≤50 ng/dL, Eastern Cooperative Oncology Group performance status of 0 or 1, and life expectancy of ≥12 months. Patients with systemic treatments for mCRPC (except androgen deprivation therapy and first-generation antiandrogens) are excluded. Approximately 900 patients will be randomized 1:1 to receive mevrometostat (875 mg, twice daily) with enzalutamide (160 mg, once daily) or placebo with enzalutamide. The primary endpoint is blinded independent central review-assessed radiographic progression-free survival per Response Evaluation Criteria in Solid Tumours 1.1 (soft tissue) or Prostate Cancer Working Group 3 criteria (bone). Key secondary endpoints are overall survival and time to pain progression (Brief Pain Inventory – Short Form question 3 or opioid use). Hazard ratios and 95% confidence intervals will be estimated using a Cox proportional hazard model, stratified by prior docetaxel and presence of hepatic metastases. *P*-values will be provided using a stratified log-rank test. Safety and tolerability will also be assessed. Clinical trial information: NCT06629779. Research Sponsor: This study is sponsored by Pfizer Inc. Enzalutamide for the study will be provided by Astellas Pharma Inc. Medical writing support was provided by Michelle Mancher, Allison TerBush, and Rosie Henderson of Onyx (a division of Prime), funded by Pfizer Inc.

TPS5117 Poster Session

A first-in-human, phase 1 dose escalation and expansion study evaluating the safety, tolerability, and anti-tumor activity of [225Ac]Ac-FL-020, an anti-PSMA radioconjugate, in patients with metastatic castration-resistant prostate cancer (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). Alpha emitting [^{225}Ac]Ac-FL-020 represents a new generation of PSMA-targeted radioconjugates (RDC) with potential improvements in pharmacokinetics and pharmacodynamics, aiming to enhance tumor uptake while minimizing healthy tissue exposure, including the salivary glands. This novel compound was discovered using our proprietary Clear-X technology platform. This Phase 1 study evaluates the safety, tolerability, and anti-tumor activity of [^{225}Ac]Ac-FL-020 in patients with mCRPC. **Methods:** This first-in-human, open-label, multicenter Phase 1 study consists of two parts: dose escalation (Part 1) and cohort expansion (Part 2). In Part 1, the study aims to establish the safety profile and maximum tolerated dose/recommended Phase 2 dose (MTD/RP2D) of [^{225}Ac]Ac-FL-020, guided by a Bayesian logistic regression model (BLRM) with overdose control. Eligible patients must show PSMA-positive lesions on a PSMA PET/CT scan, have histologically confirmed mCRPC with documented progression, and have received prior treatments including androgen receptor signaling inhibitors or CYP17 inhibitors, along with at least 1 previous taxane regimen. Exclusion criteria include patients with extensive PSMA-negative disease. The dose escalation follows cohorts starting with 1-3 patients, expanding to 3-6 patients, with provisional dose levels from 1 to 5 MBq. Part 2, the cohort expansion, will commence once the RP2D is established, enrolling an additional 18 patients to further evaluate safety and gather preliminary efficacy data. The primary objective is to establish the safety profile and determine the MTD/RP2D of [^{225}Ac]Ac-FL-020 in mCRPC patients. Secondary objectives include assessing pharmacokinetics, dosimetry, and anti-tumor activity, with the overarching goal of exploring the potential of this novel actinium RDC for improving outcomes in patients with mCRPC. The study is enrolling in Australia and US, with European sites planned to open later in 2025. Clinical trial information: NCT06492122. Research Sponsor: Full-Life Technologies GmbH.

TPS5118 **Poster Session**

Trial in progress (XALute): Phase 3 study of xaluritamig vs investigator's choice of cabazitaxel or second androgen receptor directed therapy (ARDT) in post-taxane metastatic castration-resistant prostate cancer (mCRPC).

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Background: The median overall survival of patients with mCRPC remains under 2 years even with newer therapies. Xaluritamig, an XmAb 2+1 T-cell engager that targets the six-transmembrane epithelial antigen of prostate 1 (STEAP1), facilitates lysis of STEAP1-expressing cancer cells, such as those in advanced prostate cancer. In a first-in-human study, xaluritamig demonstrated encouraging efficacy and a manageable safety profile for patients with mCRPC refractory to standard of care therapies (Kelly WK, et al. Cancer Discov. 2024;14(1): 76-89). **Methods:** XALute is a randomized, multicenter, open-label, phase 3 study to evaluate the efficacy and safety of xaluritamig vs cabazitaxel or second ARDT in men with mCRPC previously treated with taxane chemotherapy. Enrollment in the control arm treatments will be split evenly between cabazitaxel and second ARDT. Stratification factors include LDH $\leq$ or $>$ 260 IU/L, liver metastases (Y/N), prior prostate-specific membrane antigen radioligand therapy (PSMA-RLT) (Y/N) and the intention to treat with cabazitaxel or ARDT switch. Approximately 675 patients will be enrolled. Participants will be randomly assigned in a 2:1 ratio to xaluritamig monotherapy or standard care. Participants will receive treatment until radiographic disease progression per Prostate Cancer Clinical Trials Working Group 3 (PCWG3), unacceptable toxicity, initiation of other anticancer therapy, withdrawal of consent, death, or end of study as determined by the sponsor. The primary efficacy endpoint is overall survival. The key secondary efficacy endpoint is radiographic progression-free survival per PCWG3 by blinded independent central review. Key inclusion criteria are pathological/cytological confirmation of prostate adenocarcinoma; mCRPC with at least one metastatic lesion; evidence of progressive disease; prior treatment with at least one ARDT; one taxane therapy in the mCRPC setting, and ongoing androgen deprivation with serum testosterone levels ($<$50 ng/dL or $<$1.7 nmol/L). Prior treatment with PSMA-RLT, poly ADP-ribosylation inhibitors, and immune checkpoint inhibitors are permitted. Exclusion criteria include prior STEAP1-targeted therapy, any anticancer therapy within 4 weeks prior to first dose of study treatment (not including androgen deprivation therapy), prior PSMA-RLT within 2 months of first dose of study treatment unless less than 2 cycles received, and prior radionuclide therapy (radium-223) within 2 months of first dose of study treatment To mitigate risk of cytokine release syndrome, xaluritamig will be administered with step dosing. Cabazitaxel or second ARDT will be administered according to regional prescribing information. Funded by Amgen Inc. Clinical trial information: NCT06691984. Research Sponsor: Amgen Inc.

TPS5119 Poster Session

A phase 3 trial of the androgen receptor ligand-directed degrader, BMS-986365, versus investigator's choice in patients with metastatic castration-resistant prostate cancer (CA071-1000 - rechARge).

Kim N. Chi, Rana R. McKay, Shahneen Sandhu, Jose Angel Arranz Arija, Philippe Barthelemy, Boris A. Hadaschik, Nobuaki Matsubara, Neal D. Shore, Dingwei Ye, Teresa Cascella, Irina Irincheeva, Stephanie Kreiser, Antoine Thiery-Vuillemin, Dana Rathkopf; Department of Medical Oncology, BC Cancer Agency, Vancouver, BC, Canada; University of California, San Diego, CA; University of Melbourne, Melbourne, VIC, Australia; Gregorio Marañón University Hospital, Madrid, Spain; Oncology Department, Institut de Cancérologie Strasbourg Europe (ICANS), Strasbourg, France; Department of Urology, University of Duisburg-Essen, Essen, Germany; National Cancer Center Hospital East, Kashiwa, Japan; Carolina Urologic Research Center/AUC Urologists, Myrtle Beach, SC; Fudan University Cancer Hospital, Xuhui, Shanghai, China; Bristol Myers Squibb Research and Development, Boudry, Switzerland; Bristol Myers Squibb, Princeton, NJ; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Prostate cancer relies on the androgen receptor (AR) pathway as a key oncogenic driver. BMS-986365 is a heterobifunctional, orally bioavailable ligand-directed degrader targeting the AR via a first-in-class dual mechanism of AR degradation and antagonism. Results from the first-in-human phase 1 study showed that BMS-986365 was well tolerated with a manageable safety profile and demonstrated antitumor activity in heavily pretreated patients with metastatic castration resistant prostate cancer (mCRPC) regardless of AR gene alterations (Rathkopf et al. *Ann Oncol* 2025;36:76–88). Here, we present the study design of rechARge (NCT06764485), a phase 3, 2-part, randomized, open-label trial evaluating the efficacy and safety of BMS-986365 versus investigator's choice of AR pathway inhibitor (ARPI) or docetaxel, in patients with mCRPC who have failed treatment with 1 prior ARPI. **Methods:** Approximately 960 patients will be randomized in this phase 3, 2-part study. In Part 1 (dose selection), patients will be randomized 1:1:1 to receive either BMS-986365 400 or 300 mg BID Q28D, or investigator's choice comprising ARPI (enzalutamide [160 mg QD] or abiraterone [1000 mg QD + prednisone] Q28D); or docetaxel 75 mg/m^2 + prednisone Q21D up to a maximum of 10 cycles. In Part 2, patients will be randomized 1:1 to receive either BMS-986365 (dose determined from Part 1) or investigator's choice treatment (same as Part 1). Randomization is stratified by prior type of ARPI and investigator's choice (2nd ARPI vs docetaxel). Patients will be treated until radiographic progressive disease by blinded independent central review (BICR) or unacceptable toxicity; all patients must continue androgen deprivation therapy as part of the standard of care. Key inclusion criteria include no more than 1 previous ARPI, confirmed progressive mCRPC defined by having ≥1 of the following: prostate-specific antigen (PSA) progression or radiographic disease progression in soft tissue based on RECIST 1.1 criteria or bone defined as the appearance of ≥2 new lesions on a bone scan; ECOG PS of 0–1, asymptomatic or mildly symptomatic from prostate cancer (Brief Pain Inventory-Short Form, worst pain in last 24 hr <4), no liver metastases, and no prior chemotherapy in the mCRPC setting (docetaxel permitted for mCSPC if >12 months since completion). The primary endpoint is radiographic progression-free survival by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria. The key secondary endpoint is overall survival. Other secondary endpoints include safety, overall response rate, confirmed PSA response rate (PSA30 and PSA50), and patient reported outcomes. The study is recruiting at 230 sites in 24 countries/territories across North America, Europe, Latin America, and East Asia. Clinical trial information: NCT06764485. Research Sponsor: Bristol Myers Squibb.

TPS5120 **Poster Session**

The impact of DNA repair genetic alterations identified by circulating tumor DNA on sensitivity to radium-223 in bone metastatic, castration-resistant prostate cancer.

Steven M. Blinka, Sarah K. Holt, Aaron Lin, Daniel M. Lim, Jorge Ramos, Thomas Murphy, Nathan Conrad, Chelsea Brammeier, Jarey Wang, John M. Floberg, Jessica E. Hawley, Heather H. Cheng, Todd Yezefski, Andrew Caleb Hsieh, Justin Thomas, Ana Ponce Kiess, Glenn Liu, Colin C. Pritchard, Evan Y. Yu; Fred Hutchinson Cancer Center, Seattle, WA; Department of Urology, University of Washington, Seattle, WA; University of Washington School of Medicine, Seattle, WA; Pfizer Inc., Bothell, WA; Bozeman Health Cancer Center, Bozeman, MT; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; University of Wisconsin Carbone Cancer Center, Madison, WI; Division of Hematology & Oncology, University of Washington & Fred Hutchinson Cancer Center, Seattle, WA; University of Wisconsin Carbone Cancer Center, University of Wisconsin School of Medicine and Public Health, Madison, WI; Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA

Background: Selection, timing, and sequencing of therapy for men with bone metastatic castration-resistant prostate cancer (mCRPC) for optimal clinical outcomes is not well-defined. Accordingly, identification of predictive biomarkers for response and outcomes to a given therapy is critical to guide clinical decision-making. Prior research from our group and others has demonstrated that a high proportion (up to 25%) of mCRPC patients harbor aberrations in DNA damage repair (DDR) genes. These findings are clinically meaningful given the efficacy of PARP inhibitors in treating a subset of mCRPC patients with DDR defects. Radium-223 acts by delivering high-energy alpha particles selectively to bone metastases leading to double-stranded DNA breaks. Retrospective studies have shown patients with DDR alterations who are treated with radium-223 have overall survival benefit, improved alkaline phosphatase (ALP) response, and more commonly complete radium-223 treatment. Therefore, we hypothesize that mCRPC with alterations in DDR genes should be particularly vulnerable to treatment with radium-223 and should be evaluated for resultant outcomes prospectively. **Methods:** This Phase 2, multi-center, prospective single-arm biomarker trial aims to enroll 60 patients. Eligible patients must have mCRPC, radiographic evidence of bone disease, symptoms, and PSA ≥10 to ensure successful ctDNA analysis. All patients will receive radium-223 (55 kBq/kg) for up to 6 doses. Patients who have received prior platinum containing chemotherapy will be excluded. ctDNA will be obtained for OncoPlexCT to determine if a patient has a DDR gene alteration (results will not affect treatment plan). Leukocyte analysis will be performed to confirm whether specific alterations are germline vs somatic. The primary objective is to determine the response rate of bone mCRPC with DDR deficiency to treatment with radium-223. Response will be defined as having PSA and/or ALP decline of ≥30% from baseline. The null hypothesis is that the true response rate is 0.40, and the alternate hypothesis is the true response rate is 0.80 (TOPARP, NCT01682772). It is estimated that 25% of the patient population will have DDR alterations and outcomes will be compared with those who are DDR proficient. Using 90% power and an alpha of 0.05, we will accrue 60 patients to ensure the goal of 12 patients with DDR alterations is met. Secondary objectives include determining whether patients who received a prior PARP inhibitor have no decrement in response, overall survival, number of cycles of radium-223 received, and effect of germline vs somatic alterations on response. This trial is currently open to enrollment at Fred Hutch, University of Wisconsin, and Johns Hopkins, and 22/60 patients have already been enrolled. Clinical trial information: NCT04489719. Research Sponsor: Fred Hutch Cancer Center is the primary sponsor of this study. Bayer provided some financial support for this research.

TPS5121 Poster Session

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

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Background: The U.S. Food and Drug Administration (FDA) approved ^{177}Lu-PSMA-617 radiopharmaceutical therapy (RPT) for patients with metastatic castration-resistant prostate cancer (mCRPC) with a fixed dosing schedule: Six cycles of 7.4 GBq administered in six-week intervals. However, a patient-tailored more flexible and extended dosing schedule of ^{177}Lu-PSMA RPT may increase treatment efficacy. In this randomized trial in men with mCRPC, we aim to determine the efficacy of a response-based flexible dosing schedule of ^{177}Lu-PSMA-617 RPT administered up to 12 treatment cycles compared to the current standard of care. **Methods:** This is an investigator-initiated prospective phase 2, open-label, randomized, controlled, parallel group, single-center trial. The aim is to assess the 2-year survival rate in mCRPC patients treated with a flexible dosing schedule of ^{177}Lu-PSMA RPT up to 12 cycles in comparison to the fixed dosing schedule of 6 cycles. Patients with progressive mCRPC post-ARSI, post taxane-based chemotherapy are eligible by PSMA positron emission tomography (PET) VISION trial criteria. Exclusion criteria include prior RPT and less than 6 weeks since the last myelosuppressive therapy. We hypothesized 2-year survival rates of 55% in the investigational group and 30% in the control group. A two-sided log rank test with an overall sample size of 90 subjects (45 treatment group, 45 control group) achieves 80.3% power at a 0.05 significance level to detect a hazard ratio of 0.050. Patients will be randomized in a 1:1 ratio: The investigational arm is treated with up to 12 cycles including potential "treatment holidays" depending on the treatment response (n=45); the control arm receives 6 cycles administered in six-week intervals (n=45). Imaging response to RPT is assessed using ^{177}Lu-PSMA-617 SPECT/CT after each cycle and PSMA PET/CT during treatment holidays (every 12 weeks), respectively. In the investigational arm, RPT will be re-started after a treatment holiday if the patient experiences a ≥25% PSA progression and an imaging progression according to the Response Evaluation Criteria in PSMA PET/CT (RECIP). Primary endpoint is the 2-year survival rate calculated from the date of the first cycle of RPT. Secondary endpoints include safety by Common Terminology Criteria for Adverse Events (CTCAE) and dosimetry, and determination of overall and progression-free survival (evidence of progression as defined by either radiographic, PSA, or clinical progression, or death from any cause). The FLEX-MRT trial has been approved by the FDA (IND #168362), and the UCLA IRB (#23-000931). The trial is registered on ClinicalTrials.gov (NCT06216249). The FLEX-MRT trial is currently recruiting. Start of enrollment was in August 2024. As of January 27th, 2025, 19 patients have been enrolled. Clinical trial information: NCT06216249. Research Sponsor: Prostate Cancer Foundation; Deutsche Forschungsgemeinschaft (DFG, German Research Foundation); 545058105; Novartis.

TPS5122 **Poster Session**

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: For patients (pts) with mCRPC there are numerous treatment options including single agent docetaxel after treatment with androgen receptor pathway inhibitors (ARPI). Despite the availability of varied treatments, overall survival (OS) for pts with mCRPC after ARPI remains poor (12-19 months). Improvements in outcomes are desperately needed. 25% of pts have alterations in DDR genes and are potentially sensitive 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:** PR25 is a phase III randomised controlled trial led by the Canadian Cancer Trials Group comparing docetaxel to docetaxel and carboplatin in pts with DDR alterations. Pts have to 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 5% (2 sided) level test with power of 80%. Conduct to date: Study activation – October 2024. First patient enrolled - December 2024. Accrual to date: 2 Supported by CIHR grant #189966, NCTN grant #CA180863 and CCS grant #707213. Clinical trial information: NCT06439225. Research Sponsor: Canadian Institutes of Health Research; 189966; NCI's National Clinical Trials Network; CA180863; Canadian Cancer Society; 707213.

TPS5123 Poster Session

A randomized, open-label, phase 2b study of the BET bromodomain inhibitor (BETi) ZEN-3694 plus enzalutamide vs. enzalutamide in patients with metastatic castration resistant prostate cancer (mCRPC).

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Background: Androgen receptor signaling inhibitors (ARSI), such as enzalutamide (Enza), and abiraterone (Abi), are standard therapies for metastatic hormone-sensitive and metastatic castration-resistant prostate cancer (mHSPC, mCRPC). Patients who respond to the initial ARSI are frequently prescribed a 2nd ARSI upon progression. A suboptimal response to first line ARSI, including the ~ 20% treated with an ARSI for mHSPC who progress within 12 months of treatment initiation, may enrich for cancers harboring AR-independent mechanisms of resistance including treatment-emergent neuroendocrine prostate cancer (t-NEPC). BETi have been shown pre-clinically to block the neuroendocrine prostate cancer lineage plasticity program through modulating E2F1, a transcription factor involved in stemness and cell differentiation. Prior results from a mCRPC Ph. 1b/2a trial of ZEN-3694+ Enza support this notion, as lower AR transcriptional activity in baseline tumor biopsies was associated with longer radiographic progression-free survival (rPFS). Additionally, mCRPC patients who were primary refractory to 1st line abiraterone had prolonged rPFS with ZEN-3694 + Enza, suggesting that the patients with primary resistance may benefit from the combination. To test this hypothesis, a Ph. 2b randomized trial was initiated, enriching for mCRPC with suboptimal response to 1st line ARSI. **Methods:** This is a multi-national (USA and China), open-label, randomized, two cohort, Ph. 2b study of ZEN-3694 + Enza vs. Enza in mCRPC patients who have progressed on Abi (NCT04986423). Cohort A (N = 150): Patients with poor response to Abi defined either as progression in $<$ 12 months or failure to achieve PSA nadir of 0.2 ng/mL while taking Abi in HSPC setting, or progression in $<$ 6 months and/or failure to achieve a PSA50 response while taking Abi in the CRPC setting. Cohort B (N = 50): Patients who responded to Abi, defined as $>$ 12 months duration without progression while on Abi in the HSPC setting and achieving a nadir PSA $<$ 0.2 ng/mL, or $>$ 6 months duration without progression while on Abi in the CRPC setting and confirmed PSA50 response. The primary endpoint is radiographic progression-free survival (rPFS) by blinded independent central review (BICR) in Cohort A evaluated by PCWG3. Key secondary endpoints include rPFS by BICR for Cohorts A + B, PFS by investigator assessment, overall survival, PSA50 response rate, objective response rate by RECIST 1.1, efficacy endpoints for only USA patients, and patient-reported health status and quality of life, evaluated in Cohorts A, and Cohorts A + B together. The trial, conducted in collaboration with Newsoara has dosed approximately 150 of 200 patients to date. Astellas is providing enzalutamide for this study. Clinical trial information: NCT04986423. Research Sponsor: Newsoara Biopharma Co., Ltd; Zenith Epigenetics; Astellas Pharma Inc.

TPS5125 Poster Session

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

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Background: Prostate cancer (PC) is common and despite recent advances in treatment options, patients with metastatic disease still have poor outcomes. The double PSMA binding moiety of SAR-bisPSMA in ^{64}Cu-SAR-bisPSMA (imaging) and ^{67}Cu-SAR-bisPSMA (therapy) may offer advantages compared to currently used single-target PSMA agents. Clinical evidence demonstrated 2-3 times higher uptake of ^{64}Cu-SAR-bisPSMA compared to the single-target PSMA agent, ^{68}Ga-PSMA-11. Pre-clinical efficacy data of ^{67}Cu-SAR-bisPSMA in mice showed statistically significant tumor growth inhibition and increased survival in a PC xenograft study. These results led to the development of the SECuRE trial, which aims to assess the safety and anti-tumor efficacy of ^{67}Cu-SAR-bisPSMA in patients with metastatic castrate resistant PC (mCRPC). **Methods:** SECuRE is a Phase I/IIa multi-center, open-label, non-randomized, dose-escalation and cohort expansion study of ^{64}Cu-SAR-bisPSMA and ^{67}Cu-SAR-bisPSMA in patients with mCRPC. The target population is patients who have progressed despite having at least one androgen receptor pathway inhibitor and demonstrate positivity on ^{64}Cu-SAR-bisPSMA PET. The study comprises 3 phases: Dosimetry (N=6), Dose Escalation (N~24) and Cohort Expansion (N=24). The ^{67}Cu-SAR-bisPSMA dose levels investigated in the Dose Escalation Phase are: 4 GBq (cohort 1, single dose), 8 GBq (cohort 2, single dose), 12 GBq (cohort 3, single dose) and 24 GBq across two doses (cohort 4, two doses at the maximum tolerated dose or maximum feasible dose [MTD/MFD] established in cohorts 1-3; two additional doses may be offered in case of radiological non-progression). In the Cohort Expansion phase, participants will receive 2 doses of ^{67}Cu-SAR-bisPSMA at the recommended dose determined in the Dose Escalation Phase (those with radiological non-progression may be offered up to 2 additional doses). A recent protocol amendment increased the number of participants from 14 to 24 in the Cohort Expansion phase, in which 8 will receive combination therapy of ^{67}Cu-SAR-bisPSMA with enzalutamide. The primary and key secondary objectives include assessment of ^{64}Cu- and ^{67}Cu-SAR-bisPSMA's safety and dosimetry and determining the anti-tumor efficacy of ^{67}Cu-SAR-bisPSMA. Response to ^{67}Cu-SAR-bisPSMA will be assessed biochemically ($\geq$50% decline in prostate-specific antigen) and radiographically (by RECIST V1.1 and PCWG3). Clinical trial information: NCT04868604. Research Sponsor: Clarity Pharmaceuticals.

TPS5126 **Poster Session**

A phase 3 study of 177Lu-rosptamab plus standard of care vs. standard of care alone in patients with metastatic castration-resistant prostate cancer (ProstACT Global).

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Background: The treatment of advanced prostate cancer (PC) is challenging, with undesirable side effects that impact patient quality of life. Radioimmunotherapy (RIT) can localize therapy to specific tumor cells in multiple organs to reduce or eliminate damage to normal tissue. The cell surface glycoprotein prostate-specific membrane antigen (PSMA) is an ideal therapeutic target as it is highly expressed by malignant prostate cells. There is a strong rationale for further investigation of the ^{177}Lu-labeled, chelator-conjugated antibody, ^{177}Lu-rosopatamab, as a potential first-line RIT candidate for the treatment of PC. **Methods:** This multinational, multicenter, prospective, randomized, open label phase 3 study will have 2 parts: a dosimetry and safety lead-in (n=30) and a randomized treatment expansion (n=490). In Part 1, patients will be divided into 3 groups (n=10 each) to receive 2 single intravenous (IV) injections of 76 millicuries (mCi) each, 14 days apart, of ^{177}Lu-rosopatamab with best standard of care (SoC) combinations with abiraterone, enzalutamide, or docetaxel to fully characterize biodistribution and safety profiles of ^{177}Lu-DOTA-rosopatamab + SoC. SoC received will be determined prior to treatment with ^{177}Lu-rosopatamab. In Part 2, patients will be enrolled in a 2:1 ratio to receive either the best SoC or 2 single IV injections of 76 mCi each of ^{177}Lu-rosopatamab, given 14 days apart, plus best SoC. SoC will be determined prior to randomization. Eligible patients must have PSMA-expressing metastatic castration-resistant PC (mCRPC) that have progressed despite prior therapy with either enzalutamide or abiraterone plus prednisone, and 1 line of prior taxane therapy or have refused or are ineligible for taxanes. Patients must have adequate organ function including at least 150x10^9/L platelets, hemoglobin 10 g/dL, and have PSMA-positive disease on ^{68}Ga-PSMA-11 PET/CT imaging as confirmed by a central reader. Key exclusion criteria include small cell histology, increased risk of hemorrhage or bleeding, known brain or hepatic metastases, or history of stroke, seizure, or treatment with radioisotopes within 6 months prior to randomization. The primary endpoint is radiographic progression-free survival (rPFS). Key secondary endpoint is OS. Additional secondary endpoints include 5-year overall survival, tumor objective response rate, time to symptomatic skeletal event, and health-related quality of life. An alpha control and 95% confidence intervals will be used; patients will be substratified between TLX591 + 2nd ARPI or TLX591 + docetaxel. This study is currently enrolling. Clinical trial information: NCT06520345. Research Sponsor: Telix Pharmaceuticals.

TPS5127 Poster Session

PSMA-delay castration (DC): An open-label, multicenter, randomized phase 3 study of [^{177}Lu]Lu-PSMA-617 versus observation in patients with metachronous PSMA-positive oligometastatic prostate cancer (OMPC).

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Background: Androgen deprivation therapy (ADT) ± androgen receptor pathway inhibitor therapy is a primary treatment for metastatic hormone-sensitive prostate cancer, but is noncurative and has significant toxicities when used long-term. In patients with OMPC for whom delaying ADT is appropriate, metastasis-directed therapy such as stereotactic body radiation therapy (SBRT) has been shown to provide local disease control. However, many patients do not experience a complete prostate-specific antigen (PSA) response and develop poly-metastatic disease. [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) is a prostate-specific membrane antigen (PSMA)-targeted radioligand therapy with demonstrated efficacy and a manageable safety profile in patients with PSMA-positive metastatic castration-resistant prostate cancer in the VISION and PSMAfore trials. PSMA-DC (NCT05939414) is an ongoing, international, randomized phase 3 trial to evaluate the efficacy of ^{177}Lu-PSMA-617 versus observation after SBRT in delaying castration and disease progression in patients with PSMA-positive OMPC. **Methods:** Eligible patients have histologically confirmed prostate cancer, biochemical recurrence post-definitive treatment, OMPC with ≤ 5 PSMA-positive metastatic lesions including ≥ 1 distant metastasis on PSMA PET/CT scans (all must be amenable to SBRT), PSA doubling time < 10 months and non-castration testosterone levels (> 100 ng/dL). Exclusion criteria include distant metastasis by conventional imaging (CI; CT/MRI and bone scans) at screening, prior ADT (except adjuvant ADT completed > 12 months before randomization), or other systemic therapy for metastatic prostate cancer. Patients (N = ~450) will be randomized 2:1 to ^{177}Lu-PSMA-617 or observation and will receive SBRT to all metastatic lesions within 14 days, completed within 3 weeks. Patients will then receive either intravenous ^{177}Lu-PSMA-617 (7.4 GBq/6 weeks; 4 cycles), starting 7–21 days after SBRT, or undergo observation only. Additional SBRT for new lesions is allowed. ADT is allowed after a metastasis-free survival (MFS) event by CI confirmed by blinded independent review committee (BIRC). Safety follow-up will occur 42 days after the last ^{177}Lu-PSMA-617 dose and at the week 24 visit for the observational arm. Long-term follow-up for the ^{177}Lu-PSMA-617 arm will include safety assessments every ~32 weeks. The primary endpoint is MFS by CI as assessed by BIRC using RECIST v1.1, or death. To provide 90% power to detect a hazard ratio of 0.6, 187 MFS events are required. The key secondary endpoint is time to next hormonal therapy. Additional secondary endpoints include time to PSA progression, radiographic progression-free survival, symptomatic progression, patient-reported health-related quality of life, overall survival and safety. Shore et al. PSMA-delay castration (DC): an open-label, multicenter, randomized phase 3 study of [^{177}Lu]Lu-PSMA-617 versus observation in patients with metachronous PSMA-positive oligometastatic prostate cancer (OMPC). J Urol 2025;213 (5S2_suppl):e28. https://www.auajournals.org/doi/10.1097/01.JU.0001110444.53548.eb. Reused with permission; ©American Urological Association, 2025. This abstract previously presented at 2025 AUA Annual Meeting. Clinical trial information: NCT05939414. Research Sponsor: Novartis.

TPS5128 **Poster Session**

METANOVA: A phase II trial of metastasis-directed radiotherapy for de novo oligometastatic prostate cancer treated with long-term androgen deprivation therapy in the STAMPEDE trial.

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Background: Men with de novo oligometastatic hormone-sensitive prostate cancer (omHSPC) represent a unique subgroup where metastasis-directed radiotherapy (MDRT) may improve outcomes when added to systemic therapy. Retrospective data suggest potential survival benefits of MDT in oligometastatic prostate cancer (PCa), but prospective randomized evidence in the de novo setting is lacking. The METANOVA trial aims to determine whether MDRT, combined with standard systemic therapy (SST) and prostate-directed local therapy, improves outcomes for these patients. **Methods:** METANOVA is a phase II, randomized, open-label trial enrolling 200 men with histologically confirmed de novo omHSPC (NCT06150417). Oligometastatic disease defined as 1–5 metastatic sites by traditional imaging (MRI, CT, or ^{99m}Tc bone scan) or 1–10 sites by PSMA PET/CT. Patients are allowed up to 30 days of androgen deprivation therapy (ADT) prior to enrollment. Patients are randomized 1:1 to standard of care (SOC) or SOC + MDRT to all metastatic sites. SOC includes 12 months of SST (ADT, with addition of an androgen receptor signaling inhibitor; triplet therapy is not allowed) and definitive treatment of the primary. Planned local therapy may be prostate-directed radiation therapy with definitive dose (moderate hypofractionation and ultra-hypofractionation allowed) or radical prostatectomy (maximum 50 patients to receive surgery), determined prior to randomization. MDRT will be delivered using stereotactic body radiation therapy (SBRT) to all metastatic lesions on conventional imaging or PSMA PET/CT. Patients are stratified to the use of PSMA PET/CT to stage, number of bone metastasis (0 vs 1-3 vs 4-10), local treatment (RT vs RP), and plan to MDRT all sites of PSMA disease (yes vs no). The primary endpoint is failure-free survival (FFS), defined as the time from randomization to biochemical failure, local or distant progression, skeletal-related event, any salvage intervention after 12 months planned SOC therapy, or death from prostate cancer. Secondary endpoints include overall survival, radiographic progression-free survival, quality of life (EPIC-26 domains), and toxicity. Correlative studies will explore imaging and molecular features from the primary, metastasis, and circulating disease to develop a predictive biomarker of which patients would derive the greatest benefit from MDRT. This study is designed to demonstrate a 34% relative reduction in the hazard of FFS from the addition of MDRT to SOC, providing 80% power at a one-sided alpha level of 0.05. The trial activated in July 2024, aims to complete accrual within 3 years. Data from this trial is preplanned to be pooled with the STAMPEDE2 (NCT06320067) trial in the United Kingdom, which is assessing overall survival benefit of MDRT in men with de novo omHSPC. Funding: NIH U01CA257638. Clinical trial information: NCT06150417. Research Sponsor: NIH-NCI.

TPS5129 Poster Session

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).

Michael Ong, Alexandra Sokolova, Sebastien J. Hotte, Tanya B. Dorff, Kim N. Chi, Alexander William Wyatt, Amir Goldkorn, Michael Paul Kolinsky, Michael Donald Brundage, Akunne Ndika, Seth P. Lerner, Wendy R. Parulekar, Keyue Ding, Mariam Jafri; The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; Oregon Health & Science University, Knight Cancer Institute, Portland, OR; Juravinski Cancer Institute, McMaster University, Hamilton, ON, Canada; City of Hope Comprehensive Cancer Center, Duarte, CA; University of British Columbia, BC Cancer, Vancouver Cancer Centre, Vancouver, BC, Canada; University of British Columbia, Vancouver, BC, Canada; USC Norris Comprehensive Cancer Center, Los Angeles, CA; Cross Cancer Institute, Edmonton, AB, Canada; Cancer Centre Southeastern Ontario At KGH, Kingston, ON, Canada; Canadian Cancer Trials Group, Kingston, ON, Canada; Baylor College of Medicine, Houston, TX; Queen's University, Canadian Cancer Trials Group, Kingston, ON, Canada

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). Recent analyses of phase III ADT + ARPI trials show that mCSPC with suboptimal PSA response (≥0.2ng/ml at 6-12 months) have poor prognosis, short time to castration-resistance (CRPC) and 30-36 month median overall survival (OS). While docetaxel could also be utilized in mCSPC, there is equipoise about its use in ARPI-treated pts because of 1) an absence of randomized data for docetaxel in this setting, 2) toxicity of docetaxel with impact on quality of life for pts, and 3) selection of docetaxel treatment by disease volume rather than disease biology. CCTG-PR26 (TRIPLE-SWITCH) is a joint CCTG-SWOG trial run through the NCI National Clinical Trials Network. This study investigates whether adding docetaxel prior to development of CRPC, regardless of disease volume, will improve OS in ARPI-treated mCSPC pts that show evidence of suboptimal response. **Methods:** This international, open-label, randomized phase III trial compares standard ADT + ARPI against the addition of docetaxel to ADT + ARPI in mCSPC pts with suboptimal PSA response, defined as 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. Arm 1 will continue standard ADT + ARPI (abiraterone acetate with prednisone, apalutamide, enzalutamide or darolutamide). Arm 2 will receive docetaxel 75mg/m^2 IV every 3 weeks for up to 6 cycles in addition to continuing standard ADT + ARPI. Sample size is 830 pts in order 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 progression or biochemical progression on ADT prior to enrolment. Primary endpoint is overall survival. 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 (ctDNA) and the association between molecular signatures in primary prostate cancer tissue and clinical outcomes. Enrolment has been initiated in January 2025 and is ongoing. Clinical trial information: NCT06592924. Research Sponsor: Canadian Institutes of Health Research; 195838; NCI National Clinical Trials Network (NCTN); CA180863; Canadian Cancer Society; 707213.

TPS5130 Poster Session

A phase II study of niraparib (N), abiraterone acetate (AA) plus prednisone (P) for Hispanic/Latino (HL) and non-Hispanic Black (NHB) patients with metastatic hormone sensitive prostate cancer (mHSPC) and deleterious homologous recombination repair alterations (HRRa; HARMONY).

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Background: Patients with prostate cancer and deleterious HRRa have poorer prognosis but derive benefit from poly (ADP-ribose) polymerase (PARP) inhibition. However, prevalence of HRRa and response to PARP inhibition are less well defined in racial/ethnic minorities. We designed the HARMONY trial to evaluate the efficacy of N/AA/P in HL and NHB patients with mHSPC and deleterious HRRa. **Methods:** This multicenter, open label, phase II study is open through the Hoosier Cancer Research Network in the United States. The trial enrolls patients who self-identify as HL or NHB and have mHSPC with HRRa including *BRCA 1/2*, *BRIP1*, *CHEK2*, *FANCA*, *PALB2*, *RAD51B*, and/or *RAD54L*. Eligible patients will have hormone sensitive, treatment naïve or minimally treated prostate cancer (i.e., bicalutamide $\leq$ 45 days, androgen deprivation therapy [ADT] $\pm$ AA plus P $\leq$ 45 days allowed). Prostate cancer variants, other therapy in mHSPC setting, or symptomatic brain metastases are exclusionary. Enrolled patients will receive 24 weeks (w) of ADT plus N/AA dual action tablet (DAT) plus P, followed by an adaptive approach based on prostate specific antigen (PSA) response. Subjects in Arm A (PSA $>$ 4.0 ng/mL at 24 w) can continue ADT/N/AA/P for max 2 years or stop N and escalate therapy to ADT/AA/P plus 6 cycles of docetaxel followed by standard of care (SOC) therapy. Subjects in Arm B (PSA $\leq$ 4.0 ng/mL at 24 w) will continue ADT/N/AA/P for a total of 12 months. At 12 months in Arm B, subjects with PSA $\geq$ 0.2 ng/mL will continue ADT/N/AA/P for max 2 years, and subjects achieving PSA $<$ 0.2 ng/mL have the option to continue ADT/N/AA/P for max 2 years or discontinue all therapy with the option to start SOC treatment at disease progression. PSA decline to $<$ 0.2 ng/mL at 24w (primary endpoint) will be evaluated for each racial/ethnicity group against a historic rate of 50%. Thirty patients per racial/ethnic cohort will give 80% power at 0.1 significance to determine noninferiority with a no-inferiority margin of 0.185. Estimating 5% drop out, 64 patients will be enrolled (n=32 HL and n=32 NHB). Key secondary/exploratory endpoints include PSA reduction $\geq$ 90%, overall response rate, PSA/radiographic progression free survival, overall survival, time to subsequent anti-cancer therapy, quality of life and safety. Key genomic correlatives will be evaluated. ClinicalTrials.gov: NCT06392841. Study support of drug and funding: Janssen Scientific Affairs LLC. Clinical trial information: NCT06392841. Research Sponsor: Janssen Scientific Affairs LLC.

TPS5131 Poster Session

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

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Background: Patients with prostate cancer treated with radiotherapy (RT) or radical prostatectomy (RP) as primary therapy may develop BCR – a prostate-specific antigen (PSA) increase with no evidence of metastases on conventional imaging (e.g. magnetic resonance imaging/computed tomography). Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) is more sensitive than conventional imaging and may detect lesions in patients with BCR that conventional imaging cannot. BCR is an indicator of disease progression and warrants effective treatment to delay further progression, particularly if lesions are detected by PSMA PET/CT. The androgen receptor inhibitor darolutamide is structurally different by design to deliver robust clinical efficacy with a differentiated tolerability profile. In the phase 3 ARAMIS trial, darolutamide significantly improved metastasis-free survival (MFS) and overall survival (OS) in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC). ARASTEP is a phase 3 trial (NCT05794906) evaluating whether darolutamide plus ADT improves radiological progression-free survival (rPFS) by PSMA PET/CT vs placebo plus ADT in patients with high-risk BCR and PSMA PET/CT-positive lesions following primary therapy. **Methods:** Key eligibility criteria included: prior primary RT or RP ± adjuvant RT (ART) or salvage RT (SRT), with high-risk BCR (PSA doubling time [PSADT] <12 months and PSA ≥0.2 ng/mL after primary RP [± ART/SRT] or PSA ≥2 ng/mL above nadir after primary RT only), ≥1 PSMA PET/CT-positive prostate cancer lesion with no visible lesions on conventional imaging, and serum testosterone ≥150 ng/dL. ARASTEP is planned for 750 patients from 23 countries to be randomized 1:1 to oral darolutamide 600 mg twice daily or placebo, both with ADT, for 24 months or until disease progression, unacceptable toxicity, or withdrawal of consent. During the 24-month treatment period, patients will be monitored for safety every 12 weeks, and every 24 weeks for PSMA PET/CT and conventional imaging events. After 24 months, patients with PSA values ≥0.2 ng/mL will continue study treatment as part of active follow-up until PSMA PET/CT progression is confirmed by blinded independent central review (BICR), followed by long-term follow-up for conventional imaging progression. Patient stratification factors are PSADT (<6 vs ≥6–<12 months), intent to treat baseline PSMA PET/CT lesions with image-guided RT/surgery (Yes vs No), and distant ± locoregional vs locoregional-only lesions. The primary endpoint is rPFS by PSMA PET/CT assessed by BICR. Secondary endpoints include MFS on conventional imaging by BICR, time to CRPC, OS, quality of life, and safety. As of January 2025, 458 patients have been randomized from 220 sites. Clinical trial information: NCT05794906. Research Sponsor: Bayer.

TPS5132 Poster Session

Androgen suppression combined with elective nodal irradiation and dose escalated prostate treatment: A non-inferiority, phase III randomized controlled trial of stereotactic body radiation therapy versus brachytherapy boost in patients with unfavourable risk localized prostate cancer (ASCENDE-SBRT; CCTG PR24; NCT06235697).

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Background: External beam radiotherapy (EBRT), brachytherapy boost and androgen deprivation therapy (ADT) is the evidence-based standard of care for unfavourable (unfavourable intermediate, high and very high) risk non-metastatic prostate cancer. Preliminary data demonstrate that treatment with 5 fractions of stereotactic body radiotherapy (SBRT) delivered to the pelvis and prostate with ADT is efficacious and tolerable in this patient population (Murthy Int J Rad Onc Biol Phys 2025) Other potential advantages associated with this treatment strategy include fewer treatment visits, lower cost, avoidance of a general anesthetic and decreased resource utilization. Rigorous evaluation of this treatment strategy within a clinical trial is required to inform adoption in practice. **Methods:** PR24 is a Canadian Cancer Trials Group led, intergroup, randomized phase III, non-inferiority study comparing pelvic EBRT + brachytherapy boost to SBRT (5 fractions delivering 40Gy to prostate and 25Gy to pelvis) in brachytherapy eligible, unfavourable risk, non-metastatic prostate cancer patients. All patients will receive risk-adapted duration of ADT. The primary objective is to determine if SBRT is non-inferior to conventional EBRT with brachytherapy boost in terms of disease progression free survival (PFS). Secondary objectives include a comparison between arms of: safety and tolerability; efficacy including PSA response rate at 4 years, metastasis-free survival, prostate cancer cause-specific survival, overall survival; patient-reported and economic outcomes. Biobanking for future correlative studies is included in study design. Statistical design: The target accrual is 710 patients over 3.6 years with 5-year follow-up up to rule out a target HR 1.65 (6.5% inferiority difference at 5-years) in PFS, using type 1 error rate 5% (one sided) and 80% power with 5% lost to follow-up. Conduct to Date: Study activation - March 2024. First patient enrolled - April 2024. Accrual to date: 45. Supported by CIHR grant #183644, NCTN grant #CA180863 and CCS grant #707213. Clinical trial information: NCT06235697. Research Sponsor: CIHR; 183644; NCTN; CA180863; CCS; 707213.