Therapeutic Innovations in Advanced Prostate Cancer: A Real-World Comparative Effectiveness Evaluation

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Abstract

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Background: Metastatic prostate cancer is a major source of cancer mortality among US men. Since 2015, the treatment landscape for metastatic hormone-sensitive prostate cancer (mHSPC) has expanded to include four guideline-endorsed doublet regimens combining androgen deprivation therapy (ADT) with docetaxel or one of three androgen receptor pathway inhibitors (ARPIs)—abiraterone, apalutamide, or enzalutamide—yet no head-to-head randomized trial has compared these regimens. In metastatic castration-resistant prostate cancer (mCRPC), lutetium-177 PSMA-617 (Lu-PSMA) and cabazitaxel are both used after progression on docetaxel and an ARPI, but their comparative survival benefit has not been established in US practice. Real-world evidence is needed to inform first-line selection, sequencing, and value assessment.

Objective: To estimate the real-world comparative effectiveness and cost-effectiveness of contemporary doublet therapies for mHSPC and the comparative effectiveness of Lu-PSMA versus cabazitaxel for mCRPC in a US population.

Methods: Two real-world comparative effectiveness analyses were conducted using the Komodo Health administrative claims database and the target trial emulation framework, and a decision-analytic cost-effectiveness model was built from the Aim 1 outputs. Aim 1 identified 9,141 men with mHSPC who initiated ADT with abiraterone, apalutamide, enzalutamide, or docetaxel. Overlap propensity score weighting with Cox proportional hazards models estimated overall survival (OS) and progression-free survival (PFS), while Fine-Gray competing risk models estimated time to mCRPC progression (TTP), and time to next treatment initiation (TTNT). Aim 2 populated a three-state partitioned survival cost-effectiveness model with the propensity-weighted survival curves from Aim 1 to estimate lifetime costs and quality-adjusted life-years (QALYs) for each regimen from the US healthcare sector perspective, with probabilistic sensitivity analysis. Aim 3 identified men with mCRPC who received Lu-PSMA or cabazitaxel following prior docetaxel and at least one ARPI; average treatment effect in the treated (ATT) propensity score weighting and weighted Cox models estimated OS and PFS.

Results: In Aim 1, all three ARPI doublets demonstrated superior PFS versus docetaxel (abiraterone aHR 0.60, 95% CI 0.55–0.66; apalutamide aHR 0.64, 95% CI 0.56–0.73; enzalutamide aHR 0.57, 95% CI 0.51–0.64), with comparable OS across regimens and no significant differences among ARPIs. Time to mCRPC progression and time to next treatment also favored ARPI doublets. In Aim 2, abiraterone yielded 5.37 QALYs at $716,701 and was the most cost-effective option across all evaluated willingness-to-pay thresholds; docetaxel was dominated by abiraterone, apalutamide was dominated by enzalutamide, and the incremental cost-effectiveness ratio for enzalutamide versus abiraterone was $1,214,802 per QALY. In Aim

3, Lu-PSMA was associated with significantly longer OS (aHR 0.87, 95% CI 0.76–0.99) and PFS (aHR 0.41, 95% CI 0.36–0.46) compared with cabazitaxel.

Conclusions: ARPI doublets are the preferred first-line treatment for mHSPC, with abiraterone offering superior value driven by generic availability. In post-docetaxel, post-ARPI mCRPC, Lu-PSMA improves both overall and progression-free survival relative to cabazitaxel. These findings provide real-world comparative evidence to inform clinical decision-making, value assessment, and Inflation Reduction Act drug price negotiation.

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CHAPTER 1: INTRODUCTION

1.1 Background

Prostate cancer is the most commonly diagnosed malignancy and the second leading cause of cancer-related death among men in the United States, with an estimated 299,010 new cases and 35,250 deaths projected for 2024.[1] Although most patients present with localized, potentially curable disease, approximately 8% present with de novo metastatic disease, and a substantial proportion of those treated for localized disease eventually develop metastatic recurrence.[2] Once metastases are established, the disease progresses through two clinically distinct phases: metastatic hormone-sensitive prostate cancer (mHSPC), in which tumor growth remains responsive to androgen deprivation therapy (ADT), and metastatic castration-resistant prostate cancer (mCRPC), defined by biochemical, radiographic, or clinical progression despite castrate testosterone levels.[3] Median overall survival on ADT alone is three to four years, and nearly all patients progress to mCRPC within two to three years of treatment initiation.[3]

Since 2015, the mHSPC treatment landscape has been transformed by pivotal randomized controlled trials demonstrating that intensifying ADT with either docetaxel chemotherapy (CHAARTED, STAMPEDE) or an androgen receptor pathway inhibitor (ARPI)—abiraterone (LATITUDE, STAMPEDE), enzalutamide (ARCHES, ENZAMET), or apalutamide (TITAN)—significantly delays disease progression and improves overall survival.[4–9] Doublet therapy is now the standard of care recommended by the National Comprehensive Cancer Network and the European Society for Medical Oncology.[10],[11] The mCRPC armamentarium has expanded in parallel, most recently with the 2022 approval of lutetium-177 PSMA-617 (Lu-PSMA) for PSMA-positive disease following progression on prior ARPI and taxane therapy, based on the phase III VISION trial.[12]

1.2 Evidence Gaps in Comparative Effectiveness and Value

Despite the proliferation of approved doublet regimens for mHSPC, no head-to-head randomized trial has compared abiraterone, apalutamide, enzalutamide, and docetaxel, leaving clinicians, payers, and patients without direct evidence to guide first-line selection.[13] The four regimens differ substantially in pharmacologic mechanism, toxicity profile, mode of administration, and acquisition cost: generic docetaxel and generic abiraterone remain inexpensive, while enzalutamide and apalutamide remain under patent protection at tens of thousands of dollars per month.[14] Existing economic evaluations rely on indirect treatment comparisons or trial-derived survival inputs that may not reflect routine US clinical practice.[15],[16]

In the post-docetaxel, post-ARPI mCRPC setting, cabazitaxel has historically served as the standard second-line cytotoxic option, yet the VISION trial excluded chemotherapy from its control arm, leaving the comparative survival benefit of Lu-PSMA versus cabazitaxel unresolved.[12],[17] The phase II TheraP trial enrolled only 200 Australian patients with restrictive dual PSMA/FDG-PET eligibility and was not powered for survival, and the phase III PSMAfore trial enrolled taxane-naive patients.[18],[19] Real-world comparative evidence is therefore needed to inform sequencing decisions in the broader US population.

1.3 Methodological Framework

This dissertation applies a unified pharmacoepidemiologic and decision-analytic framework to address the above gaps using the Komodo Health administrative claims database, which captures longitudinal medical and pharmacy claims for more than 330 million US patients. Comparative effectiveness analyses follow the target trial emulation framework, in which protocol elements of a hypothetical pragmatic trial—eligibility, treatment strategies, assignment, follow-up, and outcomes—are explicitly specified and then emulated in observational data to minimize prevalent-user, immortal-time, and selection biases.[20]

Confounding by indication is addressed using propensity score weighting: overlap weights for the four-arm mHSPC comparison, which yield exact covariate balance and emphasize the subpopulation in clinical equipoise,[21] and average treatment effect in the treated (ATT) weights for the mCRPC comparison, where the PSMA-PET screening requirement for Lu-PSMA defines the target population. Time-to-event outcomes are estimated with weighted Cox proportional hazards models, with Fine-Gray competing-risks models for secondary outcomes. The cost-effectiveness analysis applies a three-state partitioned survival model populated with parametric extrapolations of the propensity score-weighted survival curves, following ISPOR-SMDM good research practices and CHEERS reporting standards.[22],[23]

1.4 Clinical Relevance

The findings of this dissertation have direct implications for routine prostate cancer care. In the first-line mHSPC setting, oncologists and urologists must choose among four guideline-endorsed doublet regimens that have never been compared head-to-head, and current National Comprehensive Cancer Network and European Association of Urology recommendations group all three ARPIs together without prioritization.[10],[11] Aim 1 generates the first US-based head-to-head comparison of all four regimens in a contemporary, real-world cohort that includes the older, frailer, and more comorbid patients typically underrepresented in the CHAARTED, LATITUDE, ARCHES, ENZAMET, and TITAN trials. By estimating treatment-specific overall survival, progression-free survival, time to mCRPC progression, and time to next treatment, Aim 1 provides clinicians with comparative evidence to support shared decision-making conversations that weigh efficacy alongside tolerability, route of administration, monitoring requirements, and patient preference.

Aim 2 translates these effectiveness estimates into a value framework that is directly actionable for payers, formulary committees, and oncology practices participating in alternative payment models. Because generic abiraterone has fundamentally altered the cost structure of mHSPC

therapy, conclusions drawn from earlier cost-effectiveness analyses based on brand-name pricing or trial-derived efficacy estimates may no longer reflect contemporary practice. Aim 2 provides updated incremental cost-effectiveness ratios anchored to real-world survival, supporting both individual-patient value discussions and population-level resource allocation.

Aim 3 addresses a high-stakes sequencing question in mCRPC, where prognosis is poor and treatment tolerability is paramount. Cabazitaxel's toxicity profile leads many clinicians to defer or avoid it in older or frailer patients, while Lu-PSMA offers a targeted, generally better-tolerated alternative whose comparative survival benefit relative to cabazitaxel has not been established in a US population. Real-world comparative estimates from Aim 3 directly inform the post-docetaxel, post-ARPI sequencing decisions that practicing oncologists face daily and that current guidelines acknowledge are supported by limited evidence.

1.5 Policy Context

These analyses are situated within a rapidly evolving US drug-pricing landscape. The Inflation Reduction Act of 2022 authorizes the Centers for Medicare and Medicaid Services to negotiate maximum fair prices for selected high-expenditure Part B and Part D drugs, with comparative clinical effectiveness evidence and unmet medical need explicitly listed among the statutory negotiation factors.[24] Enzalutamide (Xtandi) was selected for the second negotiation cycle, with negotiated prices effective January 2027, and other prostate cancer agents are plausible candidates in subsequent cycles.[25] Real-world evidence on comparative survival, treatment patterns, and value will increasingly inform both federal price negotiation and independent value assessment by bodies such as the Institute for Clinical and Economic Review.

1.6 Specific Aims

This dissertation addresses three specific aims:

Aim 1: To estimate the real-world comparative effectiveness of abiraterone, apalutamide, enzalutamide, and docetaxel doublets for mHSPC using target trial emulation and overlap propensity score weighting in a US claims-based cohort.

Aim 2: To evaluate the cost-effectiveness of the four mHSPC doublet regimens from the US healthcare sector perspective using a three-state partitioned survival model parameterized with the real-world survival estimates from Aim 1.

Aim 3: To estimate the real-world comparative effectiveness of Lu-PSMA versus cabazitaxel in mCRPC patients previously treated with docetaxel and an ARPI, using target trial emulation and ATT propensity score weighting.

1.7 Dissertation Organization

The remainder of this dissertation is organized as follows. Chapter 2 presents the Aim 1 comparative effectiveness analysis of mHSPC doublet therapies. Chapter 3 presents the Aim 2 cost-effectiveness analysis. Chapter 4 presents the Aim 3 mCRPC comparative effectiveness analysis of Lu-PSMA versus cabazitaxel. Chapter 5 synthesizes findings across aims and discusses clinical, methodological, and policy implications, study limitations, and directions for future research.

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CHAPTER 2：Real-World Comparative Effectiveness of Abiraterone, Apalutamide, Enzalutamide, and Docetaxel Doublets for Metastatic Hormone-Sensitive Prostate Cancer (Aim 1)

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2.1. Abstract

PURPOSE

To evaluate the real-world comparative effectiveness of androgen receptor pathway inhibitors (ARPIs) – abiraterone, apalutamide, enzalutamide – and docetaxel, plus androgen deprivation therapy (ADT) for metastatic hormone-sensitive prostate cancer (mHSPC)

METHODS

We identified US men with mHSPC who initiated ADT within 4 months of diagnosis and were treated with abiraterone, apalutamide, enzalutamide, or docetaxel within 4 months of ADT initiation between January 2019 and December 2023, with follow-up through June 2025. Primary outcomes were progression-free survival (PFS) and overall survival (OS). Secondary outcomes included time to mCRPC progression (TTP) and time to new treatment initiation (TTNT). Cox proportional hazard and Fine-Gray models with overlapping propensity score weights were used to estimate primary and secondary outcomes, respectively. Subgroup analyses by timing of metastasis and sensitivity analyses using inverse probability of treatment weights were conducted for primary outcomes.

RESULTS

Among 9,141 US men with mHSPC, ARPI doublets demonstrated superior PFS versus docetaxel doublets (abiraterone: aHR: 0.60, 95% CI: 0.55-0.66; apalutamide: aHR: 0.64, 95% CI: 0.56-0.73; enzalutamide: aHR: 0.57, 95% CI: 0.51-0.64), with no significant differences among ARPI regimens. OS was comparable among all doublet regimens. Neither PFS nor OS differed by timing of disease. TTP (abiraterone: aHR: 0.52, 95% CI: 0.47-0.58; apalutamide: aHR: 0.59, 95% CI: 0.52-0.68; enzalutamide: aHR: 0.51, 95% CI: 0.45-0.57), and TTNT (abiraterone: aHR: 0.46, 95% CI: 0.42-0.51; apalutamide: aHR: 0.53, 95% CI: 0.46-0.61;

enzalutamide: aHR: 0.47, 95% CI: 0.42-0.53) showed similar patterns favoring ARPI doublets. Sensitivity analyses showed consistent findings.

CONCLUSION

ARPI doublets demonstrated superior PFS, but similar OS compared to docetaxel doublet, with no differences among individual ARPIs. Patients receiving ARPI doublets were less likely to progress to mCRPC or initiate new treatment.

2.2. Introduction

Prostate cancer is the second most commonly diagnosed malignancy and the second leading cause of cancer deaths among men in the United States[1]. Metastatic hormone-sensitive prostate cancer (mHSPC), characterized by initial responsiveness to testosterone suppression, represents a critical juncture in disease management where therapeutic intervention can substantially alter patient outcomes and survival trajectories. The therapeutic landscape for mHSPC has undergone a transformative evolution over the past decade, shifting from androgen deprivation therapy (ADT) monotherapy to combination regimens.

Pivotal phase III trials established doublet therapies as the standard of care in mHSPC. CHAARTED[2] and STAMPEDE[3] demonstrated survival benefits with docetaxel plus ADT. Subsequently, LATITUDE, ARCHES, TITAN, and ARANOTE established the efficacy of androgen receptor pathway inhibitors (ARPIs) plus ADT, with each trial evaluating abiraterone/prednisone[4], enzalutamide[5], apalutamide[6], and darolutamide[7], respectively. While docetaxel has been used off-label within the United States, ARPI doublets received FDA approvals in 2018 (abiraterone), 2019 (apalutamide and enzalutamide), and 2025 (darolutamide). Recently, triple combination therapies incorporating ADT, docetaxel, and ARPIs (abiraterone or darolutamide) have shown further survival improvements in PEACE-1[8] and ARASENS[9], respectively, prompting updated clinical guidelines recommending their use in high-volume disease[10].

Despite these advances, a critical evidence gap persists: no prospective randomized controlled trials have directly compared available doublet therapies for mHSPC. This absence of head-to-head comparative evidence leaves clinicians without robust data to guide treatment selection. While a few real-world studies have emerged, they suffer from significant limitations, including small sample sizes[11,12], restriction to specialized populations[13,14], lack of survival outcomes[15,16], restriction to comparisons between only two treatments, and potential industry

conflicts of interest[17,18]. Moreover, conflicting results and methodological concerns regarding study design and potential bias further constrain the interpretability and clinical utility of existing observational studies.

This study addresses existing evidence gaps by evaluating the real-world comparative effectiveness of existing doublet therapies – abiraterone, apalutamide, enzalutamide, and docetaxel – among men with a mHSPC diagnosis in the United States. By providing comprehensive head-to-head comparisons across available doublet therapies, this study offers critical evidence to guide personalized treatment selection, inform clinical practice guidelines, and optimize patient outcomes.

2.3. Methods

This study followed the target trial emulation framework to minimize bias and strengthen causal inference[19,20]. We explicitly defined protocol components for a hypothetical randomized controlled trial (Table S1), then operationalized them using observational claims data.

2.3.1. Study Design & Data Source

This retrospective cohort study utilized de-identified claims data from Komodo Healthcare Map, a comprehensive database containing medical and pharmacy claims for over 330 million patients across the United States from diverse payer sources. The database provides longitudinal capture of diagnoses, procedures, medications, and insurance status, with mortality data linkage from multiple third-party sources, including government records, private claims, and obituaries. The study period spanned from January 2018 to June 6, 2025 (Figure S1).

2.3.2 Study Population

The study population comprised men aged 18 years and older with mHSPC. We identified mHSPC patients using a validated algorithm by Freedland et al that screens for hormone

sensitivity through associated diagnosis codes, procedure codes, and treatment patterns while excluding castration resistance[21] (Figure 1). Metastatic disease was defined as the presence of diagnosis codes indicating distant metastasis on or after the initial prostate cancer diagnosis. Patients were included if they initiated ADT within 4 months of mHSPC diagnosis and subsequently received index treatment with abiraterone, apalutamide, enzalutamide, or docetaxel within 4 months following ADT between January 2019 and December 2023 (index period), with follow-up through June 6, 2025 (end of study period). The 4-month window for defining doublet therapy was based on clinical expert consensus and published evidence characterizing optimal timing for first-line doublet therapy, thereby distinguishing primary combination treatment from subsequent intensification following inadequate response to ADT monotherapy[22–24]. The index period start date was selected to ensure all four treatments were available for selection based on their approval year, thereby satisfying the positivity assumption required for causal inference. Patients were required to have at least 12 months of continuous enrollment before the index date for assessment of baseline characteristics. We excluded patients with other cancer types, those receiving multiple index treatments on the same day, or receiving both ARPI and docetaxel within the 4-month window after ADT (triplet therapy).

2.3.3. Study Outcomes

The primary outcomes were progression-free survival (PFS) and overall survival (OS). PFS was defined as time from index treatment initiation to metastatic castration-resistant prostate cancer (mCRPC) progression or death. Progression to mCRPC was identified if patients met any of the following criteria, whichever occurred first[21]:

(i) receipt of medications indicated for mCRPC only (Table S2)

(ii) initiation of docetaxel or alternative ARPI indicated for both mHSPC and mCRPC (abiraterone and enzalutamide) ≥90days after index date (Table S2). This was done to account for treatment switching unrelated to disease progression (e.g., due to side effects)

(iii) diagnosis codes indicating hormone resistance (Tables S5).

OS was defined as time from index treatment initiation to death from any cause. Secondary outcomes were time to mCRPC progression (TTP) and time to new treatment initiation (TTNT), defined as time to initiation of any new subsequent systemic treatment for metastatic prostate cancer (Table S2). Patients were followed from the index date until the earliest of outcome occurrence, end of the study period (June 6, 2025), or loss of insurance enrollment.

2.3.4. Statistical analysis

To balance baseline characteristics across the four treatment groups, we estimated propensity scores using generalized boosted models (GBM) with 5,000 trees (Table S6), a machine-learning approach well-suited for studies with multiple treatment groups[25]. Baseline covariates included age, geographical region, insurance type, year of treatment initiation, timing of metastasis, metastatic sites, ADT type, comorbidities, emergency department (ED) visits, prior treatment (e.g., opioid use), and time to index treatment (full list of baseline characteristics details are displayed in Table 1, and specific prior treatments are shown in Table S3). We estimated overlapping weights, derived as the harmonic mean of propensity scores, to emphasize the study population with the most overlap in baseline characteristics across all treatment groups[26–28]. Covariate balance was examined using standardized mean differences (SMD), with values ≤ 0.1 deemed satisfactory. The four treatment strategies were compared using Cox proportional hazard regression models with overlap weighting to estimate adjusted hazard ratios (aHR) and 95% confidence intervals for OS and PFS across all six pairwise comparisons. Fine-Gray models accounting for the competing risk of death were used for TTP

and TTNT assessments. The proportional hazards assumption was verified using Schoenfeld residuals tests. Kaplan-Meier curves with log-rank tests were generated for unweighted and weighted samples, with standard errors estimated using robust sandwich variance estimators. Pre-specified subgroup analyses stratified by timing of metastatic diagnosis (de novo versus metachronous) and sensitivity analyses using inverse probability of treatment weighting (IPTW) were conducted. Statistical significance was set at $p < 0.05$ (two-sided). To account for multiple hypothesis testing, the Holm-Bonferroni correction was applied, thereby reducing the risk of false positive results (Type I errors)[29]. E-values were computed to quantify the robustness of findings to unmeasured confounding, with adjustment for common outcomes. All statistical analyses were performed using R Statistical Software version 4.2.0[30], employing the following R packages: comorbidity[31], forestplot[32], survival[33], survminer[34], survey[35], tableone[36], tidyverse[37], and WeightIt[38].

2.4. Results

2.4.1. Characteristics of study cohort

This study included 9,141 US men with mHSPC who met eligibility criteria. Treatment distribution was as follows: abiraterone plus ADT (43%, n=3,968), docetaxel plus ADT (24%, n=2,175), enzalutamide plus ADT (21%, n=1,902), and apalutamide plus ADT (12%, n=1,096). The mean age was 69.4 years, with most patients residing in the Midwest (29%) and covered by Medicare (63%). Bone metastases were most common (73.3%), and nearly 60% presented with de novo metastatic disease. The most prevalent comorbidities were hypertension (65.1%) and diabetes (25.9%). Approximately half of patients had prior use of first-generation antiandrogens (49.6%) and bone health agents (48%), while almost 60% had a history of opioid use. Mean time to index treatment (ARPI or docetaxel) was 10 months from initial prostate cancer diagnosis, 1.7 months from metastasis detection, and 1 month from ADT initiation. GnRH agonists were the predominant ADT type (64.9%), with only 7.3% receiving

surgical castration. Compared to patients receiving ARPI doublets, those treated with docetaxel plus ADT were younger (mean age 65.9 years), had lower comorbidity burden (mean Charlson Comorbidity Index: 1.9; mean Elixhauser Comorbidity index: 6.5), higher metastatic burden (bone: 88.2%; visceral: 21.3%), and were more likely to present with de novo metastasis (74.3%), have history of emergency department visits (32%), and prior use of opioid analgesics (69.7%) and bone health agents (63.1%).

2.4.2. Overall survival

In the weighted analysis, there was no significant difference in overall survival comparing any of the evaluated doublet regimens (Figure 3B and 4B). Median OS was not reached. Findings were similar in patients with de novo metastasis. Apalutamide (aHR: 0.68 [95% CI: 0.48 – 0.99]) showed superior overall survival compared to docetaxel doublet in patients with metachronous metastasis (Table S15). However, this result was not statistically significant after adjusting for multiple hypothesis testing (p=0.29).

2.4.3. Progression-free survival

The adjusted median PFS time for each doublet regimen was as follows (Figure 2B): abiraterone (45.4 months [95% CI: 41.6 – 51.3]), apalutamide (42.4 months [95% CI: 36.8 – 54.7]), enzalutamide (50.5 months [95% CI: 42.2 – 61.3]), and docetaxel (20.9 months [95% CI: 18.2 – 23.3]). After weighting, abiraterone (aHR: 0.60 [95% CI: 0.55 – 0.66]), apalutamide (aHR: 0.64 [95% CI: 0.56 – 0.73]), and enzalutamide (aHR: 0.57 [95% CI: 0.51 – 0.64]) doublet regimens were each associated with a lower risk of mCRPC or death compared to docetaxel plus ADT (Figure 4A). However, PFS results were similar among the individual ARPI doublets. Results did not differ by timing of disease (Tables S12 and S16). While enzalutamide doublet was associated with a lower risk of death or mCRPC progression (aHR: 0.88 [95% CI: 0.78 – 0.99]) relative to the abiraterone regimen among patients with de novo

metastasis (Table S12), this finding was not statistically significant after applying Holm-Bonferroni correction (p = 0.10).

2.4.4. Progression criteria and subsequent treatments at progression

Among 3,379 patients with mCRPC progression, 68.8% were identified through initiation of an ARPI or docetaxel at least 90 days after the index date (criterion 2), with a consistent distribution across index groups (68.4% to 69.6%). Hormone resistance diagnosis coding (criterion 3) and receipt of mCRPC-only therapies (criterion 1) accounted for 17.1% and 14.1% of progressors, respectively, with criterion 1 being most frequent in the docetaxel group (16.8%) and least frequent in the apalutamide group (11.5%). More details provided in Table S19.

Subsequent treatment patterns reflected the predominance of treatment switching as the primary progression signal. Sequential ARPI use was the most common post-progression strategy across all ARPI groups, with enzalutamide received by 54.9% of abiraterone progressors, abiraterone by 57.7% of enzalutamide progressors, and either abiraterone or enzalutamide by 71.5% of apalutamide progressors (Table S20). Similarly, in the docetaxel group, ARPIs accounted for approximately 80% of subsequent therapies. Cabazitaxel was received by only 10.5% of docetaxel progressors, and novel agents including lutetium Lu-177 vipivotide and PARP inhibitors were used in fewer than 5% of patients across all groups.

2.4.5. Time to progression (TTP)

After weighting, patients treated with abiraterone (aHR: 0.52 [95% CI: 0.47 – 0.58]), apalutamide (aHR: 0.59 [95% CI: 0.52 – 0.68]), or enzalutamide (aHR: 0.51 [95% CI: 0.45 – 0.57]) had a lower risk of mCRPC progression compared to those treated with docetaxel doublet (Figure 5A). Among the ARPIs, apalutamide had a higher risk of mCRPC compared

to enzalutamide (aHR: 1.17 [95% CI: 1.01 – 1.36]); however, this finding was no longer statistically significant after correcting for multiplicity (p=0.10).

2.4.6. Time to new treatment initiation (TTNT)

In the weighted analysis, abiraterone (aHR: 0.46 [95% CI: 0.42 – 0.51]), apalutamide (aHR: 0.53 [95% CI: 0.46 – 0.61]), and enzalutamide (aHR: 0.47 [95% CI: 0.42 – 0.53]) doublets were each independently associated with a lower likelihood of initiating a new systemic treatment compared to patients receiving docetaxel. TTNT was similar across the ARPI doublets after applying the Holm-Bonferroni correction (Figure 5B).

2.4.7. Sensitivity analyses

OS and PFS results were consistent using inverse probability of treatment weights (Tables S21 – S24). E-values for the point estimates of the adjusted hazard ratios for ARPI doublets versus docetaxel doublet ranged from 2.06 to 2.31 for progression-free survival, 2.24 to 2.56 for time to mCRPC progression, and 2.47 to 2.80 for time to next systemic treatment, with corresponding E-values for the upper confidence limit of 1.79 to 2.06, 1.94 to 2.31, and 2.16 to 2.56 (Table S25)

2.5. Discussion

This retrospective cohort study examined 9,141 US men with mHSPC to compare outcomes across four common ADT-based doublet regimens: abiraterone, apalutamide, enzalutamide, and docetaxel. Baseline characteristics were balanced after overlap weighting (SMD < 0.1). Each ARPI doublet demonstrated superior PFS compared to docetaxel regimen. PFS was similar across all ARPI doublets. There was no difference in overall survival comparing each ARPI doublet versus the docetaxel regimen, nor within the ARPI doublets. In subgroup analyses, neither OS nor PFS differed by timing of disease (de novo vs metachronous metastasis). Sensitivity analyses showed consistent findings. For secondary outcomes, the risk of mCRPC progression was similar across all ARPI doublet comparisons, while ARPI doublets

had delayed disease progression compared to docetaxel doublets. Patients receiving ARPI doublets were less likely to initiate new systemic treatment compared to those receiving docetaxel, with no differences among ARPI regimens. Findings revealed a high prevalence of sequential ARPI use following mCRPC progression, despite well-characterized cross-resistance within this drug class, and suggest limited uptake of guideline-recommended cytotoxic and novel mCRPC therapies in routine practice.

2.5.1. Clinical and policy relevance

In the absence of head-to-head randomized trials comparing doublet therapies for mHSPC, this study provides comprehensive real-world evidence on the comparative effectiveness of available doublet regimens for mHSPC. These findings may inform treatment selection and clinical decision-making in advanced prostate cancer care. Remarkably, our results provide empirical support for current National Comprehensive Cancer Network (NCCN) guidelines, which recommend against using docetaxel as a doublet therapy, reserving its use as a triplet regimen (combined with an ARPI and ADT) in de novo, high-volume patients who can tolerate chemotherapy[10]. This alignment between real-world evidence and clinical practice guidelines underscores the clinical validity of our findings.

Beyond clinical practice, comparative effectiveness evidence is increasingly relevant for health policy and drug pricing decisions. Enzalutamide (Xtandi) and apalutamide (Erleada) have been selected for Medicare drug price negotiation under the Inflation Reduction Act for the initial price applicability year (IPAY) 2027[39,40], and other mHSPC treatments may be selected in subsequent negotiation cycles. The comparative effectiveness data generated by this study may inform value assessments and negotiations by providing real-world evidence on relative treatment benefits across available therapeutic options. Moreover, the FDA has increasingly recognized the value of such real-world evidence in supporting regulatory decision-making[41].

2.5.2. Comparison with similar studies

Our findings align with prior observational studies demonstrating comparable OS across ARPI and docetaxel doublets, with superior PFS for ARPIs. In the United States, studies conducted among Veteran Affairs (VA) beneficiaries found no OS differences between ARPIs and docetaxel in de novo mHSPC regardless of disease volume, while noting improved PFS with ARPIs[14], and no difference in OS between abiraterone and enzalutamide[13]. Evidence from Europe also showed similar OS between ARPI and docetaxel, with delayed progression with ARPI[42,43]. Likewise, there was no difference in overall survival comparing the individual ARPIs among mHSPC patients in Japan[12], Korea[44], and Spain[11]. Multiple network meta-analyses further support our findings [45–47].

However, our results diverge from three manufacturer-affiliated, US-based observational studies reporting superior OS with apalutamide versus abiraterone (aHR: 0.72 [95% CI: 0.59 – 0.88])[18], enzalutamide (aHR: 0.77 [95% CI: 0.62 – 0.96])[17], and docetaxel (aHR: 0.38 [95% CI: 0.28 – 0.52)[48]. The latter OASIS study was a multi-treatment investigation that similarly documented better OS and PFS for apalutamide over abiraterone and enzalutamide doublet regimens[48]. We hypothesize these discrepancies may stem from key methodological differences. First, none of these studies defined a grace period for treatment initiation after mHSPC diagnosis, potentially introducing immortal time bias and systematic differences between early and late treatment initiators. Second, two studies had overlapping enrollment and follow-up periods, potentially precluding adequate outcome assessment for late enrollees [17,18]. In contrast, our target trial emulation design specified a 4-month window for ADT initiation following mHSPC diagnosis and required index treatment within 4 months of ADT initiation, based on clinical expert consensus and published evidence. This approach achieved a mean 1.7-month interval from mHSPC diagnosis to index treatment initiation, minimizing selection bias while ensuring time-zero alignment[19]. Additionally, our recruitment period ended

in December 2023 with follow-up through June 2025, allowing sufficient outcome assessment while maintaining non-informative administrative censoring.

For prostate-specific antigen (PSA) response, existing literature reports conflicting results. While some studies demonstrated similar rates for ≥90% or ≥ 95% PSA decline within the ARPI class[12,44], Lowentritt et al documented that patients receiving apalutamide were more likely to achieve ≥90% PSA decline compared to those treated with abiraterone[16] or enzalutamide[15]. Studies also documented superior rates of achieving nadir PSA or decline to ≤0.2 ng/mL with apalutamide and enzalutamide compared to abiraterone[11,44].

2.5.3. Methodological strength

This study uses a comprehensive, nationally representative real-world database with a large, diverse sample size (n = 9,141), strengthening the external validity and generalizability of findings to the US population with mHSPC. Komodo's linkage with mortality data, which captures 98% of oncology-related deaths, enabled an accurate assessment of survival outcomes rather than reliance on claims-based proxies. The use of overlap weighting focused analyses on patients at clinical equipoise, where treatment decisions are most uncertain, thereby approximating the population typically enrolled in randomized trials and improving the clinical relevance of effect estimates[28]. Unlike the conventional IPTW, empirical evidence shows that use of overlapping weights avoids extreme weights and produces estimates with less bias and variance[26,27,49]. The target trial emulation framework used in this study minimizes biases typically associated with observational data by closely replicating the design and conduct of a hypothetical randomized trial. Prior research validating this approach across 32 clinical trials demonstrated strong concordance between real-world studies and randomized trials when trial design is closely emulated, with Pearson correlations reaching 0.93 for studies with rigorous emulation[50].

2.5.4. Limitations

This study has certain limitations. First, claims data lack clinical variables including PSA values, ECOG performance status, and Gleason scores, raising potential concerns about unmeasured confounding. Given that these factors indicate more aggressive disease, patients with poorer prognostic profiles may have been preferentially treated with docetaxel rather than ARPIs, which may inflate the event rate in the docetaxel arm and bias the hazard ratio toward zero, in favor of ARPIs. However, the impact is likely minimal, as multiple electronic health record (EHR)-based studies accounting for these covariates reported similar findings[12,13,43,44]. Moreover, the E-values indicate that such unmeasured confounders would need to be associated with both treatment selection and outcome by more than two-fold on the risk-ratio scale, beyond the measured covariates balanced by overlap weighting, to nullify the observed advantage of ARPI doublets. Second, we defined disease progression based on treatment patterns and diagnosis codes for hormone resistance rather than standard Prostate Cancer Working Group 3 criteria[51]; though our results remained consistent with studies employing biochemical, radiographic, and clinical progression criteria[14,44]. Third, the absence of granular data on bone metastasis number and location precluded stratification by disease volume, a clinically relevant subclassification.

Additionally, we did not evaluate darolutamide doublets due to recent regulatory approval in 2025 and limited follow-up data, nor triplet therapies, which have gained adoption since 2022[22]. As mature survival data emerge, future studies may consider investigating the effectiveness of triplet therapies versus ARPI doublets, as existing clinical trials only provide evidence against docetaxel doublets[8,9]. Finally, OS estimates do not account for treatment discontinuation or switching, which may not reflect true treatment effects under optimal adherence.

2.6. Conclusion

In this large, nationally representative cohort study employing target trial emulation methodology, ARPI-based doublets demonstrated superior progression-free survival but comparable overall survival to docetaxel doublet therapy in patients with mHSPC, with no significant differences among individual ARPIs in the overall population. These findings provide robust real-world evidence supporting current guidelines that prioritize ARPI doublets over docetaxel doublets for mHSPC management. Given similar survival outcomes among ARPI doublets, treatment selection may be guided by cost, toxicity profiles, and patient-specific factors. This study has important implications for clinical practice, shared decision-making, and health policy discussions, including value-based pricing negotiations. As survival data mature, future research may evaluate triplet regimens versus ARPI doublets to further inform mHSPC treatment selection.

Table 1. Baseline characteristics

Baseline characteristics	Unweighted population						Weighted population[a]					
	Overall (n = 9,141)	DOC+ ADT (n=2,175)	ABI + ADT (n = 3,968)	APA + ADT (n = 1,096)	ENZ + ADT (n=1,902)	SMD[b]	Overall (n = 9,141)	DOC+ ADT (n=2,175)	ABI + ADT (n = 3,968)	APA + ADT (n = 1,096)	ENZ + ADT (n=1,902)	SMD[b]
Age, mean (SD)	69.4 (8.9)	65.9 (8.1)	69.6 (8.8)	71.7 (8.9)	71.9 (8.9)	0.75	69.5 (8.0)	69.5 (8.0)	69.5 (8.1)	69.2 (8.0)	69.5 (8.0)	0.046
Region, n (%)												
Midwest	2,654 (29.0)	664 (30.5)	1,130 (28.5)	281 (25.6)	579 (30.4)	0.11	2,603 (28.5)	613 (28.2)	1,130 (28.5)	315 (28.8)	545 (28.6)	0.021
Northeast	2,294 (25.1)	485 (22.3)	1,148 (28.9)	204 (18.6)	457 (24.0)	0.35	1,933 (21.1)	443 (20.4)	855 (21.5)	227 (20.7)	408 (21.4)	0.026
South	2,548 (27.9)	665 (30.6)	941 (23.7)	390 (35.6)	552 (29.0)	0.25	2,892 (31.6)	705 (32.4)	1,239 (31.2)	354 (32.3)	593 (31.2)	0.03
West	1,645 (18.0)	361 (16.6)	749 (18.9)	221 (20.2)	314 (16.5)	0.09	1,714 (18.8)	414 (19.0)	744 (18.8)	200 (18.2)	357 (18.7)	0.009
Insurance type, n (%)												
Commercial	2,622 (28.7)	777 (35.7)	1,177 (29.7)	273 (24.9)	395 (20.8)	0.33	2,484 (27.2)	567 (26.1)	1,069 (27.0)	319 (29.1)	529 (27.8)	0.071
Medicaid	722 (7.9)	243 (11.2)	298 (7.5)	49 (4.5)	132 (6.9)	0.26	646 (7.1)	156 (7.2)	286 (7.2)	71 (6.5)	134 (7.0)	0.023
Medicare	5,762 (63.0)	1,139 (52.4)	2,484 (62.6)	771 (70.3)	1368 (71.9)	0.41	5,976 (65.4)	1,446 (66.5)	2,595 (65.4)	703 (64.2)	1,232 (64.8)	0.0055
Unknown	35 (0.4)	16 (0.7)	9 (0.2)	3 (0.3)	7 (0.4)	0.08	35 (0.4)	6 (0.3)	18 (0.4)	3 (0.3)	7.7 (0.4)	0.0022
Index treatment year, n (%)												
2019	1,398 (15.3)	446 (20.5)	730 (18.4)	78 (7.1)	144 (7.6)	0.44	977 (10.7)	232 (10.7)	435 (11.0)	111 (10.1)	199 (10.5)	0.034
2020	1,697 (18.6)	490 (22.5)	618 (15.6)	206 (18.8)	383 (20.1)	0.17	1,899 (20.8)	466 (21.4)	818 (20.6)	229 (20.9)	386 (20.3)	0.026
2021	1,917 (21.0)	456 (21.0)	746 (18.8)	250 (22.8)	465 (24.4)	0.13	2,116 (23.2)	504 (23.1)	912 (23.0)	261 (23.8)	440 (23.1)	0.021
2022	1,999 (21.9)	404 (18.6)	867 (21.8)	274 (25.0)	454 (23.9)	0.15	2,088 (22.8)	496 (22.8)	904 (22.8)	249 (22.7)	439 (23.1)	0.016
2023	2,130 (23.3)	379 (17.4)	1,007 (25.4)	288 (26.3)	456 (24.0)	0.21	2,062 (22.6)	477 (21.9)	900 (22.7)	247 (22.5)	438 (23.0)	0.025
De novo metastasis[c], n (%)	5,380 (58.9)	1,616 (74.3)	2,137 (53.9)	555 (50.6)	1,072 (56.4)	0.48	5,546 (60.7)	1327 (61.0)	2,406 (60.6)	664 (60.6)	1,149 (60.4)	0.017
Location of metastasis, n (%)												
Bone	6,700 (73.3)	1,919 (88.2)	2,514 (63.4)	796 (72.6)	1,471 (77.3)	0.61	7,242 (79.2)	1,768 (81.3)	3,115 (78.5)	865 (78.9)	1,495 (78.6)	0.0066
Visceral	1,131 (12.4)	464 (21.3)	385 (9.7)	92 (8.4)	190 (10.0)	0.41	1,035 (11.3)	254 (11.7)	454 (11.4)	119 (10.8)	209 (11.0)	0.034
Lymph	3,144 (34.4)	769 (35.4)	1,485 (37.4)	376 (34.3)	514 (27.0)	0.22	3,003 (32.8)	696 (32.0)	1,313 (33.1)	373 (34.1)	621 (32.6)	0.052
Bone + Visceral	927 (10.1)	397 (18.3)	294 (7.4)	79 (7.2)	157 (8.3)	0.28	857 (9.4)	206 (9.5)	372 (9.4)	105 (9.5)	175 (9.2)	0.014
ADT group, n (%)												
GnRH agonist	5,928 (64.9)	1,523 (70.0)	2,544 (64.1)	601 (54.8)	1,260 (66.2)	0.31	5,792 (63.4)	1,376 (63.3)	2539 (64.0)	680 (62.0)	1,197 (62.9)	0.045
GnRH antagonist	2,548 (27.9)	532 (24.5)	1,061 (26.7)	423 (38.6)	532 (28.0)	0.31	2,744 (30.0)	645 (29.6)	1,173 (29.6)	345 (31.5)	581 (30.6)	0.050
Surgical castration	665 (7.3)	120 (5.5)	363 (9.1)	72 (6.6)	110 (5.8)	0.15	605 (6.6)	154 (7.1)	256 (6.5)	71 (6.5)	124 (6.5)	0.036
CCI score, mean (SD)[d]	1.9 (2.2)	1.9 (2.2)	1.9 (2.2)	1.8 (2.2)	1.9 (2.3)	0.34	1.8 (2.1)	1.8 (2.1)	1.8 (2.1)	1.7 (2.0)	1.8 (2.1)	0.027
CCI category, n (%)[d]												
None: 0	3,286 (35.9)	785 (36.1)	1,414 (35.6)	400 (36.5)	687 (36.1)	0.19	3,375 (36.9)	804 (36.9)	1,451 (36.6)	418 (38.2)	703 (36.9)	0.023
Mild: 1-2	3,189 (34.9)	762 (35.0)	1,373 (34.6)	395 (36.0)	659 (34.6)	0.09	3,301 (36.1)	793 (36.5)	1,435 (36.2)	392 (35.8)	681 (35.8)	0.018
Moderate: 3-4	1,459 (16.0)	362 (16.6)	653 (16.5)	157 (14.3)	287 (15.1)	0.10	1,344 (14.7)	301 (13.8)	596 (15.0)	159 (14.5)	288 (15.1)	0.012
Severe: ≥5	1,207 (13.2)	266 (12.2)	528 (13.3)	144 (13.1)	269 (14.1)	0.31	1,121 (12.3)	278 (12.8)	486 (12.3)	126 (11.5)	231 (12.1)	0.025
ECI score, mean (SD)	6.5 (8.5)	6.6 (8.5)	6.4 (8.5)	6.6 (8.6)	6.6 (8.8)	0.23	6.3 (8.2)	6.4 (8.3)	6.3 (8.2)	6.3 (8.1)	6.3 (8.1)	0.017
Select comorbidities, n (%)												
Myocardial infarction	569 (6.2)	115 (5.3)	223 (5.6)	77 (7.0)	154 (8.1)	0.12	572 (6.3)	136 (6.2)	250 (6.3)	72 (6.6)	114 (6.0)	0.019
CHF	983 (10.8)	156 (7.2)	404 (10.2)	139 (12.7)	284 (14.9)	0.26	964 (10.5)	224 (10.3)	429 (10.8)	119 (10.8)	192 (10.1)	0.022
PVD	1,523 (16.7)	307 (14.1)	653 (16.5)	174 (15.9)	389 (20.5)	0.18	1,467 (16.0)	353 (16.2)	637 (16.0)	173 (15.8)	304 (16.0)	0.015
CVD	801 (8.8)	136 (6.3)	356 (9.0)	108 (9.9)	201 (10.6)	0.16	719 (7.9)	167 (7.7)	321 (8.1)	80 (7.3)	152 (8.0)	0.045
Dementia	169 (1.8)	16 (0.7)	72 (1.8)	29 (2.6)	52 (2.7)	0.17	135 (1.5)	31 (1.4)	64 (1.6)	15 (1.4)	24.8 (1.3)	0.017
CPD	1,477 (16.2)	318 (14.6)	627 (15.8)	188 (17.2)	344 (18.1)	0.09	1,507 (16.5)	364 (16.7)	655 (16.5)	190 (17.3)	298 (15.6)	0.028
Mild liver disease	1,268 (13.9)	332 (15.3)	528 (13.3)	139 (12.7)	269 (14.1)	0.08	1,260 (13.8)	293 (13.5)	551 (13.9)	157 (14.3)	259 (13.6)	0.014
Diabetes	2,367 (25.9)	494 (22.7)	912 (23.0)	325 (29.7)	636 (33.4)	0.24	2,480 (27.1)	579 (26.6)	1,090 (27.5)	299 (27.3)	513 (27.0)	0.019
Renal Disease	1,542 (16.9)	273 (12.6)	634 (16.0)	200 (18.2)	435 (22.9)	0.28	1,503 (16.4)	363 (16.7)	651 (16.4)	185 (16.8)	305 (16.0)	0.014
Hypertension	5,947 (65.1)	1,322 (60.8)	2,594 (65.4)	723 (66.0)	1,308 (68.8)	0.17	5,909 (64.6)	1,409 (64.8)	2,572 (64.8)	715 (65.2)	1,213 (63.8)	0.018

Baseline characteristics	Unweighted population						Weighted population[a]					
	Overall (n = 9,141)	DOC+ ADT (n=2,175)	ABI + ADT (n = 3,968)	APA + ADT (n = 1,096)	ENZ + ADT (n=1,902)	SMD[b]	Overall (n = 9,141)	DOC+ ADT (n=2,175)	ABI + ADT (n = 3,968)	APA + ADT (n = 1,096)	ENZ + ADT (n=1,902)	SMD[b]
Prior treatments[e], n (%)												
Opioid use	5,401 (59.1)	1,517 (69.7)	2,249 (56.7)	554 (50.5)	1,081 (56.8)	0.39	5,399 (59.1)	1,281 (58.9)	2,346 (59.1)	655 (59.8)	1,117 (58.7)	0.027
First-generation antiandrogen	4,532 (49.6)	1,126 (51.8)	1,965 (49.5)	457 (41.7)	984 (51.7)	0.20	4,427 (48.4)	1,042 (47.9)	1,935 (48.8)	537 (49.0)	914 (48.0)	0.011
Bone health agents	4,385 (48.0)	1,372 (63.1)	1,532 (38.6)	524 (47.8)	957 (50.3)	0.49	4,728 (51.7)	1,147 (52.7)	2,041 (51.4)	556 (50.7)	984 (51.7)	0.044
ED visit, n (%)	2,598 (28.4)	697 (32.0)	1,039 (26.2)	296 (27.0)	566 (29.8)	0.13	2,638 (28.9)	628 (28.9)	1,143.4 (28.8)	319 (29.1)	548 (28.8)	0.0046
Time (months) to index treatment, Mean (SD)												
Initial prostate cancer diagnosis	10.0 (18.5)	6.4 (13.8)	9.8 (17.9)	13.0 (21.5)	12.7 (21.5)	0.39	9.1 (17.0)	9.1 (17.0)	9.2 (17.0)	8.7 (16.4)	9.2 (17.1)	0.033
Initial metastasis	1.7 (1.3)	1.6 (1.1)	1.8 (1.3)	1.7 (1.4)	1.8 (1.4)	0.14	1.7 (1.3)	1.7 (1.3)	1.7 (1.3)	1.7 (1.2)	1.7 (1.2)	0.013
ADT initiation	1.0 (1.0)	0.9 (0.9)	1.0 (1.0)	1.0 (1.1)	1.1 (1.1)	0.16	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	0.013

ABI: abiraterone, **APA**: apalutamide, **ADT:** androgen deprivation therapy, **CCI**: Charlson comorbidity index, **CHF**: congestive heart failure, **CPD:** chronic pulmonary disease, **CVD**: cerebrovascular disease, **ED**: emergency department, **DOC**: docetaxel, **ECI**: Elixhauser comorbidity index, **ENZ**: enzalutamide, **GnRH**: gonadotrophin releasing hormone, **PVD**: peripheral vascular disease, **SMD**: standardized mean difference, **SD**: standard deviation

[a]Overlapping weights normalized to sum up to 1 within each treatment group and scaled to original population. Frequency counts rounded to nearest integer and might not sum up to the total patients per treatment group

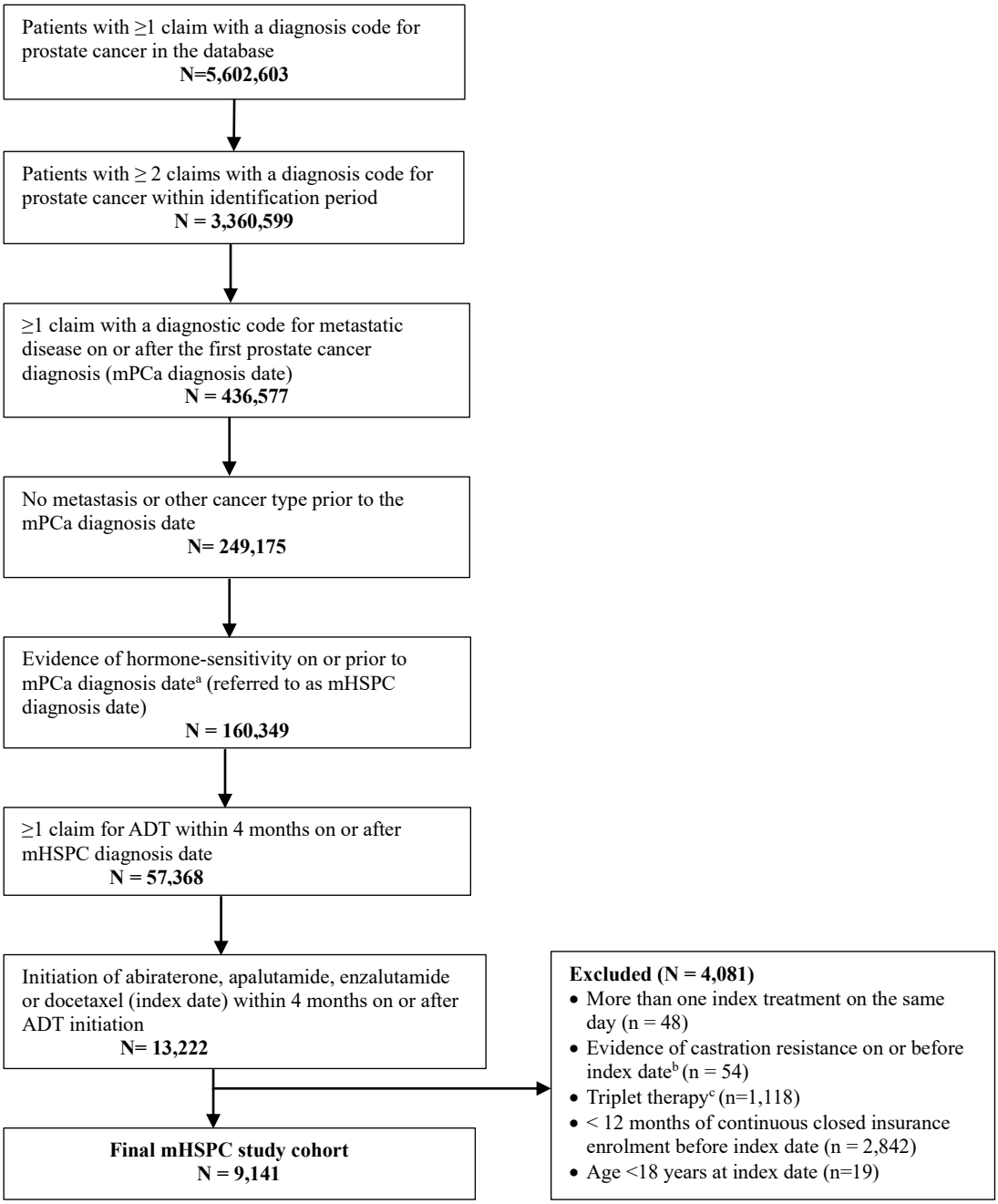
[b]Maximum standardized mean difference across all pairwise comparisons

[c]De novo metastasis defined as having evidence of metastasis within 30 days of initial prostate cancer diagnosis

[d]CCI and ECI computations excluded prostate cancer and associated metastasis

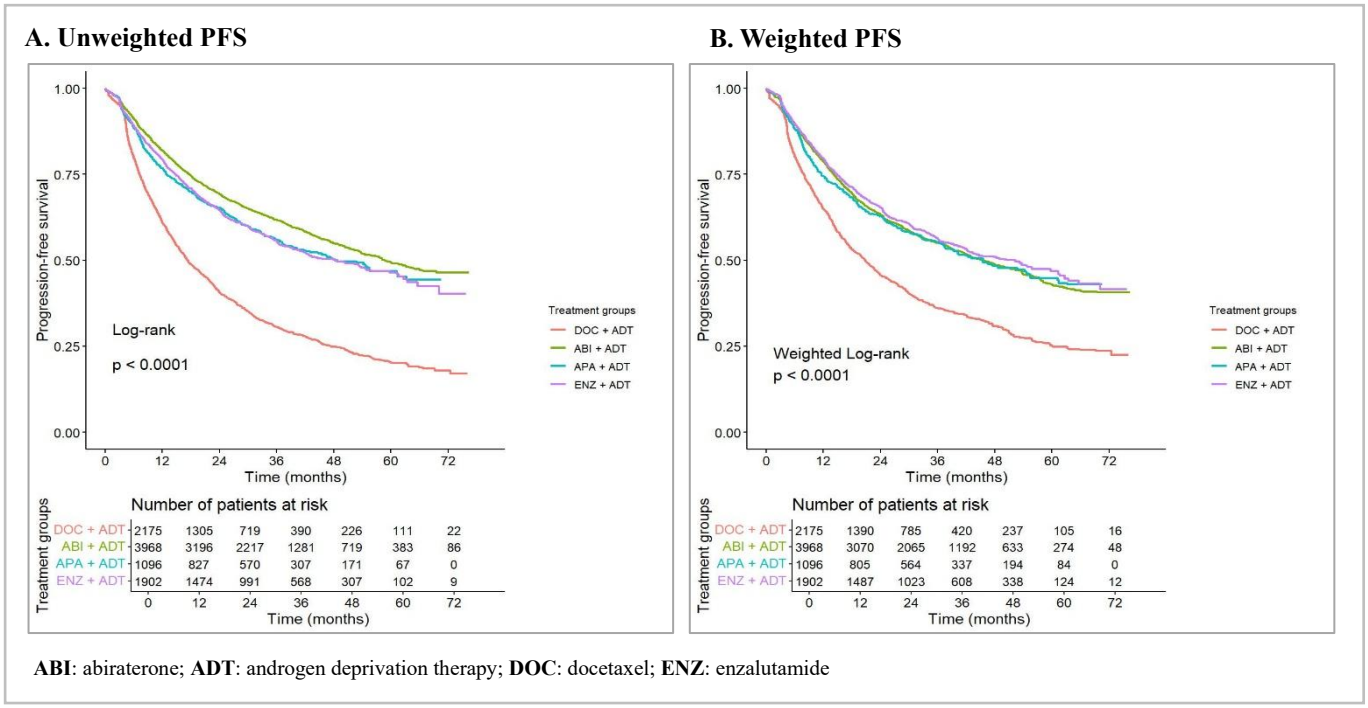
[e]Drugs listed in **Table S3**

Figure 1. CONSORT flow diagram for study cohort



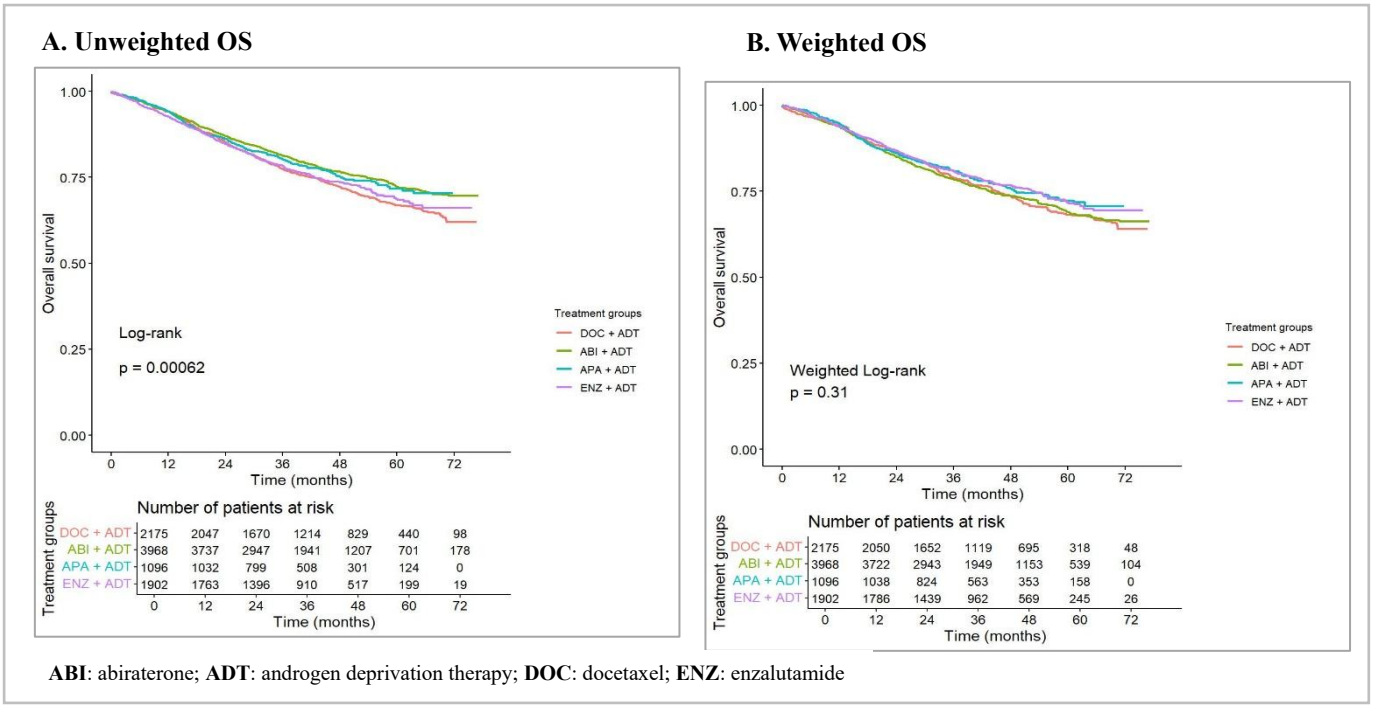
[a] (i) ≥1 diagnosis code for hormone sensitivity malignancy status (Z19.1) within 12 months before the mPCa diagnosis date, or (ii) No claim for surgical or medical castration (ADT) before mPCa diagnosis date
[b] (i) ≥ diagnosis code indicating hormone resistance (Z19.2) on or before the index date, or (ii) ≥1 claim for drugs used solely for mCRPC on or prior to index date
c. ≥1 claim for any ARPI (abiraterone, apalutamide, enzalutamide, darolutamide) and docetaxel within 4 months on or after the index date
ADT: androgen deprivation therapy, **mPCa**: metastatic prostate cancer

Figure 2. Kaplan-Meier Progression-free Survival (PFS)



ABI: abiraterone; **ADT**: androgen deprivation therapy; **DOC**: docetaxel; **ENZ**: enzalutamide

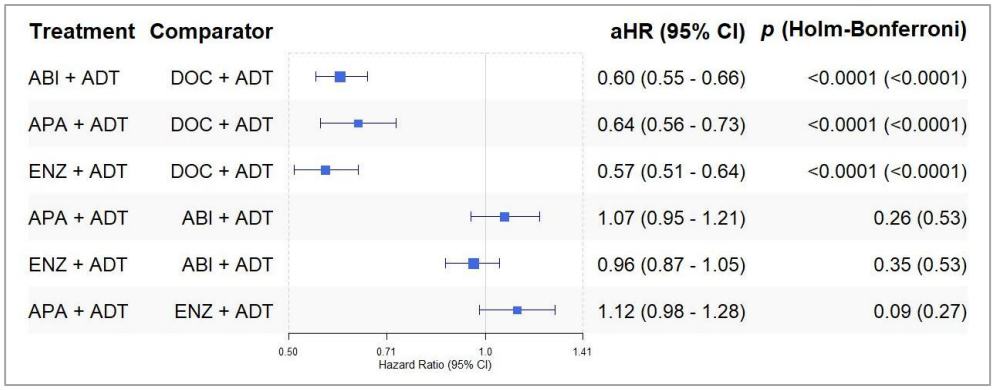
Figure 3. Kaplan-Meier Overall Survival (OS)



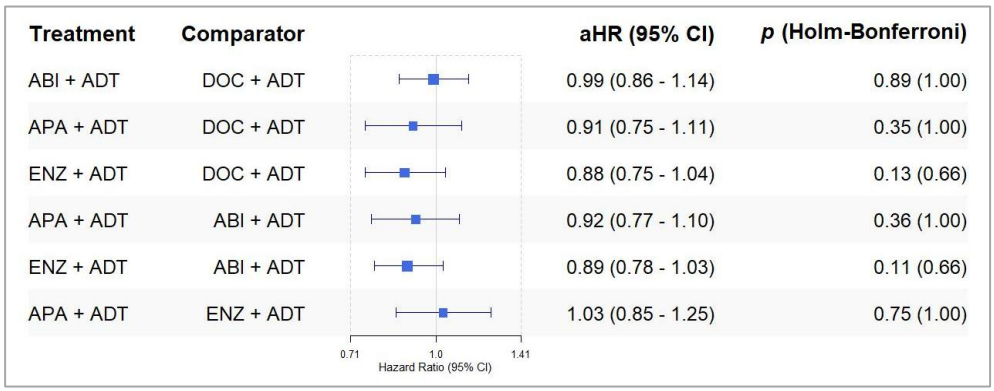
ABI: abiraterone; **ADT**: androgen deprivation therapy; **DOC**: docetaxel; **ENZ**: enzalutamide

Figure 4. Primary outcomes (weighted)

A. Adjusted hazard ratio (aHR) for progression-free survival (PFS)



B. Adjusted hazard ratio (aHR) for overall survival (OS)

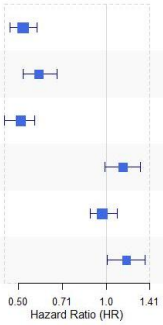


ABI: abiraterone; **ADT**: androgen deprivation therapy; **DOC**: docetaxel; **ENZ**: enzalutamide

Figure 5. Secondary outcomes (weighted)

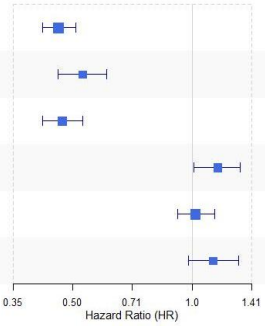
A. Adjusted hazard ratio (aHR) for time to progression (TTP)

Treatment	Comparator	aHR (95% CI)	*p* (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.52 (0.47 - 0.58)	<0.0001 (<0.0001)
APA + ADT	DOC + ADT	0.59 (0.52 – 0.68)	<0.0001 (<0.0001)
ENZ + ADT	DOC + ADT	0.51 (0.45 – 0.57)	<0.0001 (<0.0001)
APA + ADT	ABI + ADT	1.14 (0.99 – 1.37)	0.062 (0.12)
ENZ + ADT	ABI + ADT	0.97 (0.88 – 1.09)	0.61 (0.61)
APA + ADT	ENZ + ADT	1.17 (1.01 – 1.36)	0.034 (0.10)



B. Adjusted hazard ratio (aHR) for time to new treatment (TTNT)

Treatment	Comparator	aHR (95% CI)	*p* (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.46 (0.42 – 0.51)	<0.0001 (<0.0001)
APA + ADT	DOC + ADT	0.53 (0.46 – 0.61)	<0.0001 (<0.0001)
ENZ + ADT	DOC + ADT	0.47 (0.42 – 0.53)	<0.0001 (<0.0001)
APA + ADT	ABI + ADT	1.16 (1.01 – 1.32)	0.04 (0.12)
ENZ + ADT	ABI + ADT	1.02 (0.92 – 1.14)	0.70 (0.70)
APA + ADT	ENZ + ADT	1.13 (0.98 – 1.31)	0.13 (0.28)



ABI: abiraterone; **ADT**: androgen deprivation therapy; **DOC**: docetaxel; **ENZ**: enzalutamide

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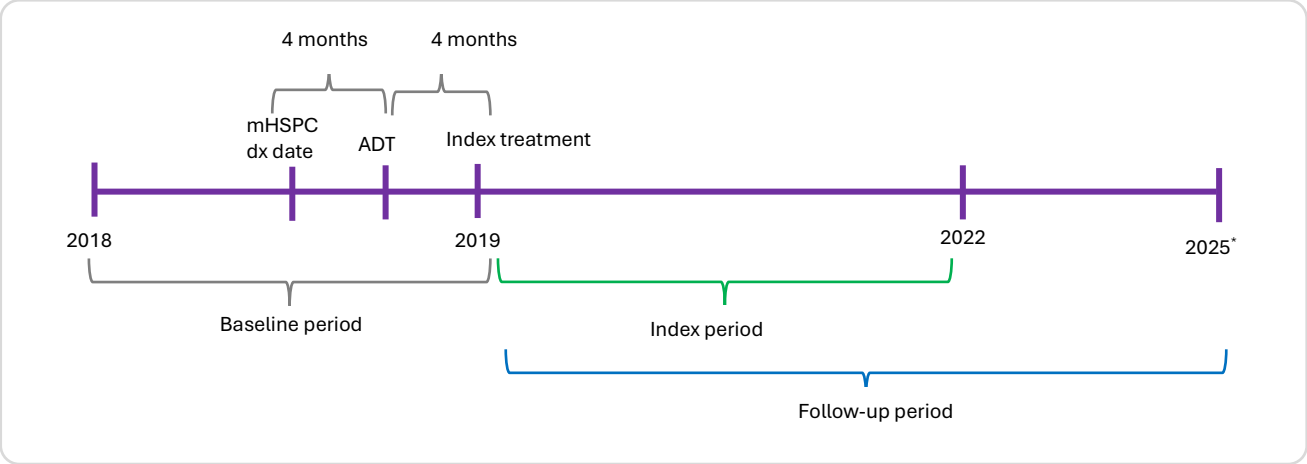
Supplementary Materials

Figure S1. Study design schematic



*Followed through June 6, 2025

ADT: androgen deprivation therapy, **dx**: diagnosis, **mHSPC**: metastatic hormone-sensitive

Table S1. Summary of target trial protocol

Protocol components	Description
Eligibility criteria	Patients will be required to be at least 18 years of age and have newly diagnosed (≤ 3 months before randomization), pathologically confirmed prostate cancer with imaging-based evidence of metastatic disease. Patients will be excluded if they have other cancers or have received prior chemotherapy, radiation therapy, or surgery for metastatic prostate cancer.
Treatment strategies	Abiraterone 1000mg daily, enzalutamide 160mg daily, apalutamide 240mg daily, and docetaxel 75mg/m^2 every 3 weeks for 6 cycles.
Assignment procedure	Patients will be randomly assigned 1:1:1:1 to receive abiraterone, apalutamide, enzalutamide, or docetaxel, in combination with ADT.
Outcomes	**Primary outcome**: Overall survival (OS), defined by time from randomization to death from any cause. Progression-free survival (PFS) is defined as the time from randomization to progression to mCRPC or death. Progression will be defined by biochemical, radiographic, or clinical assessment. Secondary outcome: Time to mCRPC progression (TTP) and time to new treatment initiation (TTNT)
Follow-up	Patients will be followed from randomization to outcome, loss to follow-up, or the end of the study period.
Causal contrasts of interest	Intention-to-treat effect
Analysis plan	Time-to-event analysis using the Cox proportional hazards model to hazard ratios and an estimated 95% confidence interval. Intention-to-treat effect analysis will estimate treatment effects among individuals assigned to each treatment strategy regardless of adherence or treatment changes.

Table S2. Prostate cancer medications assessed during the study period

Medications	HCPSC code	mHSPC and mCRPC	mCRPC only
ARPIs			
Abiraterone		X	
Apalutamide			
Enzalutamide		X	
Darolutamide			
Chemotherapy			
Docetaxel	J9170, J1971, J9172	X	
Cabazitaxel	C9276, J9043		X
Medical castration (ADT)			
GnRH Agonist			
Leuprolide	J1950, J9217, J9218, J9219, J1951, J1952, Q0057, C9430	X	
Goserelin	J902	X	
Histrelin	J9225, J9226, J1675, S0133, Q2020	X	
Triptorelin	J3315, J3316, J3320, J3321, C9016	X	
GnRH antagonist			
Relugolix		X	
Degarelix	J9155	X	
Radiopharmaceuticals			
Lutetium-177 vipivotide tetraxtan	A9607		X
Radium-223	A9606		X
PARP inhibitors			
Olaparib			X
Rucaparib			X
Immunotherapy			
Pembrolizumab	C9027, J9271		X
Sipeleucel-T	C9273, Q2043		X

Table S3. Prior treatments

Medications	HCPCS code
Opioid analgesics	
Morphine	J2270, J2271, J2274
Codeine sulfate	J0745
Hydrocodone	
Fentanyl	J3010
Alfentanil	
Opium/belladonna alkaloids	
Hydromorphone	J1170
Levorphanol tartrate	
Meperidine	J2175
Methadone	J1230
Oxycodone	
Oxymorphone	
Remifentanil	
Tramadol	
Tapentadol	
Sufentanil	
Bone health agents	
Denosumab	J0897, C9272
Etidronate	J1436
Ibandronate	C9229, J1740
Pamidronate	C9411, J2430
Risedronate	
Alendronate	
Zoledronic acid	C9115, J3487, J3488, J3489, Q2051, Q4095, J3487, J3488, J3489, Q2051
First-generation antiandrogens	
Bicalutamide	
Flutamide	
Nilutamide	

Table S4. Procedure codes for surgical castration

Procedure	CPT	ICD-10-PCS	ICD-10-CM
Surgical castration	54520, 54522, 54530, 54533, 54535, 54690	0VT90ZZ, 0VT94ZZ, 0VTB0ZZ,0VTB4ZZ, 0VTC0ZZ, 0VTC4ZZ, 0VB90ZZ, 0VBB0ZZ, 0VBC0ZZ	Z9079

Table S5. Medical conditions (ICD-10-CM) assessed during the study period

Medical Condition	**ICD-10-CM**
Prostate cancer	C61
Other Cancer types	
Lip, oral cavity, and pharynx	C00-C14
digestive organs	C15-C26, R18.0
respiratory and intrathoracic organs	C30-C39
bone, connective tissue, skin (bone connective tissue skin)	C40-C49
Malignant neoplasm of the breast	C50
genitourinary organ (excluding prostate cancer)	C51-C58, C60, C62-C68
lymphatic and hematopoietic tissue	C81-C96
Eye, brain, and other parts of the central nervous system	C69-C72
Thyroid and other endocrine glands	C73-C75, C7A, C7B, E31.20- E31.23
Other specified	C76
Other unspecified	C80
Metastasis	
Any	C77.0 to C80.0, C7B
Bone	C79.5
Lymph node	C77.0 to C77.9
Visceral	C78.0 to C79.4; C79.6 to C79.9; C80.0; C7B
Hormone-sensitivity status	
Hormone-sensitive malignancy	Z19.1
Hormone-resistance malignancy	Z19.2

Generalized boosted model (GBM)

Table S6. GBM specifications (WeightIt package in R)

Parameter	Specification	Comments
Number of trees	5,000	This represents the maximum number of regression trees or iterations to be used. It controls model complexity and the risk of overfitting.
Estimand	ATO	Estimates average treatment effect in the population with the most overlap in baseline characteristics
Criterion	smd.mean	Minimizes the average absolute standardized mean difference among covariates across all treatment groups. The goal is to ensure overall balance by minimizing the average imbalance (preferred choice)
Interaction depth	3	Determines the complexity of interactions between variables in the model. Higher values indicate a better ability to capture nonlinear and nonadditive relationships.
Shrinkage	0.01	This denotes the learning rate of the model and is applied to the trees. The lower the shrinkage, the more trees one may have to include to achieve the optimum.

ATO: average treatment effect in the overlapping population, **smd:** standardized mean difference

Number of trees, interaction depth, and shrinkage were fine-tuned iteratively before arriving at the combination, shown in Table S6, that yielded the most balance in balance characteristics across all treatment groups (i.e., lowest SMD)

Figure S2. Plot of average SMD against number of trees (GBM)

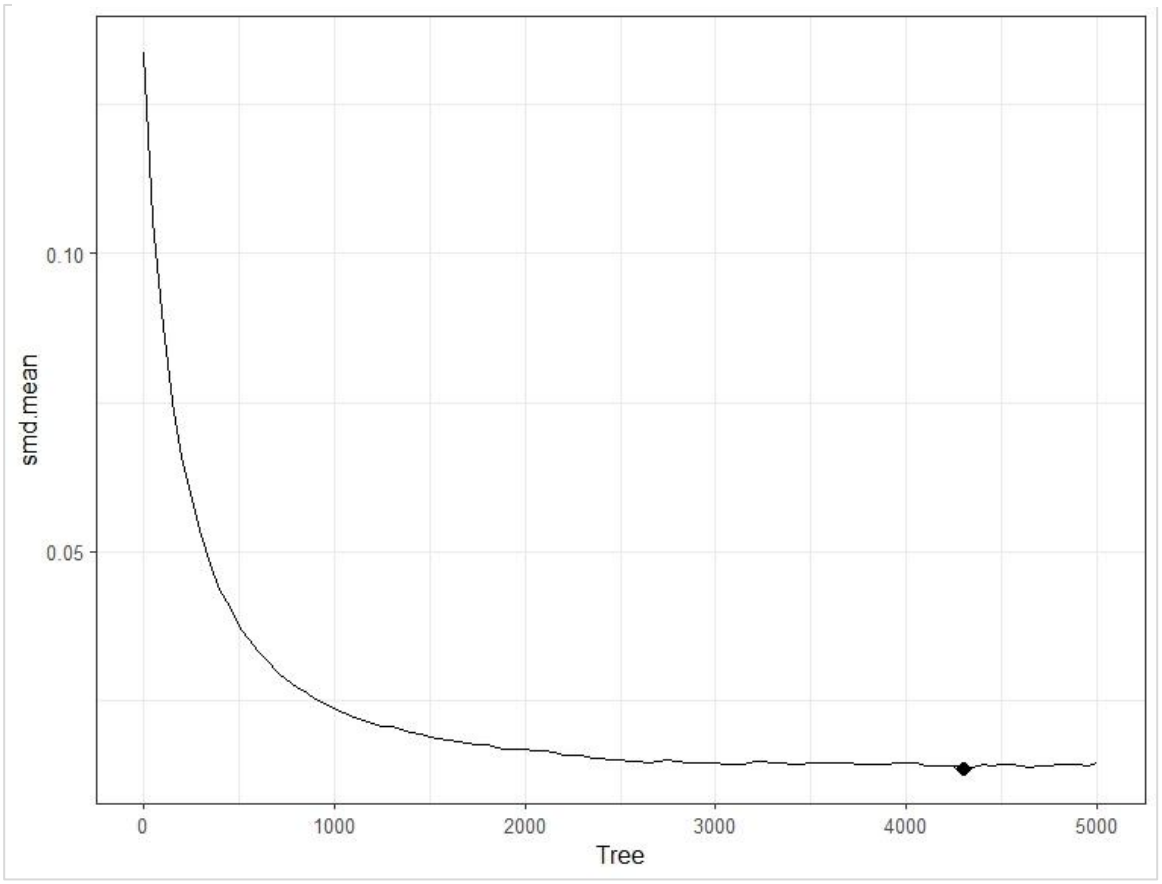
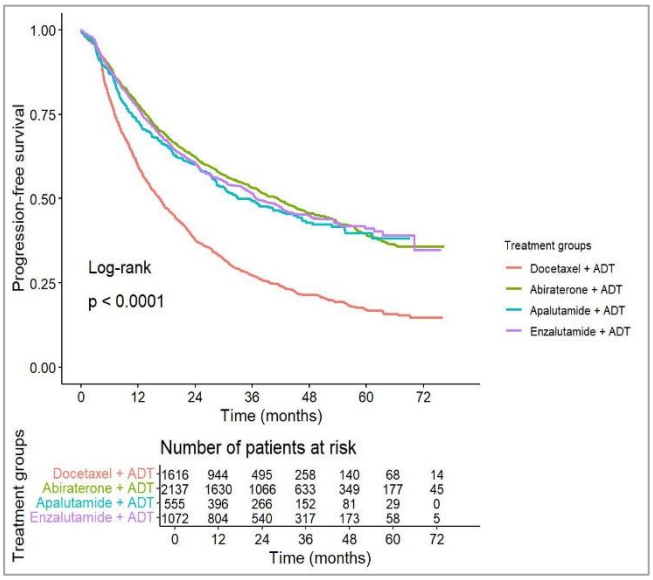
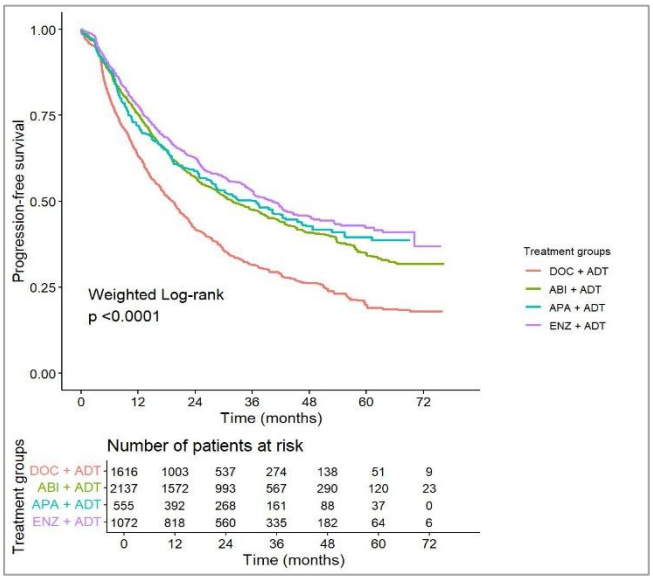


Figure S3. PFS (de novo metastasis)

A. Unweighted PFS



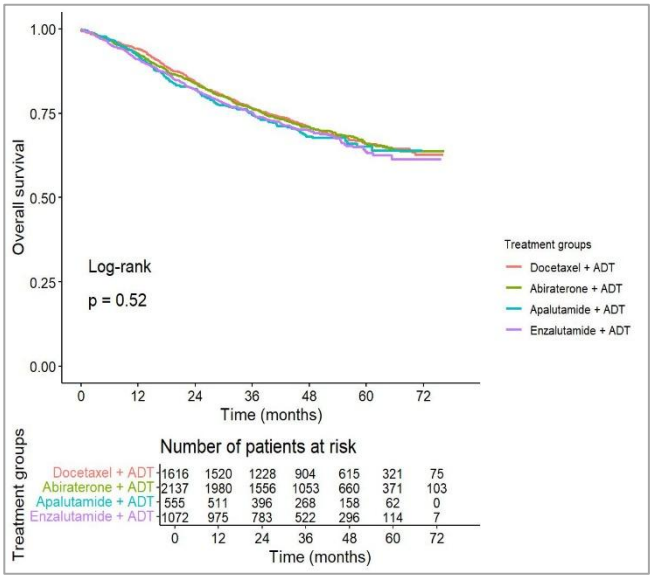
Weighted PFS



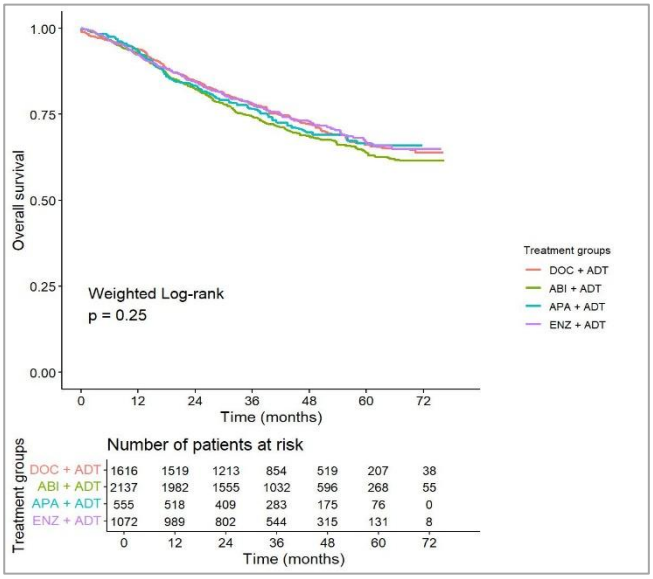
ABI: abiraterone; **ADT**: androgen deprivation therapy; **DOC**: docetaxel; **ENZ**: enzalutamide; **PFS**: progression-free survival

Figure S4. OS (de novo metastasis)

A. OS Unweighted



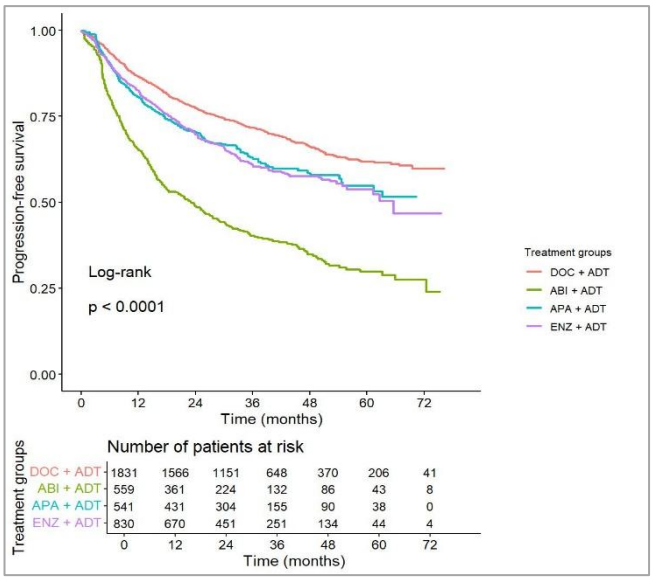
B. OS Weighted



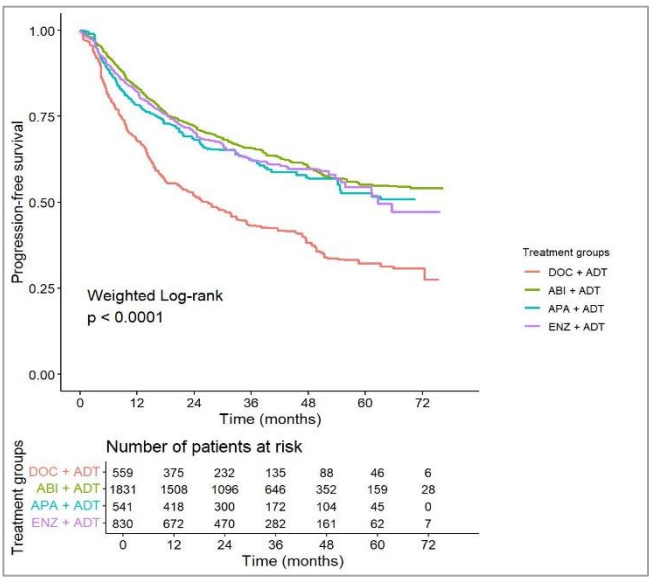
ABI: abiraterone; **ADT**: androgen deprivation therapy; **DOC**: docetaxel; **ENZ**: enzalutamide; **OS**: overall survival

Figure S5. PFS (metachronous metastasis)

A. PFS Unweighted



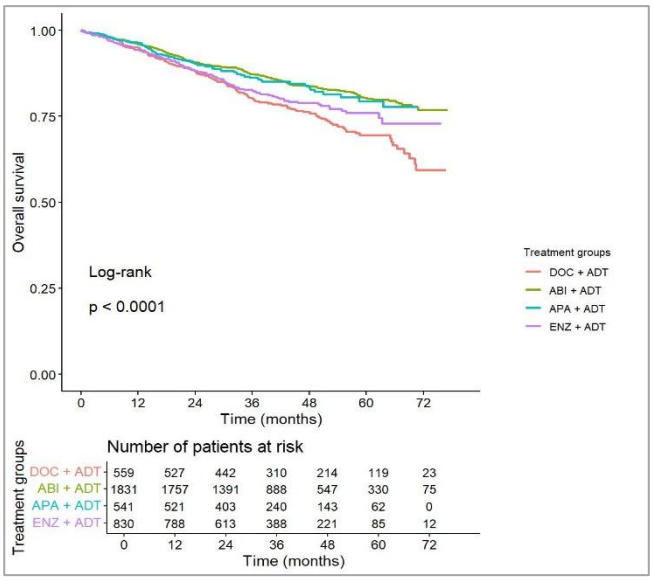
B. PFS Weighted



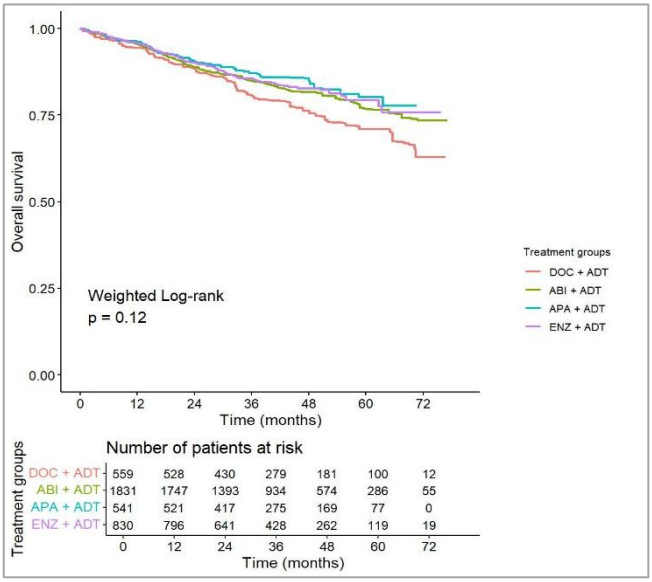
ABI: abiraterone; **ADT**: androgen deprivation therapy; **DOC**: docetaxel; **ENZ**: enzalutamide; **PFS**: progression-free survival

Figure S6. OS (metachronous metastasis)

A. OS Unweighted



B. OS Weighted



ABI: abiraterone; **ADT**: androgen deprivation therapy; **DOC**: docetaxel; **ENZ**: enzalutamide; **OS**: overall survival

Unweighted analysis of primary and secondary outcomes

Table S7. Unweighted Progression-free survival (entire cohort)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.43 (0.40 – 0.47)	<0.0001 (<0.0001)
APA + ADT	DOC + ADT	0.49 (0.44 – 0.55)	<0.0001 (<0.0001)
ENZ + ADT	DOC + ADT	0.51 (0.46 – 0.55)	<0.0001 (<0.0001)
APA + ADT	ABI + ADT	1.14 (1.03 – 1.27)	0.01 (0.02)
ENZ + ADT	ABI + ADT	1.17 (1.07 – 1.27)	0.00046 (0.014)
APA + ADT	ENZ + ADT	0.98 (0.87 – 1.10)	0.69 (0.69)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S8. Unweighted overall survival (entire cohort)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.81 (0.73 – 0.90)	0.00012 (0.0072)
APA + ADT	DOC + ADT	0.86 (0.74 – 1.01)	0.064 (0.26)
ENZ + ADT	DOC + ADT	0.96 (0.85 – 1.09)	0.54 (0.8)
APA + ADT	ABI + ADT	1.06 (0.92 – 1.23)	0.4 (0.8)
ENZ + ADT	ABI + ADT	1.18 (1.05 – 1.32)	0.004 (0.02)
APA + ADT	ENZ + ADT	0.90 (0.77 – 1.05)	0.19 (0.57)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S9. Unweighted time to mCRPC progression (entire cohort)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.35 (0.33 – 0.38)	< 0.0001 (< 0.0001)
APA + ADT	DOC + ADT	0.42 (0.37 – 0.47)	< 0.0001 (< 0.0001)
ENZ + ADT	DOC + ADT	0.37 (0.34 – 0.41)	< 0.0001 (< 0.0001)
APA + ADT	ABI + ADT	1.17 (1.03 – 1.33)	0.01 (0.03)
ENZ + ADT	ABI + ADT	1.05 (0.95 – 1.17)	0.33 (0.33)
APA + ADT	ENZ + ADT	1.11 (0.97 – 1.28)	0.13 (0.26)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S10. Unweighted time to new treatment initiation (entire cohort)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.33 (0.31 – 0.35)	< 0.0001 (< 0.0001)
APA + ADT	DOC + ADT	0.40 (0.36 – 0.45)	< 0.0001 (< 0.0001)
ENZ + ADT	DOC + ADT	0.37 (0.34 – 0.41)	< 0.0001 (< 0.0001)
APA + ADT	ABI + ADT	1.23 (1.10 – 1.39)	0.0005 (0.0015)
ENZ + ADT	ABI + ADT	1.14 (1.04 – 1.26)	0.0071 (0.14)
APA + ADT	ENZ + ADT	1.08 (0.94 – 1.23)	0.25 (0.23)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S11. Weighted overall survival (de novo metastasis)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	1.15 (0.98 – 1.35)	0.09 (0.54)
APA + ADT	DOC + ADT	1.08 (0.85 – 1.37)	0.53 (1.00)
ENZ + ADT	DOC + ADT	1.00 (0.82 – 1.21)	0.97 (1.00)
APA + ADT	ABI + ADT	0.94 (0.75 – 1.16)	0.55 (1.00)
ENZ + ADT	ABI + ADT	0.87 (0.73 – 1.02)	0.09 (0.54)
APA + ADT	ENZ + ADT	1.08 (0.85 – 1.37)	0.52 (1.00)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S12. Weighted progression-free survival (de novo metastasis)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.67 (0.60 – 0.74)	<0.0001 (<0.0001)
APA + ADT	DOC + ADT	0.68 (0.58 – 0.80)	<0.0001 (<0.0001)
ENZ + ADT	DOC + ADT	0.58 (0.51 – 0.66)	<0.0001 (<0.0001)
APA + ADT	ABI + ADT	1.02 (0.87 – 1.20)	0.77 (0.77)
ENZ + ADT	ABI + ADT	0.88 (0.78 – 0.99)	0.034 (0.10)
APA + ADT	ENZ + ADT	1.17 (0.98 – 1.38)	0.08 (0.170)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S13. Unweighted overall survival (de novo metastasis)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	1.01 (0.89 – 1.14)	0.88 (1.00)
APA + ADT	DOC + ADT	1.10 (0.91 – 1.32)	0.32 (1.00)
ENZ + ADT	DOC + ADT	1.09 (0.94 – 1.26)	0.24 (1.00)
APA + ADT	ABI + ADT	1.09 (0.91 – 1.30)	0.36 (1.00)
ENZ + ADT	ABI + ADT	1.08 (0.94 – 1.25)	0.27 (1.00)
APA + ADT	ENZ + ADT	1.00 (0.83 – 1.22)	0.96 (1.00)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S14. Unweighted progression-free survival (de novo metastasis)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.53 (0.48 – 0.57)	<0.0001 (<0.0001)
APA + ADT	DOC + ADT	0.57 (0.50 – 0.65)	<0.0001 (<0.0001)
ENZ + ADT	DOC + ADT	0.54 (0.49 – 0.61)	<0.0001 (<0.0001)
APA + ADT	ABI + ADT	1.07 (0.94 – 1.24)	0.29 (0.87)
ENZ + ADT	ABI + ADT	1.03 (0.93 – 1.15)	0.55 (1.00)
APA + ADT	ENZ + ADT	1.04 (0.90 – 1.21)	0.59 (1.00)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S15. Weighted overall survival (metachronous metastasis)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.81 (0.62 – 1.07)	0.13 (0.52)
APA + ADT	DOC + ADT	0.68 (0.48 – 0.99)	0.049 (0.29)
ENZ + ADT	DOC + ADT	0.75 (0.56 – 1.02)	0.07 (0.35)
APA + ADT	ABI + ADT	0.86 (0.63 – 1.18)	0.34 (1.0)
ENZ + ADT	ABI + ADT	0.93 (0.72 – 1.19)	0.55 (1.0)
APA + ADT	ENZ + ADT	0.93 (0.66 – 1.31)	0.67 (1.0)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S16. Weighted progression-free survival (metachronous metastasis)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.50 (0.42 – 0.60)	<0.0001 (<0.0001)
APA + ADT	DOC + ADT	0.53 (0.42 – 0.66)	<0.0001 (<0.0001)
ENZ + ADT	DOC + ADT	0.53 (0.43 – 0.64)	<0.0001 (<0.0001)
APA + ADT	ABI + ADT	1.05 (0.86 – 1.28)	0.65 (1.00)
ENZ + ADT	ABI + ADT	1.05 (0.88 – 1.25)	0.60 (1.00)
APA + ADT	ENZ + ADT	1.00 (0.80 – 1.25)	0.99 (1.00)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S17. Unweighted overall survival (metachronous metastasis)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.61 (0.50 – 0.75)	<0.0001 (<0.0001)
APA + ADT	DOC + ADT	0.66 (0.50 – 0.87)	0.0033 (0.015)
ENZ + ADT	DOC + ADT	0.83 (0.66 – 1.05)	0.11 (0.30)
APA + ADT	ABI + ADT	1.07 (0.84 – 1.39)	0.56 (0.56)
ENZ + ADT	ABI + ADT	1.36 (1.11 – 1.66)	0.003 (0.15)
APA + ADT	ENZ + ADT	0.80 (0.60 – 1.04)	0.10 (0.30)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S18. Unweighted progression-free survival (metachronous metastasis)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.37 (0.32 – 0.43)	<0.0001 (<0.0001)
APA + ADT	DOC + ADT	0.48 (0.40 – 0.58)	<0.0001 (<0.0001)
ENZ + ADT	DOC + ADT	0.51 (0.43 – 0.60)	<0.0001 (<0.0001)
APA + ADT	ABI + ADT	1.30 (1.10 – 1.54)	0.0022 (0.004)
ENZ + ADT	ABI + ADT	1.37 (1.19 – 1.59)	<0.0001 (<0.0001)
APA + ADT	ENZ + ADT	0.95 (0.79 – 1.14)	0.58 (0.58)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S19. Distribution of qualifying criteria for mCRPC progression

Qualifying criterion	Overall (N=3,379)	DOC + ADT (n=1,331)	ABI + ADT (n=1,123)	APA + ADT (n=355)	ENZA + ADT (n=570)
mCRPC-only treatment	476 (14.1%)	223 (16.8%)	142 (12.6%)	41 (11.5%)	70 (12.3%)
ARPI or docetaxel ≥90 days after index date	2,326 (68.8%)	920 (69.1%)	768 (68.4%)	247 (69.6%)	391 (68.6%)
Hormone resistance diagnosis code	577 (17.1%)	188 (14.1%)	213 (19%)	67 (18.9%)	109 (19.1%)

ARPI: androgen receptor pathway inhibitor mCRPC: metastatic hormone resistance prostate cancer

Table S20. Subsequent Treatment Received at mCRPC progression by treatment group

Subsequent Treatment	Treatment groups			
	Docetaxel (N=1,143)	Abiraterone (N=910)	Apalutamide (N=288)	Enzalutamide (N=461)
Abiraterone	541 (47.3%)	—	115 (39.9%)	266 (57.7%)
Cabazitaxel	120 (10.5%)	11 (1.2%)	2 (0.7%)	3 (0.7%)
Docetaxel	—	268 (29.5%)	41 (14.2%)	125 (27.1%)
Enzalutamide	379 (33.2%)	500 (54.9%)	91 (31.6%)	—
Lutetium Lu-177 Vipivotide	55 (4.8%)	42 (4.6%)	7 (2.4%)	16 (3.5%)
Mitoxantrone	—	—	—	—
Niraparib	—	1 (0.1%)	—	—
Olaparib	22 (1.9%)	38 (4.2%)	14 (4.9%)	18 (3.9%)
Pembrolizumab	1 (0.1%)	1 (0.1%)	—	—
Radium-223	19 (1.7%)	39 (4.3%)	16 (5.6%)	30 (6.5%)
Rucaparib	5 (0.4%)	1 (0.1%)	—	—
Talazoparib	1 (0.1%)	9 (1.0%)	2 (0.7%)	3 (0.7%)

[a]Among patients who progressed based on criterion 1 (specific mCRPC treatments) or criterion 2 (ARPIs or docetaxel ≥90 days after index date).

Sensitivity analyses (ATE) – entire cohort

Table S21. Weighted progression-free survival – IPTW (entire cohort)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.56 (0.51 – 0.62)	< 0.0001 (<0.0001)
APA + ADT	DOC + ADT	0.57 (0.50 – 0.66)	< 0.0001 (<0.0001)
ENZ + ADT	DOC + ADT	0.56 (0.50 – 0.63)	< 0.0001 (<0.0001)
APA + ADT	ABI + ADT	1.01 (0.90 – 1.16)	0.77 (1.0)
ENZ + ADT	ABI + ADT	1.00 (0.91 – 1.10)	0.98 (1.0)
APA + ADT	ENZ + ADT	1.02 (0.88 – 1.17)	0.81 (1.0)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S22. Weighted overall survival – IPTW (entire cohort)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.98 (0.86 – 1.12)	0.75 (1.0)
APA + ADT	DOC + ADT	0.91 (0.74 – 1.10)	0.33 (1.0)
ENZ + ADT	DOC + ADT	0.95 (0.81 – 1.11)	0.54 (1.0)
APA + ADT	ABI + ADT	0.93 (0.77 – 1.11)	0.4 (1.0)
ENZ + ADT	ABI + ADT	0.97 (0.85 – 1.11)	0.68 (1.0)
APA + ADT	ENZ + ADT	0.95 (0.78 – 1.16)	0.54 (1.0)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S23. Weighted time to mCRPC progression – IPTW (entire cohort)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.47 (0.43 – 0.52)	< 0.0001 (<0.0001)
APA + ADT	DOC + ADT	0.53 (0.45 – 0.62)	< 0.0001 (<0.0001)
ENZ + ADT	DOC + ADT	0.45 (0.40 – 0.51)	< 0.0001 (<0.0001)
APA + ADT	ABI + ADT	1.12 (0.96 – 1.33)	0.12 (0.24)
ENZ + ADT	ABI + ADT	0.95 (0.86 – 1.08)	0.48 (0.48)
APA + ADT	ENZ + ADT	1.17 (0.99 – 1.38)	0.06 (0.18)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S24. Weighted time to new treatment initiation – IPTW (entire cohort)

Treatment	Comparator	HR (95% CI)	p (Holm-Bonferroni)
ABI + ADT	DOC + ADT	0.43 (0.39 – 0.35)	< 0.0001 (<0.0001)
APA + ADT	DOC + ADT	0.51 (0.44 – 0.59)	< 0.0001 (<0.0001)
ENZ + ADT	DOC + ADT	0.45 (0.41 – 0.51)	< 0.0001 (<0.0001)
APA + ADT	ABI + ADT	1.19 (1.03 – 1.37)	0.013 (0.039)
ENZ + ADT	ABI + ADT	1.06 (0.95 – 1.18)	0.27 (0.28)
APA + ADT	ENZ + ADT	1.12 (0.96 – 1.31)	0.14 (0.28)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio

Table S25. E-values for primary and secondary outcomes

Outcome	Treatment	Comparator	aHR (95% CI)	E-value, point	E-value, CI limit
PFS	ABI + ADT	DOC + ADT	0.60 (0.55–0.66)	2.20	2.00
PFS	APA + ADT	DOC + ADT	0.64 (0.56–0.73)	2.06	1.79
PFS	ENZ + ADT	DOC + ADT	0.57 (0.51–0.64)	2.31	2.06
TTP	ABI + ADT	DOC + ADT	0.52 (0.47–0.58)	2.52	2.27
TTP	APA + ADT	DOC + ADT	0.59 (0.52–0.68)	2.24	1.94
TTP	ENZ + ADT	DOC + ADT	0.51 (0.45–0.57)	2.56	2.31
TTNT	ABI + ADT	DOC + ADT	0.46 (0.42–0.51)	2.80	2.56
TTNT	APA + ADT	DOC + ADT	0.53 (0.46–0.61)	2.47	2.16
TTNT	ENZ + ADT	DOC + ADT	0.47 (0.42–0.53)	2.75	2.47

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio, **OS**: overall survival; **PFS**: progression-free survival; **TTNT**: time to next systemic treatment; **TTP**: time to mCRPC progression

CHAPTER 3: Cost-Effectiveness of Abiraterone, Apalutamide, Enzalutamide, and Docetaxel Doublets for Metastatic Hormone-Sensitive Prostate Cancer: A Real-World Evidence Analysis (Aim 2)

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3.1. Abstract

Objectives: Existing economic evaluations of metastatic hormone-sensitive prostate cancer (mHSPC) treatments rely primarily on clinical trial evidence, which may not reflect real-world value. This study evaluates the cost-effectiveness of available doublet therapies for mHSPC using real-world survival data.

Methods: We employed a three-state partitioned survival model (progression-free, progressed, and death) to estimate lifetime costs and benefits of abiraterone, apalutamide, enzalutamide, and docetaxel, each combined with androgen deprivation therapy (ADT), from the US healthcare sector perspective. Parametric survival distributions (Weibull, gamma, generalized gamma, exponential, lognormal, and log-logistic) were fit to propensity score-weighted Kaplan-Meier curves derived from treatment-specific overall survival and progression-free survival data of 9,141 mHSPC patients (mean age of 69 years) from claims-based analysis. Optimal distributions were selected based on Akaike Information Criterion, visual inspection, and clinical plausibility. Drug and administration costs were obtained from RED BOOK (apalutamide, enzalutamide), CMS National Average Drug Acquisition Cost (abiraterone), CMS average sales price (docetaxel, ADT), and CMS Physician Fee Schedule. Health state costs, utilities, and adverse event disutilities were derived from published literature. The primary outcome was the incremental cost-effectiveness ratio (ICER) in cost per quality-adjusted life year (QALY), with 3% discount applied to costs and QALYs. Probabilistic sensitivity analysis assessed model uncertainty.

Results: Abiraterone plus ADT yielded 5.37 QALYs at $716,701, compared to enzalutamide (5.80 QALYs; $1,239,303), apalutamide (5.75 QALYs; $1,248,750), and docetaxel (4.95 QALYs; $747,672). Docetaxel was dominated by abiraterone, and apalutamide was dominated by enzalutamide. The ICER for enzalutamide versus abiraterone was $1,214,802 per QALY.

Abiraterone remained the most cost-effective strategy across all evaluated willingness-to-pay thresholds.

Conclusion: Using real-world survival data, abiraterone is the most cost-effective first-line treatment for mHSPC, driven primarily by generic drug availability, and offering superior value compared to alternative androgen receptor pathway inhibitors and docetaxel-based regimens.

3.2. Introduction

Prostate cancer is the most commonly diagnosed malignancy and the second leading cause of cancer-related death among men in the United States[1]. Approximately 8% of patients present with metastatic disease at diagnosis, and a further subset develops metastases following failure of local therapy[2]. Metastatic hormone-sensitive prostate cancer (mHSPC), defined as metastatic disease that remains responsive to androgen deprivation therapy (ADT), achieved mostly with gonadotropin-releasing hormone (GnRH) agonists and antagonists, represents a critical treatment juncture, as the therapeutic decisions made at this stage have substantial implications for long-term outcomes and healthcare costs.

The mHSPC treatment landscape has undergone substantial transformation over the past decade. Historically, ADT alone was the standard of care, yet most patients inevitably progressed to metastatic castration-resistant prostate cancer (mCRPC) within two to three years, with a median overall survival of three to four years[3]. Since 2015, several pivotal randomized controlled trials (RCTs) have demonstrated that combining ADT with either docetaxel or androgen receptor pathway inhibitors (ARPIs), specifically abiraterone acetate, enzalutamide, and apalutamide, significantly delays disease progression and improves overall survival compared to ADT alone.[3–6] These agents are now recommended by the National Comprehensive Cancer Network and the European Society for Medical Oncology as first-line treatments for mHSPC[7,8]. However, these treatments differ substantially in pharmacologic mechanism, safety profile, mode of administration, and acquisition cost, presenting clinicians, payers, and policymakers with complex treatment prioritization decisions.

The economic implications of these treatment options are considerable. Drug acquisition costs range from relatively modest amounts for generic docetaxel and abiraterone acetate to tens of thousands of dollars per month for enzalutamide and apalutamide, which remain under patent

protection in the United States. Several cost-effectiveness analyses (CEAs) have been conducted to evaluate the economic value of these treatments in the mHSPC setting. In the US, Sung et al. developed a Markov model comparing all five first-line strategies and found that abiraterone plus ADT represented high-value healthcare at a willingness-to-pay (WTP) threshold of $100,000 per quality-adjusted life-year (QALY), with an incremental cost-effectiveness ratio (ICER) of $38,897 per QALY gained versus docetaxel plus ADT[9]. Similarly, Wang et al. conducted a partitioned survival model informed by network meta-analysis and reported an ICER of $58,814 per QALY for abiraterone versus docetaxel, concluding that abiraterone plus ADT was the most cost-effective strategy at WTP thresholds between $50,000 and $200,000 per QALY[10]. In Europe, Barbier et al. projected an ICER of EUR 39,814 per QALY for abiraterone versus docetaxel from a Swiss healthcare payer perspective, with apalutamide and enzalutamide both dominated by abiraterone at current prices.[11] An earlier analysis by Sathianathen et al., conducted prior to generic abiraterone availability, found docetaxel to be the most cost-effective option using brand-name abiraterone pricing, underscoring how sensitive cost-effectiveness conclusions in this disease area are to drug pricing assumptions.[12]

Despite these contributions, a critical methodological limitation characterizes all published CEAs to date: treatment survival inputs have been derived exclusively from RCTs or meta-analyses of trial data. While RCT-based evidence provides rigorous efficacy estimates under controlled conditions, it may not accurately reflect treatment effectiveness in routine clinical practice, where patients are generally older, carry greater comorbid burden, and exhibit more heterogeneous treatment patterns than trial participants. Moreover, the pivotal mHSPC trials enrolled patients across multiple countries and health systems, introducing heterogeneity in baseline characteristics, treatment practices, and healthcare infrastructure that limits the applicability of pooled survival estimates to country-specific CEAs, which are typically

conducted to inform national formulary and reimbursement decisions. Prior analyses have also not incorporated real-world ADT utilization patterns, which vary substantially across formulations and routes of administration in practice. In addition, enzalutamide and apalutamide have both been selected for Medicare drug price negotiation, a process that calls for the use of real-world evidence[13,14]. Collectively, these gaps limit the generalizability of existing economic evidence to payer decision-making in the United States.

To address this evidence gap, the present study estimates the cost-effectiveness of abiraterone acetate, apalutamide, enzalutamide, and docetaxel, each in combination with ADT, for the first-line treatment of mHSPC in the United States, using real-world survival data from a large, nationally representative administrative claims cohort. By grounding economic estimates in real-world effectiveness rather than trial-based efficacy, this analysis provides a more contextually relevant evidence base to inform clinical decision-making, formulary policy, and value-based reimbursement frameworks in the US setting.

3.3. Methods

3.3.1. Study design

We employed a partitioned survival model characterized by three health states – progression-free (mHSPC), post-progression (mCRPC), and death to estimate the cost-effectiveness of abiraterone, apalutamide, enzalutamide, and docetaxel doublet therapies. Partitioned survival models are typically used to model cancer treatments because they are intuitive, easy to construct, and rely on endpoints that can easily be obtained from individual-level survival data. State membership after each cycle was determined using overall survival (OS) and progression-free survival (PFS) curves. The height under the PFS curve represents the proportion of individuals that remained in the mHSPC state at a given time; the height under the OS curve represents the overall proportion of individuals that are alive at a given time; the height above

the OS curve represents the fraction of deceased individuals; while the height between the OS and PFS curve represents the fraction of patients that are alive but have progressed to mCRPC.

3.3.2. Study population

The study population consisted of a real-world, claims-derived cohort of 9,141 US adult men ≥18 years and older diagnosed with metastatic hormone-sensitive prostate cancer who initiated treatment with ADT within four months of diagnosis and subsequently received index treatment with abiraterone (n=3,968), apalutamide (n=1,096), enzalutamide (n=1,902), or docetaxel (n=2,175) within four months of ADT initiation. The average age of this cohort was approximately 69 years. Full cohort characteristics, including identification and selection criteria, have been reported in our prior study.

3.3.3. Treatment strategies

Four distinct treatment strategies were examined, each in combination with ADT (specific ADT strategies discussed below): (i) abiratereone acetate 1000mg (four 250mg tablets) administered by mouth once daily, (iii) apalutamide 240mg (four 60mg tablets) administered by mouth once daily, (iii) enzalutamide 160 mg (four 40mg capsules) administered by mouth once daily, and (iv) docetaxel 75 mg/m^2 intravenous injection every 3 weeks for 6 cycles. The exact dose for docetaxel was calculated using a body surface area of 2.1 m^2 based on a weight of 91kg and height of 1.75m, informed by anthropometric data for US adult men aged between 60 and 69 years [15]. We assumed no vial sharing. ADT included leuprolide 75mg administered intramuscularly every month, goserelin 3.6mg subcutaneous implantation monthly, triptorelin 3.75 mg administered intramuscularly every month, degarelix 80mg administered subcutaneously every month, relugolix 120mg by mouth daily, and one-time surgical castration (i.e., bilateral orchiectomy). The probability of receiving a particular ADT type at treatment initiation was informed by a claims-based ADT utilization pattern in the study population (Table S1 in Supplementary material).

3.3.4. Clinical efficacy and modelling

Following overlap propensity score weighting to adjust for confounding, Weibull, exponential, gamma, generalized gamma, log-logistic, and lognormal parametric survival distributions were estimated for OS and PFS for each treatment group (Figure S1 in Supplementary material). Parametric survival functions enable extrapolation of OS and PFS probabilities beyond the data cutoff point, which is necessary to estimate health state occupancy over the entire model time horizon. The best-fitting distribution was chosen based on Akaike information criterion (AIC), visual inspection, and clinical plausibility[16]. Following this selection criterion, we chose the Weibull distribution to model OS for abiraterone, apalutamide, and enzalutamide, while the exponential distribution modelled OS for docetaxel. For PFS, the log-logistic distribution was used to model all four treatment strategies (Table S2 in Supplementary material). The model used a healthcare sector perspective over a lifetime horizon with monthly cycles. Internal model validity was assessed through structured debugging and stress-testing with extreme parameter inputs, consistent with recommendations from the ISPOR-SMDM Modeling Good Research Practices Task Force on model transparency and validation[17].

3.3.5. Costs

Costs were estimated from the US healthcare sector perspective and comprised both direct medical costs incurred by payers and out-of-pocket payments covered by patients. The analysis incorporated treatment costs, health state costs, and costs associated with adverse events. All costs were estimated as monthly costs in 2025 US dollars. Costs derived from previous years were inflated to the 2025 US dollars using the healthcare component of the consumer price index[18].

Treatment costs included both drug acquisition costs and administration costs, where applicable. Drug costs were derived from sources that most closely represented the national

average prices, and generic drug prices were used if available. Given its generic availability, the cost of abiraterone was obtained from the National Average Drug Acquisition Cost (NADAC) prices. Provided by the CMS, the NADAC prices reflect the national average price retail pharmacies pay to acquire generic prescriptions durgs[19]. To reduce price volatility, CMS uses a rolling average of the most recent three months of data to determine the generic rates. To estimate the cost of apalutamide and enzalutamide, which currently have no generic alternative, we applied a 29% discount to the whole acquisition prices (WAC) obtained from Micromedex REDBOOK[20]. This approach estimates the net price and is consistent with the methodology used by the Institute of Clinical and Economic Review (ICER)[21]. Costs of docetaxel, leuprolide, goserelin, triptorelin, and degarelix were obtained from the Medicare Average Selling Price (ASP) drug pricing file[22]. The cost of relugolix, the only oral ADT, was estimated by applying a 30% discount to the WAC price. The cost of surgical castration was derived from a costing study by Paul et al.[23]. Drug administration costs for docetaxel, leuprolide, goserelin, triptorelin, and degarelix were derived from the Medicare Physician Fee Schedule[24], and estimated by multiplying the total medical relative value units (RVUs) – including work, non-facility practice expense, and malpractice – for the specific HCPCS codes by the medicare conversion factor (Table S3 in Supplementary material). Monthly drug acquisition and administration costs for each ADT type incorporated their utilization rates based on claims analysis.

Health state costs were obtained using estimates from Wang et al[10], who utilized the MarketScan Commercial Claims and Encounters and Medicare Supplemental database. Health state cost for mHSPC captured the cost of clinical encounters (inpatient, outpatient, hospice, and emergency department visits), excluding drug and administration costs. The cost of treating adverse events was obtained from both published literature and the Agency for Healthcare Research and Quality (ARHQ) Healthcare Cost and Utilization project (HCUPnet)[25]. Only

adverse events of ≥3 grade that occurred in at least 5% of any treatment arm were included. For each treatment arm, the cost of treating a given adverse event was estimated by multiplying the cost of hospitalization by the incidence of the adverse event (Table S4 in Supplementary material), which was obtained from the FDA drug label[26].

Different mCRPC health state costs were assigned to reflect differences in the subsequent treatment landscape following progression. For patients who received abiraterone acetate or enzalutamide in the mHSPC setting, these agents would not be re-prescribed upon progression to mCRPC, meaning their individual mCRPC costs were derived excluding these drugs and instead capturing the cost of alternative, often more expensive, subsequent regimens. In contrast, for patients who received docetaxel or apalutamide in the mHSPC setting, standard mCRPC treatments, including ARPIs such as abiraterone acetate and enzalutamide, remained available upon progression. As a result, their mCRPC costs reflect a broader and less restrictive subsequent treatment landscape, resulting in a lower shared cost estimate.

3.5.6 Outcomes and utility

Health outcomes were measured in terms of life-years (LYs), quality-adjusted life-years (QALYs), and equal value of life years gained (evLYGs). QALYs represent a preference-based measure of health outcome, derived by weighting LYs by a utility score ranging from 0 (death) to 1 (perfect health) that captures health-related quality of life. Utility scores varied across health states and were adjusted downward to account for the quality-of-life decrements associated with treatment-related adverse events (AEs), termed disutilities. In contrast, evLYG assumes equal quality of life for life extensions resulting from a treatment, applying a fixed utility value of 0.851 to those gained life years.

Health state utility values for the mHSPC and mCRPC states were obtained from published literature[27–29]. AE-associated disutility scores were similarly sourced from the literature and

encompassed estimates derived from multiple preference-elicitation methods, including the EQ-5D-5L, EQ-5D-3L, time trade-off, and standard gamble approaches. Health state utilities were applied monthly, corresponding to time spent in each respective health state. AE disutilities were applied as monthly decrements over the first six months following treatment initiation, consistent with evidence suggesting that the quality-of-life impact of common AEs, such as fatigue, typically resolves within this timeframe[27].

3.5.7. Model assumptions

The analytic model was informed by several assumptions. First, given the model structure, we assumed independence of health states, a fundamental feature of partitioned survival models. Secondly, all patients were assumed to receive treatment with ADT plus abiraterone, enzalutamide, apalutamide, or docetaxel (six cycles) until mCRPC progression, as recommended by treatment guidelines, and begin to accumulate mCRPC costs and utility upon progression. While OS estimation followed an intention-to-treat (ITT) approach, this assumption was applied to reflect real-world treatment patterns and guideline-concordant care. Thirdly, we assumed that patients who received ADT by bilateral orchiectomy only accrued a one-time cost associated with the surgery at the start of treatment initiation.

3.5.8. Analysis

Costs and utilities were assigned to the corresponding health state, accounting for the fraction of individuals in that health state. A discount rate of 3% per annum was applied to both cost and outcomes over the entire lifetime horizon. The incremental cost-effectiveness ratio (ICER) was used to estimate the cost-effectiveness of the four doublet therapies at a willingness to pay (WTP) threshold of $150,000 per QALY. The model was built and analyzed using TreeAge software.

3.5.9. Sensitivity analyses

Probabilistic and deterministic sensitivity analyses were conducted to evaluate uncertainty in model input parameters and identify those with the greatest influence on model outcomes. For parameters drawn from published literature that did not report standard errors (SEs) or 95% confidence intervals, an SE of ±10% of the point estimate was assumed. For drug costs, we assumed ±20% of the base case. The deterministic sensitivity analysis examined the independent effect of individual parameters on model outputs, including drug acquisition costs, health state costs, health state utilities, and adverse event disutilities. Two additional sensitivity analyses were conducted: one assuming equal mHSPC health state utility across ARPI and docetaxel regimens, and one applying hazard ratios derived from a Bayesian network meta-analysis with docetaxel as the reference curve (Table S5). The probabilistic sensitivity analysis (PSA) involved simultaneous variation of all model inputs across 10,000 Monte Carlo iterations, with each parameter sampled from a prespecified parametric distribution. Consistent with recommendations from the ISPOR-SMDM Modeling Good Research Practices Task Force[30], cost parameters were sampled from gamma distributions, while utility and disutility values, and adverse event rates were sampled from beta distributions. Detailed parameter distributions are presented in Table 1.

3.5.10. Scenario analyses

To address structural and parameter uncertainty associated with key modeling assumptions, we conducted three pre-specified scenario analyses by varying base-case drug cost inputs and the model time horizon. The first scenario examined the cost-effectiveness using the 500 mg abiraterone acetate tablet formulation as an alternative to the base-case 250mg tablet. Although both regimens ultimately deliver equivalent therapeutic doses (1,000mg once daily), the monthly acquisition cost of the 500 mg tablet is substantially higher than that of the 250 mg

tablet per the NADAC, making the 500 mg formulation a meaningfully more expensive treatment option in practice. This scenario was therefore evaluated to reflect the cost-effectiveness implications for patients dispensed the 500 mg formulation. The second scenario replaced the base-case generic abiraterone acetate acquisition cost with the branded-name price, reflecting the reality that brand-name abiraterone acetate continues to be dispensed in certain clinical and payer contexts despite generic availability since 2018. The third scenario restricted the model time horizon to five years, as opposed to the lifetime horizon adopted in the base case. The base-case lifetime horizon necessitates extrapolation of survival curves beyond the follow-up period of available clinical trial data. A five-year horizon was therefore evaluated to minimize reliance on extrapolated survival data, anchoring model outcomes more closely to the period directly supported by observed real-world evidence.

3.4. Results

3.4.1. Base case

Enzalutamide plus ADT generated the most QALYs (5.80), followed by apalutamide (5.75), abiraterone acetate (5.37), and docetaxel (4.95). Enzalutamide plus ADT was also the costliest ($1,239,303), followed by apalutamide ($1,248,750), abiraterone acetate ($716,701), and docetaxel ($747,672). Docetaxel plus ADT was dominated by abiraterone acetate, generating fewer QALYs at a higher cost. Apalutamide plus ADT was dominated by enzalutamide, likewise generating fewer QALYs at a higher cost. After excluding dominated strategies, abiraterone acetate plus ADT served as the reference comparator, and enzalutamide plus ADT was associated with an ICER of $1,214,802 per QALY gained relative to abiraterone acetate (Table 2).

3.4.2. Sensitivity analysis

The cost-effectiveness acceptability curve demonstrated that abiraterone acetate plus ADT had the highest probability of being the most cost-effective treatment strategy across all evaluated

willingness-to-pay (WTP) thresholds (Figure 1). Even at a WTP of $0, abiraterone acetate plus ADT exhibited a probability of approximately 80% of being the most cost-effective option, rising to approximately 95% at the pre-specified threshold of $150,000 per QALY, where it remained stable through $300,000 per QALY. Docetaxel plus ADT had a moderate probability of being the most cost-effective strategy at lower WTP thresholds (approximately 0.19 at $0 per QALY), reflecting its lower absolute cost, but this probability declined steadily with increasing WTP thresholds, approaching near zero by $150,000 per QALY. Apalutamide plus ADT and enzalutamide plus ADT maintained negligible probabilities of being the most cost-effective treatment across the entire range of WTP thresholds evaluated. At the reference WTP threshold of $150,000 per QALY, abiraterone acetate plus ADT was the most cost-effective treatment with a probability of approximately 0.95, with all remaining treatment strategies collectively accounting for less than 0.05 of the probability mass.

In the deterministic analyses, ICER results were mostly influenced by drug costs, health state utilities, and health state costs. Conversely, adverse effect costs and disutilities had the least impact on cost-effectiveness results (Figures 2 and Figures S2 to S6 in Supplementary material). When docetaxel was assigned the same mHSPC utility as the ARPI regimens, QALYs in the docetaxel group increased from 4.95 to 5.13; however, docetaxel remained dominated by abiraterone, generating fewer QALYs at a higher total cost. When using hazard ratios from a Bayesian network meta-analysis, abiraterone plus ADT remained the most cost-effective strategy. Docetaxel and apalutamide were both dominated by abiraterone. enzalutamide plus ADT yielded an ICER of $474,275 per QALY versus apalutamide (Table S6).

34.3. Scenario analysis

Using abiraterone 500 mg tablets (monthly drug cost: $843) generated a mean total cost of $755,550 compared to $716,701 in the base case, which assumed 250 mg tablets (monthly drug

cost: $129). Under this scenario, docetaxel plus ADT became the least costly strategy and served as the reference comparator. Abiraterone plus ADT resulted in an ICER of $18,663 per QALY compared to docetaxel plus ADT, remaining cost-effective at the WTP threshold of $150,000 (Table 3). Enzalutamide plus ADT had an ICER of $1,124,495 per QALY relative to abiraterone, while apalutamide plus ADT was dominated by enzalutamide. Abiraterone acetate plus ADT remained the most cost-effective treatment at the reference WTP threshold of $150,000, with a probability of approximately 0.87. However, at lower WTP thresholds, docetaxel plus ADT was competitive, with the two curves intersecting at approximately $10,000, below which docetaxel plus ADT had a higher probability of being the most cost-effective strategy (Figure S7). Apalutamide plus ADT and enzalutamide plus ADT maintained negligible probabilities of being the most cost-effective across all evaluated WTP thresholds.

Using the monthly price of $8,993 for brand-name abiraterone generated a mean total cost of $1,199,016, resulting in an ICER of $1,092,211 per QALY compared to docetaxel plus ADT (Table 3). Under this scenario, enzalutamide plus ADT had an ICER of $93,690 per QALY relative to abiraterone, falling below the reference WTP threshold of $150,000. Apalutamide plus ADT was dominated by enzalutamide. Probabilistic sensitivity analysis showed that docetaxel plus ADT had the highest probability of being the most cost-effective strategy at lower WTP thresholds, while enzalutamide plus ADT emerged as the preferred strategy at higher thresholds under branded abiraterone pricing (Figure S8). These results reflect the substantially higher acquisition cost of brand-name abiraterone compared to the generic price used in the base case.

In the five-year time horizon scenario analysis, abiraterone acetate plus ADT yielded 3.21 QALYs at a mean total cost of $380,979. Docetaxel plus ADT was dominated by abiraterone acetate, generating fewer QALYs (2.96) at a higher cost ($402,191). Enzalutamide plus ADT

yielded the highest QALYs at 3.41, with a mean total cost of $730,786, corresponding to an ICER of $1,779,205 per QALY gained relative to abiraterone acetate. Apalutamide plus ADT yielded 3.38 QALYs at $737,437 and was dominated by enzalutamide (Table 3). Abiraterone acetate plus ADT remained the most cost-effective treatment strategy at the reference WTP threshold of $150,000 under this scenario.

3.5. Discussion

This study estimated the real-world cost-effectiveness of four first-line mHSPC doublet treatment strategies from a US healthcare sector perspective over a lifetime horizon. Using survival data from 9,141 patients in a US administrative claims database, abiraterone acetate plus ADT was the most cost-effective treatment at the reference WTP threshold of $150,000, with a probability of approximately 0.95 in the probabilistic sensitivity analysis. Docetaxel was dominated by abiraterone, apalutamide was dominated by enzalutamide, and enzalutamide plus ADT yielded an ICER of $1,214,802 per QALY relative to abiraterone, far exceeding conventional thresholds.

3.5.1. Interpretation of findings

The dominance of docetaxel by abiraterone warrants interpretation. Despite a lower monthly drug acquisition cost and fixed, cycle-limited administration, docetaxel yielded fewer QALYs (4.95 vs. 5.37) at a higher total cost ($747,672 vs. $716,701). This is largely attributable to the superior real-world progression-free survival observed with abiraterone relative to docetaxel (aHR: 0.60, 95% CI: 0.55–0.66), which prolongs time in the lower-cost mHSPC health state and delays transition to more expensive mCRPC care, such that the higher acquisition cost of abiraterone is offset by reduced downstream expenditure, yielding a lower total cost than docetaxel despite longer treatment duration. Enzalutamide and apalutamide demonstrated similarly superior progression-free survival relative to docetaxel (aHR: 0.57, 95% CI: 0.51–

0.64 and aHR: 0.64, 95% CI: 0.56–0.73, respectively), consistent with their higher QALY estimates.

The scenario analyses provided additional contextual insights. The use of 500 mg abiraterone tablets, which carry a substantially higher monthly acquisition cost per NADAC pricing, attenuated the cost-effectiveness advantage of abiraterone over docetaxel observed in the base case, with the cost-effectiveness acceptability curves crossing at a low WTP threshold. This underscores the importance of tablet formulation in real-world prescribing decisions, where the 500 mg formulation may generate significantly different economic outcomes despite pharmacological equivalence. The branded-name abiraterone acetate scenario, consistent with findings from Sathianathen et al.,[12] confirmed that the cost-effectiveness of abiraterone is critically dependent on generic pricing and would be reversed under brand-name conditions. The five-year time horizon scenario demonstrated that even with truncated follow-up, abiraterone remained the most cost-effective strategy, providing additional confidence in the robustness of the base-case conclusion.

The dominance of apalutamide by enzalutamide may reflect two compounding dynamics. First, although the monthly drug cost difference is modest ($11,157 vs. $10,901), the per-cycle cost disadvantage compounds over a continuous treatment course, resulting in higher cumulative drug expenditure for apalutamide. Second, apalutamide patients likely spend slightly less time in the mHSPC state, suggesting inferior progression-free survival compared to enzalutamide as observed in the real-world analysis (HR:1.12; 95% CI: 0.98 – 1.28). Since mHSPC carries a higher health state utility than mCRPC, this translates directly into greater QALY accrual for enzalutamide (5.80 vs. 5.75). Despite apalutamide progressors being assigned a lower mCRPC health state cost ($13,808 vs. $15,977 per year), the savings accrued in the mCRPC phase

appear insufficient to offset the higher upstream drug costs accumulated during the mHSPC phase.

3.5.2. Comparison with existing literature

The present findings are broadly consistent with prior CEAs conducted in the US and internationally, though important differences exist. The QALY ranking observed in the present study, with enzalutamide generating the most QALYs, followed by apalutamide, abiraterone, and docetaxel, aligns with Sung et al., who reported an identical ordering and similarly found apalutamide plus ADT to be strongly dominated by enzalutamide plus ADT using a Markov model informed by trial data from a US payer perspective[9]. Sung et al. reported an ICER of $38,897 per QALY for abiraterone versus docetaxel at a WTP threshold of $100,000, concluding that abiraterone plus ADT represents high-value healthcare[9]. Wang et al. reported an ICER of $58,814 per QALY for abiraterone versus docetaxel using network meta-analysis-based survival inputs and Federal Supply Schedule drug pricing, with abiraterone dominating across WTP thresholds from $50,000 to $200,000 per QALY; enzalutamide was dominated by docetaxel, and apalutamide was not cost-effective in that analysis[10]. In a European context, Barbier et al. projected an ICER of EUR 39,814 per QALY for abiraterone versus docetaxel at a Swiss WTP threshold of EUR 70,400, with both apalutamide and enzalutamide absolutely dominated by abiraterone[11]. Across these studies, generic abiraterone consistently emerged as the preferred first-line strategy, lending cross-jurisdictional robustness to the present conclusions.

A key distinction between the present study and prior analyses is the positioning of docetaxel. In RCT-informed analyses, docetaxel was consistently cost-effective at lower WTP thresholds or generated a favorable ICER versus ADT alone[9,10]. In the landmark analysis by Sathianathen et al., which used 2017 brand-name abiraterone pricing from a US private payer perspective, docetaxel was the most cost-effective strategy with an ICER of $34,723 versus ADT alone,

while abiraterone was not cost-effective at any conventional threshold[12]. However, that conclusion may no longer be clinically relevant given generic abiraterone availability, a point reinforced by the brand-name abiraterone scenario in the present analysis, where docetaxel achieved a 100% probability of being the most cost-effective strategy, mirroring the Sathianathen et al. result. The present real-world analysis goes further in that even generic abiraterone dominates docetaxel outright, a finding that likely reflects the superior real-world effectiveness of abiraterone relative to docetaxel when evaluated in a broader, less selected patient population.

3.5.3. Strengths and clinical and policy relevance

A principal strength of this analysis is its grounding in real-world survival data, which addresses a critical limitation of existing cost-effectiveness literature in this disease area. Prior CEAs of mHSPC treatments have relied primarily on survival data from RCTs or network meta-analyses, which may overstate treatment effectiveness relative to routine practice due to strict eligibility criteria, often enrolling relatively healthier patients. Real-world patients frequently present with more comorbidities, functional limitations, and patterns of care that differ substantially from trial populations[31]. By deriving OS and PFS curves directly from 9,141 patients in a US administrative claims cohort, the present analysis generates cost-effectiveness estimates with greater external validity and generalizability to the broader US mHSPC population. Additionally, the incorporation of real-world ADT utilization patterns reflects actual clinical heterogeneity in ADT prescribing, which prior analyses have not accounted for.

From a clinical and policy standpoint, these findings carry direct implications for formulary design and value-based reimbursement. Generic abiraterone acetate, now widely available since 2018, is affirmed as the highest-value first-line treatment option in this analysis, supporting its preferential placement on lower-cost formulary tiers under value-based

formulary frameworks. Of relevance, enzalutamide received a negotiated Medicare maximum fair price (MFP) of $7,004 per 30-day supply under the Inflation Reduction Act, effective January 2027. Should this price be broadly adopted, the cost-effectiveness of enzalutamide may improve considerably, potentially narrowing the gap with abiraterone at conventional WTP thresholds. Apalutamide has been similarly selected for the third cycle of Medicare price negotiation, with an MFP anticipated in 2028. The present analysis thus provides a timely pre-negotiation benchmark for evaluating the value implications of these pricing changes. Aligning drug coverage and copayment structures with economic value has been shown to reduce expenditures without adversely affecting medication utilization or health outcomes[32,33].

3.5.4. Limitations

Several limitations warrant acknowledgment. First, the partitioned survival model assumes independence between OS and PFS health states; given that progression is often prognostic for death, this structural assumption may not fully capture endpoint dependencies, potentially affecting long-term extrapolation accuracy[34]. Second, treatment was assumed to continue uninterrupted until mCRPC progression, without accounting for dose modifications or early discontinuation common in real-world practice, which may affect both cost and survival estimates. Third, although survival inputs were derived from a large real-world claims cohort, observational data are subject to residual confounding that may persist despite propensity score weighting, and treatment effectiveness estimates may differ from those obtained in randomized settings. Fourth, drug costs were modeled using static point-in-time prices, which do not capture evolving price dynamics; patent expiries for enzalutamide and apalutamide are anticipated in the near term, and generic availability would likely shift the cost-effectiveness hierarchy substantially. Fifth, darolutamide plus ADT, recently approved for mHSPC, was not included in the analysis, as real-world effectiveness and utilization data were insufficient at the time of analysis; its comparative value warrants evaluation in future analyses. Finally, mCRPC

health state costs were derived from Wang et al.[10], which may not fully reflect costs in uninsured populations, limiting the generalizability of absolute cost estimates. Collectively, these limitations introduce uncertainty in ICER point estimates but are unlikely to alter the directional conclusion that generic abiraterone represents the highest-value first-line option in the current US mHSPC treatment landscape.

3.6. Conclusion

Using real-world survival data from a large US administrative claims cohort, abiraterone acetate plus ADT was the most cost-effective first-line treatment strategy for mHSPC at a WTP threshold of $150,000, driven primarily by the availability of generic formulations. Docetaxel plus ADT was dominated by generic abiraterone, while apalutamide plus ADT was dominated by enzalutamide, yielding ICERs far exceeding conventional thresholds. Enzalutamide plus ADT, though generating the most QALYs, yielded an ICER relative to abiraterone that far exceeds conventional thresholds. These findings were robust across sensitivity analyses but sensitive to abiraterone pricing: substitution with brand-name abiraterone reversed the cost-effectiveness conclusion in favour of docetaxel, underscoring the critical dependence of abiraterone's economic value on generic availability. These results support the preferential use of generic abiraterone plus ADT in first-line mHSPC and provide an evidence base for value-based formulary and reimbursement decisions. Future analyses may evaluate the cost-effectiveness of emerging triplet therapies and reassess the economic landscape as generic formulations of enzalutamide and apalutamide become available.

Table 1. Model parameters

Parameters	Base case	Lower bound	Upper bound	Distribution	Comment/ Reference
Drug cost ($)					
Abiraterone	129.06	103.25	154.87	Gamma	NADAC[19]
Apalutamide	11,156.61	8,925.29	13,397.93	Gamma	Applying 29% discount to WAC from REDBOOK[20]
Enzalutamide	10,900.59	8,720.47	13,080.71	Gamma	Applying 29% discount to WAC from RED BOOk[20]
Docetaxel	100.16	61.77	92.66	Gamma	CMS ASP[22]
Medical ADT cost ($)[a]					
Leuprolide	176.447	141.16	211.74	Gamma	CMS ASP[22]
Goserelin	733.67	586.93	880.40	Gamma	CMS ASP[22]
Triptorelin	474.84	379.87	569.81	Gamma	CMS ASP[22]
Degarelix	355.84	284.672	427.00	Gamma	CMS ASP[22]
Relugolix	1,933.65	1546.92	2320.38	Gamma	Applying 30% discount to WAC[20]
Surgical ADT cost ($)[ab]					
Bilateral orchiectomy (surgical castration)	14,755.935	9,481	20,031	Gamma	Paul et al[23]
Drug administration cost ($)[a]					
Docetaxel	119.36	95.49	143.23	Gamma	CMS Physican Fee Schedule[24]
Leuprolide, goserelin, triptorelin, degarelix	34.93	27.94	41.92	Gamma	CMS Physican Fee Schedule[24]
Health state cost ($)					
mHSPC	4,095.21	3032.40	5158.02	Gamma	Wang et al[10]
mCRPC (docetaxel and apalutamide)	13,808.10	12,315.32	15,300.88	Gamma	Wang et al[10]
mCRPC (enzalutamide)	15,976.66	14,249.43	17,703.89	Gamma	Wang et al[10]
mCRPC (abiraterone)	19,339.87	17,249.22	21,430.52	Gamma	Wang et al[10]
Health Utility					
mHSPC (docetaxel)	0.067	0.0602	0.0735	Beta	Morgans et al[27]
mHSPC (abiraterone, apalutamide, enzalutamide)	0.072	0.0632	0.0815	Beta	Feyerbend et al[28]
mCRPC	0.061	0.0539	0.0677	Beta	Lloyd et al[29]
Adverse event cost ($)					
Hypertension (abiraterone)	1,822.44	1,667.14	1,977.74	Gamma	ARHQ HCUPnet[25]
Hypertension (apalutamide)	754.11	698.85	818.37	Gamma	ARHQ HCUPnet [25]
Hypertension (enzalutamide)	399.5025	321.20	477.80	Gamma	
Hypokalemia (abiraterone)	881.192	855.55	906.83	Gamma	Wang et al[10]; ARHQ HCUPnet[25]
Elevated ALT (abiraterone)	530.56	487.46	573.66	Gamma	Wang et al[10]; ARHQ HCUPnet[25]
Rash (apalutamide)	463.123	398.50	527.74	Gamma	Wang et al[10]; ARHQ HCUPnet[25]
Neutropenia (docetaxel)	5,217.91	4,815.06	5,620.75	Gamma	Wang et al[10]; ARHQ HCUPnet[25]
Infections (docetaxel)	664.164	562.21	766.12	Gamma	Wang et al[10]; ARHQ HCUPnet[25]
Anaemia (docetaxel)	441.283	429.068	453.498	Gamma	Wang et al[10]; ARHQ HCUPnet[25]
Fatigue (docetaxel)	796.68	766.10	827.26	Gamma	ARHQ healthcare cost [25]
Fatigue (abiraterone)	350.54	281.83	419.25	Gamma	Wang et al[10]; ARHQ HCUPnet[25]
Fatigue (apalutamide)	159.33	128.10	190.56	Gamma	Wang et al[10]; ARHQ HCUPnet[25]
Fatigue (enzalutamide)	745.69	599.53	891.85	Gamma	Wang et al[10]; ARHQ HCUPnet[25]
Adverse event disutility					
Hypertension	-0.025	0.0201	0.0299	Beta	Sullivan et al[35]
Hypokalemia	-0.04	0.032	0.048	Beta	Sathianathen et al[12]
Elevated ALT	-0.0567	0.0563	0.0571	Beta	Sullivan et al[35]
Rash	-0.0325	0.00955	0.05545	Beta	Nafees et al.[36]
Neutropenia	-0.0897	0.0595	0.1199	Beta	Nafees et al.[36]
Infections	-0.14	0.1008	0.1792	Beta	Hall et al[37]
Anaemia	-0.119	0.116	0.1220	Beta	Swiburn et al[38]
Fatigue	-0.09	0.051	0.129	Beta	Hall et al[37]

ADT: androgen deprivation therapy, **AHRQ:** Agency for healthcare research and quality healthcare cost and utilization project, **ALT:** alanine aminotransferase, **CMS:** Centers for Medicare and Medicare services, **mHSPC:** metastatic hormone-sensitive prostate cancer, **mCRPC:** metastatic castration-resistant prostate cance

[a]monthly costs before incorporating utilization rates

[b]applied as a one-time cost

Table 2. Base case cost-effectiveness results

Treatment strategy	Cost	LYs	QALYs	evLYs	ICER (cost/QALY)	ICER (cost/evLYG)	Comparator
Abiraterone	716,701	7.50	5.37	5.37	Reference	Reference	
Docetaxel	747,672	7.47	4.95	4.95	Dominated	Dominated	Abiraterone
Enzalutamide	1,239,303	7.72	5.80	5.83	1,214,802	1,158,762	Abiraterone
Apalutamide	1,248,750	7.67	5.75	5.77	Dominated	Dominated	Enzalutamide

Table 3. Scenario analyses

Treatment strategy	Cost	LY	QALY	evLYs	ICER (cost/QALY)	ICER (cost/evLYG)	Comparator
500mg abiraterone tablet ($843/month)							
Docetaxel	747,672	7.47	4.95	4.95	Reference	Reference	
Abiraterone	755,550	7.50	5.37	5.37	18,663	18,578	Docetaxel
Enzalutamide	1,239,303	7.72	5.80	5.83	1,124,495	1,1072,847	Abiraterone
Apalutamide	1,248,750	7.67	5.75	5.77	Dominated	Dominated	Enzalutamide
Branded-name abiraterone ($8,992.57/month)							
Docetaxel	747,672	7.49	4.95	4.95	Reference	Reference	
Abiraterone	1,199,016	7.50	5.37	5.37	1,092,211	1,071,061	Docetaxel
Enzalutamide	1,239,303	7.70	5.80	5.82	93,690	89,527	Abiraterone
Apalutamide	1,248,750	7.72	5.75	5.77	Dominated	Dominated	Enzalutamide
5-year time horizon							
Abiraterone	380,979	4.15	3.21	3.21	Reference	Reference	
Docetaxel	402,191	4.16	2.96	2.96	Dominated	Dominated	Abiraterone
Enzalutamide	730,786	4.24	3.41	3.41	1,779,205	1,713,760	Abiraterone
Apalutamide	737,437	4.23	3.38	3.38	Dominated	Dominated	Enzalutamide

Figure 1. Cost-effectiveness acceptability curve (base case)

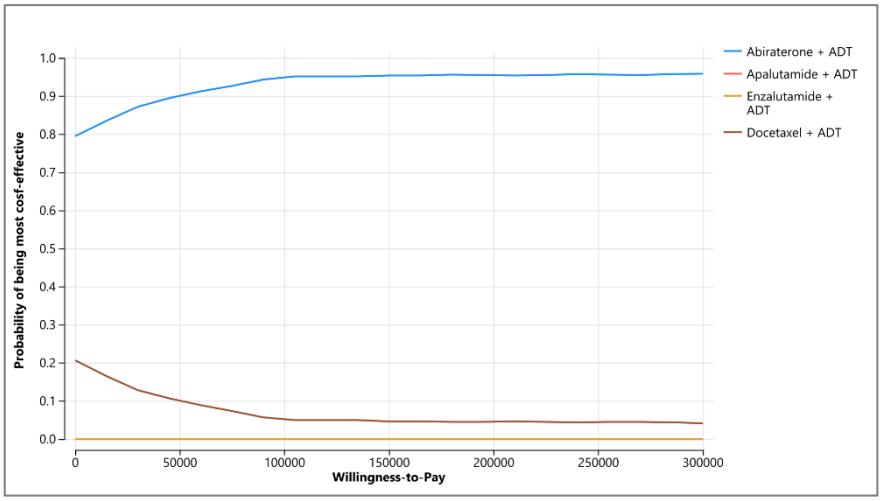
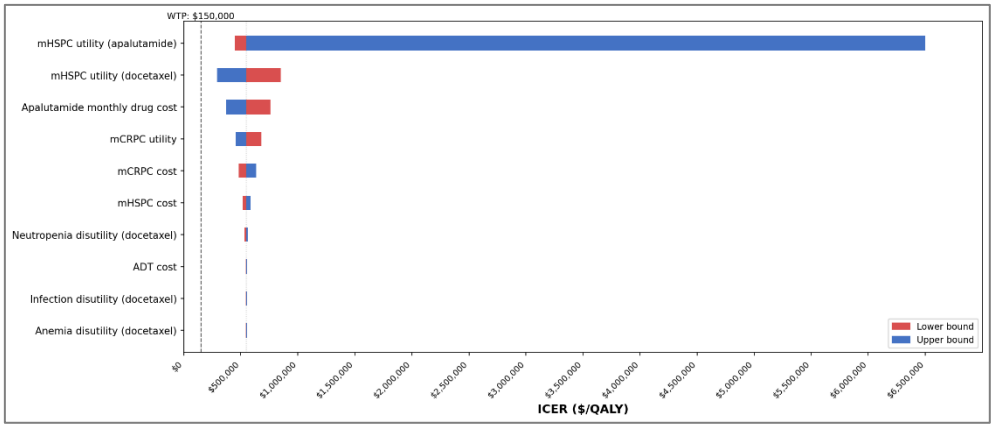


Figure 2. One-way sensitivity analysis for apalutamide plus ADT vs docetaxel plus ADT



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Supplementary Materials

Table S1. Utilization pattern for medical and surgical castration

ADT type	Utilization (%)
Leuprolide	61.5
Goserelin	0.6
Triptorelin	1.4
Degarelix	25.8
Relugolix	4.1
Surgical castration (bilateral orchiectomy)	6.6

ADT: androgen deprivation therapy

Table S2. Selected OS and PFS parametric distributions

Treatment	Distribution	Parameters	AIC
OS			
Abiraterone	Weibull	Shape: 0.9711 Scale: 164.7515	11394.4
Apalutamide	Weibull	Shape: 1.0246 Scale: 169.9427	2928.645
Enzalutamide	Weibull	Shape: 1.0360 Scale: 169.7714	5003.076
Docetaxel	Exponential	Rate: 0.006262	6332.658
PFS			
Abiraterone	Loglogistic	Shape: 0.9494 Scale: 44.6760	18458.25
Apalutamide	Loglogistic	Shape: 0.7826 Scale: 43.7654	5095.634
Enzalutamide	Loglogistic	Shape: 0.8933 Scale: 48.7505	8621.785
Docetaxel	Logistic	Shape: 1.1043 Scale: 21.8829	12401.34

AIC: Akaike information criterion, **OS**: overall survival, **PFS**: progression-free survival

Table S3. HCPCS code, RVUs, and Physician Fees Schedule for Drug Administration

HCPCS	Work RVU	PE RVU	MP RVU	Total RVU	2025 CF ($)	Physician fee ($)	Description
96413	0.28	3.35	0.06	3.69	32.3465	119.36	Chemo IV infusion, up to 1 hour
96402	0.19	0.87	0.02	1.08	32.3465	34.93	Chemotherapy, hormonal antineoplastic SQ/IM injection

CF: conversion factor, **HCPCS**: healthcare common procedure coding system, **PE**: practice expense, **MP**: malpractice, **RVU**: relative value unit

Table S4. Incidence of individual Adverse events

Grade ≥3 adverse event	Abiraterone (%)	Apalutamide (%)	Enzalutamide (%)	Docetaxel (%)
Hypertension	20.3	8.40	4.45	0.0
Hypokalemia	10.4	0.0	0.0	0.0
Elevated ALT	5.50	0.0	0.0	0.0
Rash	0.00	6.30	0.00	0.0
Neutropenia	0.0	0.0	0.0	32.0
Infections	0.0	0.0	0.0	6.0
Anaemia	0.0	1.70	0.0	5.0
Fatigue	2.2	1.00	4.68	5.0

ALT: alanine aminotransferase

Table S5. OS and PFS hazard ratios for ARPI plus ADT vs docetaxel plus ADT[1]

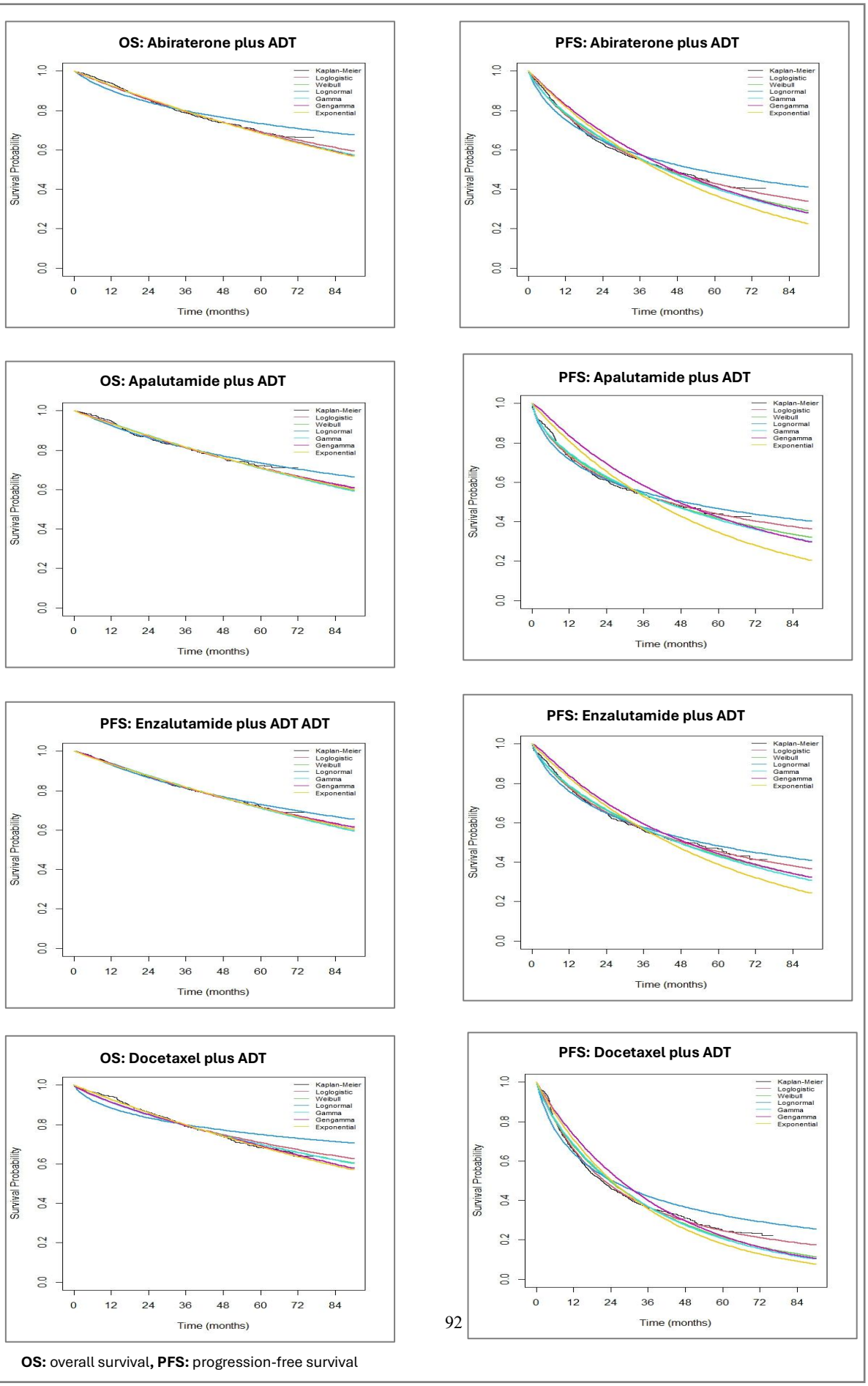
Treatment	Comparator	OS HR (95% CI)	PFS HR (95% CI)
ABI + ADT	DOC + ADT	0.91 (0.71 – 1.18)	0.59 (0.46 – 0.74)
APA + ADT	DOC + ADT	0.91 (0.59 – 1.35)	0.78 (0.52 -1.20)
ENZA + ADT	DOC + ADT	0.91 (0.63 – 1.28)	0.58 (0.42 – 0.79)

ABI: abiraterone; **ADT**: androgen deprivation therapy; **CI**: confidence interval; **DOC**: docetaxel; **ENZ**: enzalutamide; **HR**: hazard ratio, **OS**: overall survival; **PFS**: progression-free survival

Table S6. Sensitivity analysis based on hazard ratio from Bayesian network meta-analysis

Treatment strategy	Cost	LYs	QALYs	evLYs	ICER (cost/QALY)	ICER (cost/evLYG)	Comparator
Abiraterone	740,904	7.72	5.52	5.55	Reference	Reference	
Docetaxel	747,672	7.47	4.95	4.95	Dominated	Dominated	Abiraterone
Apalutamide	1,197,228	7.72	5.42	5.45	Dominated	Dominated	Abiraterone
Enzalutamide	1,254,141	7.72	5.54	5.57	474,275	490,629	Apalutamide

Figure S1. OS and PFS parametric distributions by treatment group



OS: overall survival**, PFS:** progression-free survival

Figure S2. Tornado plot for apalutamide plus ADT vs enzalutamide plus ADT

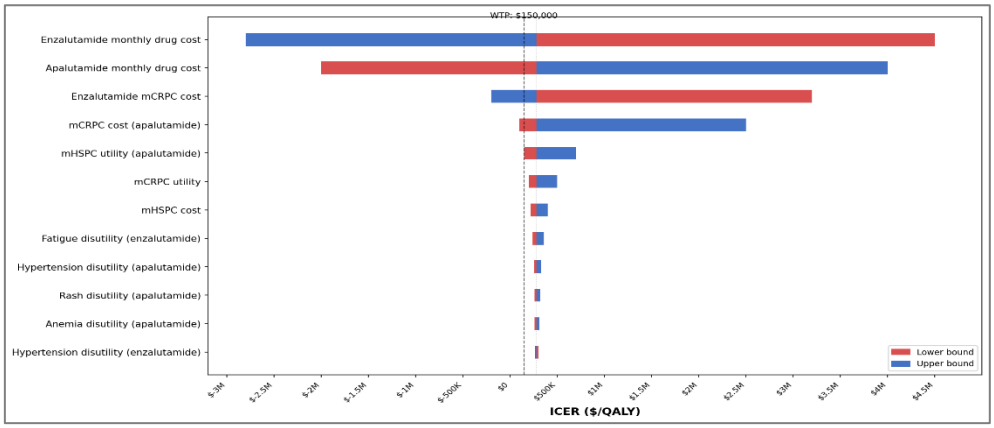


Figure S3. Tornado for Abiraterone plus ADT vs Apalutamide plus ADT

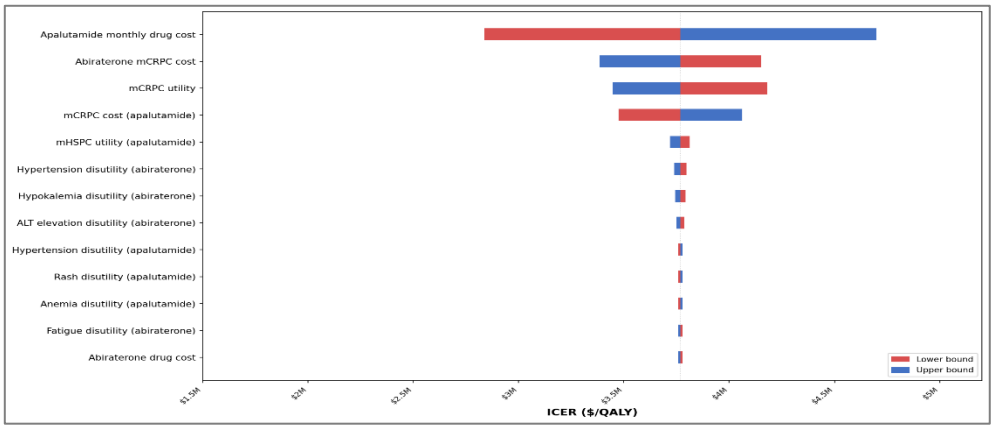


Figure S4. Tornado plot for Abiraterone plus ADT vs Enzalutamide plus ADT

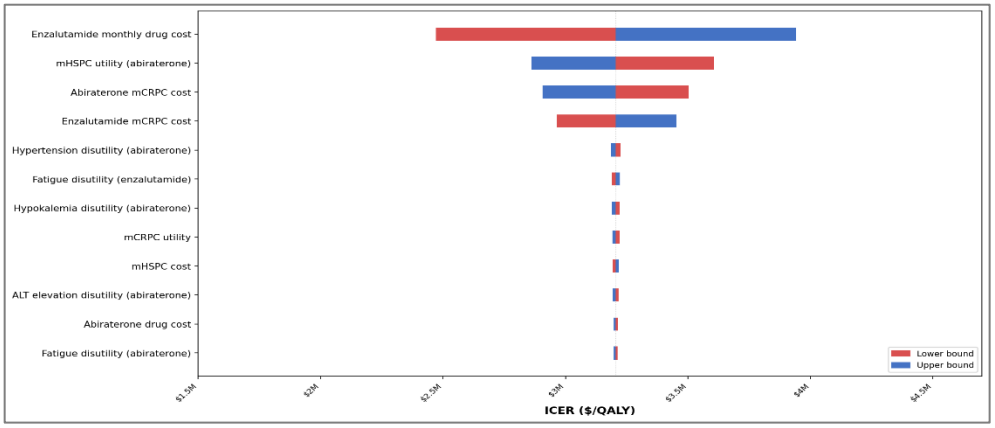


Figure S5. One-way sensitivity analysis for abiraterone plus ADT vs docetaxel plus ADT

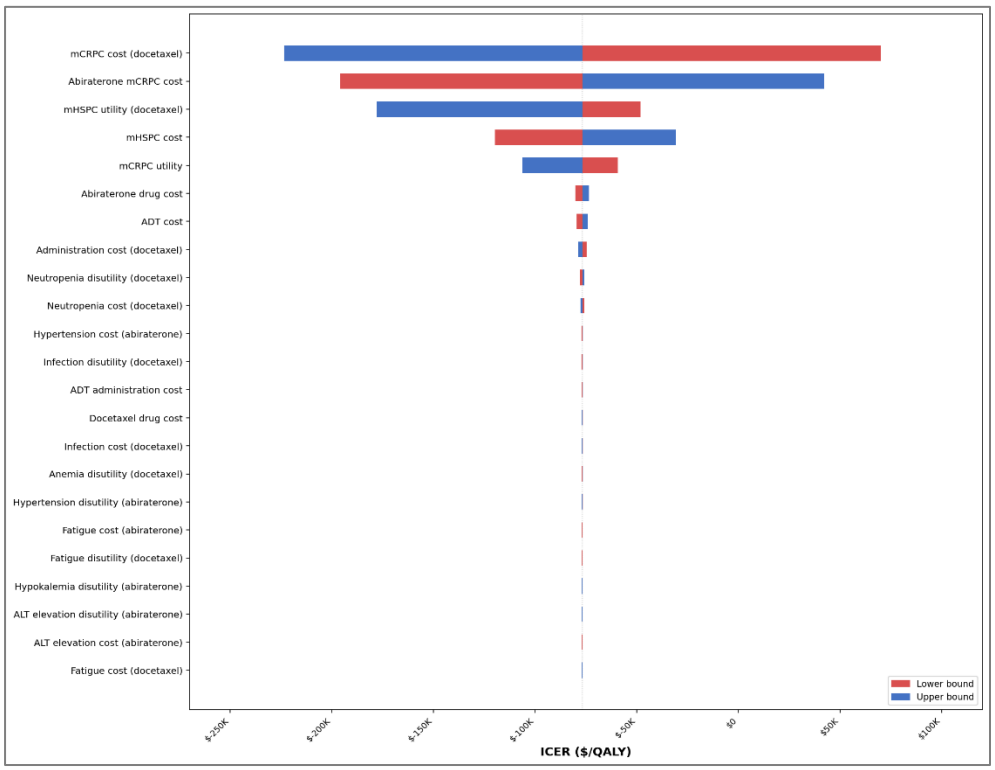


Figure S6. Tornado plot for enzalutamide plus ADT vs docetaxel plus ADT

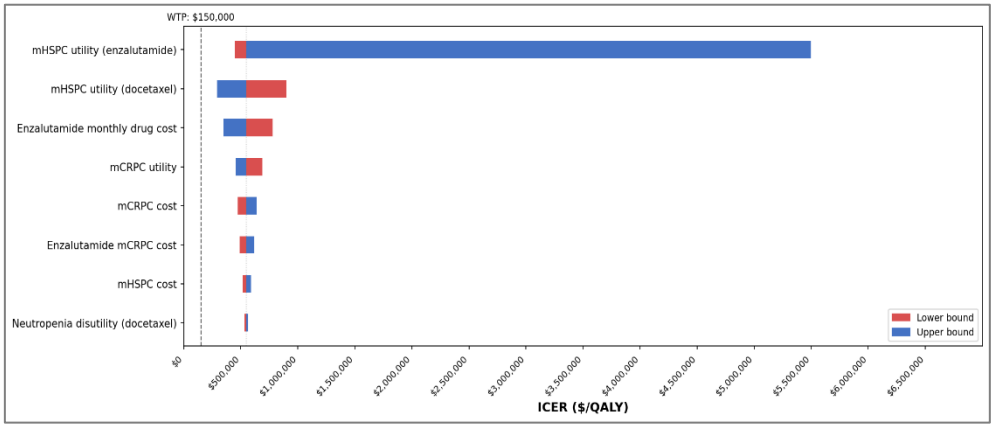


Figure S7. Cost-effectiveness acceptability curve (500mg abiraterone tablet)

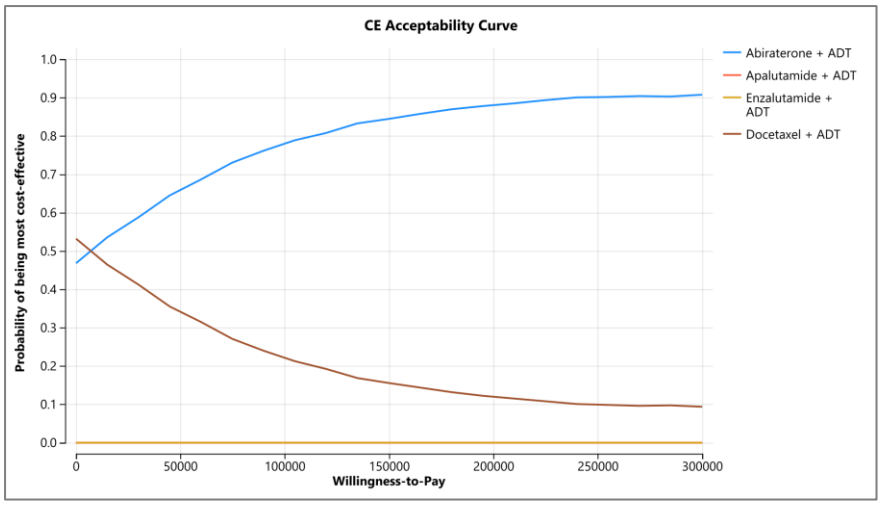
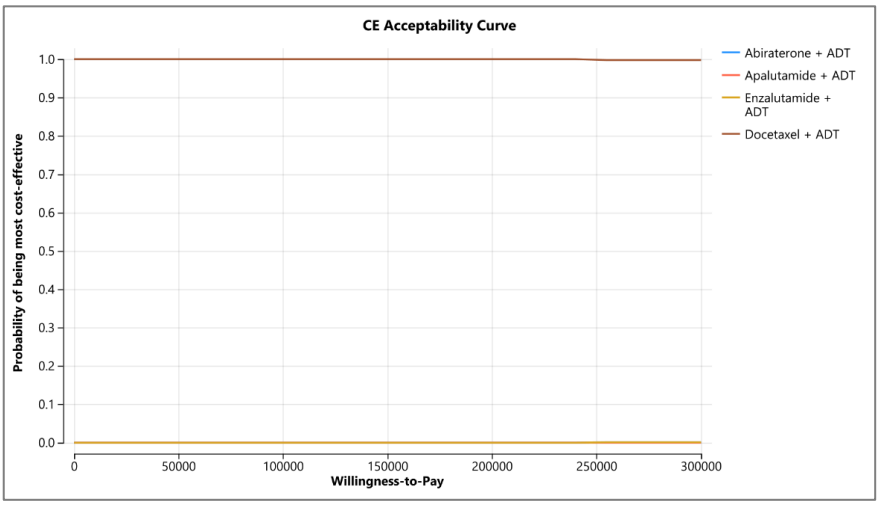


Figure S8. Cost-effectiveness acceptability curve (brand-name abiraterone price)



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CHAPTER 4: Comparative Effectiveness of Lutetium-PSMA versus Cabazitaxel in Patients Pre-treated with Docetaxel and Androgen Receptor Pathway Inhibitors for mCRPC (Aim 3)

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4.1. Abstract

Objectives: Lutetium-177-PSMA-617 (Lu-PSMA) is a novel radioligand therapy approved for PSMA-avid metastatic castration-resistant prostate cancer (mCRPC) based on survival benefit in the VISION trial; however, VISION excluded chemotherapy as a comparator, and real-world comparative evidence remains limited. We compared outcomes of Lu-PSMA versus cabazitaxel in patients previously treated with docetaxel and at least one androgen receptor pathway inhibitor (ARPI).

Methods: Using the Komodo Health Claims Database, we identified men aged ≥18 years diagnosed with mCRPC who received Lu-PSMA or cabazitaxel between January 2022 and June 2024. Patients were required to have prior treatment with docetaxel and one or more ARPI (abiraterone, apalutamide, enzalutamide, or darolutamide) before index treatment. Patients with other cancer types were excluded. Follow-up extended through June 2025. Primary outcomes included overall survival (OS; time from index treatment to death) and progression-free survival (PFS; time to new systemic mCRPC treatment initiation). Given Lu-PSMA's screening requirement, we employed weighted Cox proportional hazards models with average treatment effect in the treated (ATT) weights to estimate hazard ratios and 95% confidence intervals, controlling for baseline characteristics. Sensitivity analysis was conducted using 1:1 greedy propensity score matching.

Results: Among 2,843 patients with mCRPC, 954 received Lu-PSMA and 1,889 received cabazitaxel. After weighting, Lu-PSMA demonstrated significantly longer OS (median: not reached vs. 26.4 months [95% CI: 22.0–30.9]; aHR: 0.87 [95% CI: 0.76–0.99, p=0.04]) and PFS (median: 20.6 months [95% CI: 17.3–23.9] vs. 6.2 months [95% CI: 5.5–6.8]; aHR: 0.41 [95% CI: 0.36–0.46; p<0.0001]) compared to cabazitaxel. Findings were consistent in a propensity score-matched sensitivity analysis of 1,908 patients.

Conclusion: In this real-world analysis of mCRPC patients with prior docetaxel and ARPI exposure, Lu-PSMA demonstrated superior OS and PFS compared to cabazitaxel, supporting the clinical value of Lu-PSMA in this population.

4.2. Introduction

Metastatic castration-resistant prostate cancer (mCRPC) represents the terminal phase of prostate cancer and carries a poor prognosis despite an increasing number of available therapies[1]. Approximately 10 to 20 percent of men diagnosed with prostate cancer develop metastatic disease, with a significant proportion progressing to mCRPC[2], defined as biochemical, clinical, or radiographic disease progression despite castrate serum testosterone levels. Although therapeutic options have expanded over the past two decades, mCRPC remains uniformly fatal, and identifying the most effective treatment sequence remains a central challenge for clinicians, payers, and regulatory bodies. Among patients who have received prior androgen receptor pathway inhibitor (ARPI) therapy and docetaxel, cabazitaxel has historically represented the standard second-line cytotoxic option, supported by evidence of improved overall survival in the post-docetaxel setting[3]. However, its toxicity profile limits use in older or frailer patients, and many clinicians may defer or avoid it in practice, creating a need for alternatives capable of controlling disease with greater tolerability[4].

Lutetium-177-prostate-specific membrane antigen-617 (Lu-PSMA), a radioligand therapy that delivers targeted beta-particle radiation to PSMA-expressing tumor cells, received FDA approval in 2022 for PSMA-positive mCRPC following prior ARPI and taxane-based chemotherapy[5]. Approval was based principally on the phase III VISION trial, which demonstrated significant improvements in imaging-based progression-free survival and overall survival with Lu-PSMA added to standard of care versus standard of care alone[6]. However, VISION's control arm explicitly excluded chemotherapy, rendering it less active than current clinical practice and leaving unanswered the question of whether Lu-PSMA offers a meaningful survival advantage over cabazitaxel.

The phase II TheraP trial directly compared Lu-PSMA with cabazitaxel in 200 patients with mCRPC previously treated with docetaxel, and found a significantly higher PSA response rate

with Lu-PSMA (66% vs. 37%) and improved progression-free survival (HR: 0.63), but no significant difference in overall survival[7]. TheraP was powered for PSA response rather than survival, enrolled patients exclusively at Australian centers, and required dual PSMA and FDG-PET eligibility criteria that excluded patients with discordant disease, substantially limiting generalizability to US practice, where treatment eligibility is based solely on PSMA-PET positivity. The phase III PSMAfore trial demonstrated a significant radiographic PFS benefit of Lu-PSMA over ARPI change in taxane-naive patients (HR: 0.49 [95% CI 0·39–0·61]), but found no OS difference at interim analysis[8]. Collectively, existing trial evidence does not adequately characterize the comparative survival benefit of Lu-PSMA versus cabazitaxel in the US population.

This gap is clinically significant, as cabazitaxel represents the standard second-line cytotoxic option in the post-docetaxel, post-ARPI setting, and clinicians lack robust evidence to guide treatment sequencing for this high-risk population. This gap also carries direct policy relevance. Under the Inflation Reduction Act, CMS is required to consider comparative clinical effectiveness evidence when negotiating maximum fair prices[9]. Real-world evidence is increasingly recognized as a critical complement to trial-based efficacy data in this context, capturing treatment outcomes in broader, more heterogeneous populations that better reflect routine clinical practice. Moreover, enzalutamide has already been selected for negotiation with a maximum fair price, effective January 2027[10], and Lu-PSMA may face future negotiation cycles as utilization expands.

Consequently, comparative effectiveness studies that estimate the benefit of Lu-PSMA over established alternatives are therefore relevant to both current clinical decision-making and future value-based policy assessments. However, real-world comparative data remain limited. Available studies are largely single-center, single-arm, have small sample sizes, or are confined to non-US populations, restricting generalizability to US clinical practice[2,11–13]. To address

these evidence gaps, we evaluated the real-world comparative effectiveness of Lu-PSMA versus cabazitaxel in US patients with mCRPC previously treated with docetaxel and at least one ARPI.

4.3. Methods

This study employed a target trial emulation approach to reduce bias and enhance causal inference. We first specified the key protocol elements of a hypothetical randomized controlled trial (Table S1) and subsequently translated these components into an observational framework using claims data.

4.3.1. Study Design and Data Source

We conducted a retrospective cohort study using de-identified administrative claims from the Komodo Healthcare Map, a large, nationally representative database comprising medical and pharmacy claims for more than 330 million individuals across the United States from a range of payer types. The database enables longitudinal tracking of diagnoses, procedures, medication use, and insurance coverage, and incorporates mortality information through linkage with multiple external sources, including government records, private claims databases, and obituary data. The study period extended from January 2021 to June 6, 2025 (Figure S1).

4.3.2. Study Population

The study population included men aged 18 years and above with a diagnosis of mCRPC. Leveraging a peer-reviewed algorithm developed by Freedland et al[14], we used diagnosis codes to identify men with evidence of metastasis on or after the date of initial prostate cancer diagnosis who initiated treatment with Lu-PSMA or cabazitaxel between January 1, 2022, and June 30, 2024. Patients were then followed through June 5, 2025 (end of data availability). The

first date of use of Lu-PSMA or cabazitaxel was designated as the index date. The index period start date was selected to ensure both treatments were available for selection based on their approval year, satisfying the positivity criteria required for estimating average causal effects. Additionally, patients were required to have received prior treatment with docetaxel and at least one ARPI (abiraterone, apalutamide, enzalutamide, or darolutamide) at any point before the index date to be included in the study. To define the baseline period, patients were also required to have at least 12 months of continuous insurance enrollment before the index date for assessment of baseline characteristics. Exclusion criteria included evidence of other cancer types, receipt of both index treatments on the same day, or prior exposure to systemic mCRPC treatments such as radioligand therapy (e.g., Radium 223), pembrolizumab, poly ADP-ribose polymerase (PARP) inhibitors (e.g., rucaparib, olaparib), and sipuleucel-T during the baseline period.

4.3.3. Study outcomes

Overall survival and progression-free survival were examined. Progression-free survival was defined as time from index treatment to initiation of a new systemic therapy used in later lines of therapy, including Lu-PSMA (cabazitaxel arm only), cabazitaxel (Lu-PSMA arm only), any radioligand therapy (Radium 233), pembrolizumab, PARP inhibitors (rucaparib and olaparib), and sipuleucel-T; or death. Overall survival was defined as the time from index treatment to death from any cause. Patients were followed from the index date to the earliest of outcomes, end of study period (i.e., June 6, 2025), or the last day of insurance enrollment.

4.3.4. Statistical analysis

Propensity score weighting with average treatment effect in the treated (ATT) weights was used to adjust for confounding variables. ATT weights were employed, given the PSMA screening

requirement for initiating Lu-PSMA, which implies that not all patients in the cabazitaxel group might be eligible to receive Lu-PSMA. Hence, estimating the treatment effect of Lu-PSMA among those who actually received the treatment was considered more appropriate in this context[15]. Consequently, patients treated with Lu-PSMA were assigned a weight of 1, while individuals in the cabazitaxel group were assigned a weight of $\frac{p}{1-p}$, where p is the estimated probability of receiving Lu-PSMA given a set of baseline characteristics.

The propensity score model was estimated using a generalized boosted model (GBM) with 5,000 trees (Figure S6). To optimize covariate balance, the GBM was selected over the conventional logistic model as it accommodates complex, non-linear associations and performs well in high-dimensional settings without having to include polynomial or interaction terms[16]. Baseline covariates included age, geographical region, insurance type, year of treatment initiation, timing of metastasis, metastatic sites, ADT use, comorbidities, emergency department (ED) visits, prior treatments, and time to index treatment relative to initial prostate cancer diagnosis and initial metastasis (full details in Table 1). Standardized mean difference (SMD) was used to assess covariate balance before and after weighting, with SMD <0.1 deemed satisfactory. Overall survival and progression-free survival were examined using a weighted Cox proportional hazard model, with the proportional hazard assumption tested using Schonfeld residuals tests. Kaplan-Meier curves for both survival outcomes with log-rank tests were generated for the unweighted and weighted samples. To test the robustness of findings, a sensitivity analysis was conducted using 1:1 greedy propensity score matching without replacement. E-values were computed to quantify the robustness of findings to unmeasured confounding, with adjustment for common outcomes. All statistical analyses were performed using R Statistical Software version 4.2.0[17], employing the following R packages: comorbidity[18], survival[19], survminer[20], survey[21], tableone[22], tidyverse[23], and WeightIt[24]

4.4. Results

4.4.1. Cohort Characteristics

A total of 2,843 patients met eligibility criteria, with 954 initiating Lu-PSMA and 1,889 initiating cabazitaxel. In the cabazitaxel arm, 710 patients (37.6%) subsequently received Lu-PSMA, while no patients in the Lu-PSMA arm subsequently received cabazitaxel. Baseline characteristics of the unweighted cohort are presented in Table 1. The mean age was 71.0 years (SD 8.2); Lu-PSMA recipients were slightly older than cabazitaxel recipients (72.4 vs. 70.3 years). Most patients were Medicare-insured (74.0%), with a higher proportion in the Lu-PSMA group (79.6% vs. 71.2%). Treatment initiation was concentrated in 2023 (46.6% overall), though Lu-PSMA recipients were more likely to have initiated treatment in 2023–2024 (82.7% vs. 58.3%), consistent with the regulatory timeline of Lu-PSMA approval.

Prior treatment exposure was substantial and largely comparable between groups in the 12-month baseline period: 75.2% had received prior docetaxel, 64.8% prior ARPI therapy, and 48.1% both docetaxel and ARPI. ADT use was similarly high across both cohorts (Lu-PSMA: 88.8% vs cabazitaxel:90%). Notable differences in disease burden were observed: visceral metastases were more prevalent among cabazitaxel recipients (37.4% vs. 25.3%), as was concurrent bone and visceral involvement (35.3% vs. 23.8%). Patients receiving Lu-PSMA had longer median times from diagnosis (62.0 vs 55.2 months) and from metastasis to treatment initiation (45.5 vs. 40.8 months)

Comorbidity burden was similar between groups. Mean CCI score was 2.2 (SD 2.3) overall, with comparable distributions across severity strata. Hypertension was the most prevalent comorbidity (66.7%), followed by diabetes (28.5%), peripheral vascular disease (21.4%), and congestive heart failure (11.6%). Opioid use was higher in the cabazitaxel group (72.7% vs.

66.9%), and bone-health agent use was more common among cabazitaxel recipients (80.2% vs. 73.7%).

4.4.2. Overall survival

Over a median follow-up of 24.0 months (95% CI: 23.5–25.0) for the overall cohort, the median OS was not reached in the Lu-PSMA arm compared to 23.6 months (95% CI: 20.9–27.5) in the cabazitaxel arm (Figure 2A). The weighted median OS time was similar (not reached vs 26.4 months; 95 CI: 22 – 30.9). In the unadjusted analysis, Lu-PSMA was associated with significantly lower mortality risk relative to cabazitaxel (HR: 0.81; 95% CI: 0.72–0.92; $p < 0.001$). This survival advantage was preserved after weighting (HR: 0.87; 95% CI: 0.76–0.99; $p = 0.039$) and in the matched cohort (HR: 0.86; 95% CI: 0.75–0.99; $p = 0.030$), indicating consistent findings across all analytical approaches (Figure S3). E-values for the adjusted overall survival HR of 0.87 (95% CI, 0.76–0.99) were 1.44 for the point estimate and 1.09 for the upper confidence limit, indicating that the survival benefit could be nullified by an unmeasured confounder of modest strength.

4.4.3. Progression-free survival

Over a median follow-up of 19.4 months (95% CI: 18.9–19.9) for the overall cohort, the median PFS was substantially longer with Lu-PSMA (20.6 months; 95% CI: 17.3–23.9) than with cabazitaxel (6.7 months; 95% CI: 6.1–7.0) (Figure 3A). The weighted median PFS time was similar (20.6 months; 95 CI: 17.25 – 23.92 vs. 6.2 months; 95% CI: 5.5 – 6.8). In the unadjusted analysis, Lu-PSMA was associated with a markedly lower risk of progression or death compared to cabazitaxel (HR: 0.41; 95% CI: 0.37–0.45; $p < 0.001$). This benefit remained robust in the weighted analysis (HR: 0.41; 95% CI: 0.36–0.46; $p < 0.001$) and the matched cohort (HR: 0.39; 95% CI: 0.35–0.44; $p < 0.001$), corroborating the consistency of the PFS

advantage across all analytical approaches (Figure S4). E-values for the adjusted progression-free survival HR of 0.41 (95% CI, 0.36–0.46) were 3.09 for the point estimate and 2.80 for the upper confidence limit, indicating that only a substantially stronger unmeasured confounder, jointly associated with treatment assignment and outcome on the order of a threefold risk ratio, could nullify the observed findings.

4.5. Discussion

This study evaluated the real-world comparative effectiveness of Lu-PSMA versus cabazitaxel in patients with mCRPC previously treated with docetaxel and at least one ARPI, using a target trial emulation framework applied to a large, nationally representative US administrative claims database. After propensity score weighting to address observed confounding, Lu-PSMA was associated with a statistically significant reduction in mortality risk (HR: 0.87; 95% CI: 0.76–0.99) and a markedly lower risk of progression or death (HR: 0.41; 95% CI: 0.36–0.46) relative to cabazitaxel. The progression-free survival (PFS) advantage was large in magnitude and consistent across unweighted, weighted, and matched analyses. The overall survival (OS) benefit was more modest, which may be partly explained by the substantial crossover (37.6%) from cabazitaxel to Lu-PSMA observed during the study period.

Several baseline differences between the two treatment groups warrant careful interpretation. Lu-PSMA recipients were on average older (72.4 vs. 70.3 years), and had a lower prevalence of de novo metastasis (37.8% vs 41.6%), visceral metastases (25.3% vs. 37.4%), and concurrent bone and visceral involvement (23.8% vs. 35.3%). These observations suggest that clinicians may preferentially reserve cabazitaxel for younger patients with more aggressive disease. This selection dynamic is well documented in the comparative real-world literature. Wenzel et al., using a German single-center database, reported a median age of 72 years for Lu-PSMA versus 66 years for cabazitaxel recipients, with a higher proportion of de-novo metastasis (63% vs. 54%) in the cabazitaxel group[11]. In the multinational ARON-3 study, Lu-

PSMA recipients were more likely to be aged 70 years or older (36% vs. 25%) than those receiving cabazitaxel[2].

The adjusted OS hazard ratio of 0.87 is more modest than the 0.62 reported in the VISION phase III trial, and this difference requires careful contextual interpretation. In VISION, Lu-PSMA plus protocol-permitted standard of care was compared with standard of care alone, from which chemotherapy, immunotherapy, and systemic radioisotopes were explicitly excluded[6]. Notably, this exclusion may have rendered the control arm substantially less active than real-world clinical practice, likely inflating the apparent survival benefit. This concern is further underscored by the CARD trial, which had previously established the benefit of cabazitaxel over ARPI (abiraterone or enzalutamide) in patients previously treated with docetaxel and the alternative ARPI[25], questioning the clinical rationale for exclusion of cabazitaxel[26]. In contrast, the present study uses cabazitaxel as the active comparator, which represents a more conservative and clinically meaningful option for patients who have received docetaxel and ARPI therapy. The less active control arm in VISION may also partly explain the higher crossover rate to Lu-PSMA observed in that trial compared to the present study (57% vs. 37.6%). The adjusted PFS hazard ratio of 0.41 closely parallels VISION's imaging-based radiographic progression-free survival (rPFS) HR of 0.40, despite meaningful differences in how PFS was ascertained in each setting, a point discussed further below as a limitation.

TheraP, the only randomized phase II head-to-head comparison of Lu-PSMA versus cabazitaxel to date, demonstrated a significantly higher PSA response rate with Lu-PSMA (66% vs. 37%) and improved progression-free survival (HR: 0.63; 95 CI: 0.46 – 0.86), but no significant difference in overall survival at final analysis[7]. TheraP was, however, powered for PSA response rather than OS, enrolled only 200 patients from 11 Australian centers, and applied stringent dual PSMA and fluorodeoxyglucose (FDG) PET-CT eligibility criteria that excluded patients with discordant or any PSMA-negative disease, likely enriching the

population for high PSMA expression with a higher likelihood of response to Lu-PSMA. These constraints limit its generalizability in clinical practice, where eligibility is often based solely on PSMA-PET positivity. In the phase III PSMAfore trial of Lu-PSMA versus a change of ARPI in taxane-naive patients, the rPFS HR was 0.49 at the third data cutoff, while OS was similar between arms, an outcome that might have been confounded by the 57% crossover rate from the ARPI change group to Lu-PSMA[8]. The present study's PFS benefit (HR: 0.41) is directionally consistent with both trials, while the OS benefit is modest yet statistically significant.

Existing comparative real-world evidence further contextualizes these findings. Wenzel et al. reported a multivariable-adjusted PFS HR of 0.38 (95% CI: 0.22 – 0.79), closely mirroring our findings, but found no statistically significant OS difference after multivariable adjustment (HR: 0.98, 95% CI: 0.46 – 2.11), likely attributable to limited statistical power in a single-center German cohort of 296 patients[11]. The larger ARON-3 study by Mandel et al. (n=568 across 42 institutions in 16 countries) reported a multivariable-adjusted OS HR of 1.91 (95% CI: 1.14 – 3.19) for cabazitaxel versus Lu-PSMA, and a median time to treatment failure of 9.2 versus 5.1 months, favoring Lu-PSMA[2]. The larger magnitude of effect in ARON-3 relative to the present study may reflect differences in patient mix (international vs. US-based) and the analytical approach, which controlled for fewer covariates.

Our study has notable strengths. It is, to our knowledge, the largest US-based comparative effectiveness analysis of Lu-PSMA versus cabazitaxel in mCRPC. The use of a target trial emulation framework, including pre-specified eligibility criteria, index date assignment, outcome ascertainment, and a propensity score model estimated using a generalized boosted model capable of capturing non-linear relationships in high-dimensional data, substantially strengthens causal inference relative to conventional observational analyses. Replication of the primary results in a matched sensitivity analysis confirms the robustness of the findings. These

findings also carry direct policy significance. Lu-PSMA could be subject to Medicare drug price negotiation under the Inflation Reduction Act in the future, with enzalutamide selected for the initial price applicability year (IPAY) 2027 negotiation cycle[10]. Real-world comparative effectiveness estimates against active treatment alternatives such as cabazitaxel, generated from US clinical practice rather than international trials, can inform the evidence package submitted to the Centers for Medicare and Medicaid Services[27]. These estimates provide a more contextually appropriate basis for establishing a negotiated price that reflects the therapy's incremental clinical value within the mCRPC treatment landscape.

There are important limitations to keep in mind when interpreting findings from this study. Administrative claims data lack key clinical variables that influence treatment selection and prognosis in mCRPC, including PSA level, ECOG performance status, Gleason score, PSMA-PET scan positivity, and number and volume of metastatic lesions. Given that these factors typically indicate more aggressive disease, patients with poorer prognostic profiles may have been preferentially treated with cabazitaxel rather than Lu-PSMA, which may inflate the event rate in the cabazitaxel arm and bias the hazard ratio toward 0, in favor of Lu-PSMA. However, based on the E-values, the PFS advantage of Lu-PSMA over cabazitaxel appeared robust to residual confounding, whereas the borderline OS finding warrants confirmation in longer-term and randomized data. The absence of PSMA-PET status is a particularly important gap, as PSMA expression is a prerequisite for Lu-PSMA eligibility. Patients in the cabazitaxel arm who lacked sufficient PSMA expression to qualify for Lu-PSMA may have inherently worse prognosis, even after weighting. This potential unmeasured confounding may partially attenuate or amplify comparative estimates in ways that cannot be fully quantified within the claims-based framework. Additionally, coding inaccuracies in claims data, including potential misclassification of diagnoses, treatment sequences, and comorbidity status, may affect patient identification, covariate measurement, and outcome ascertainment.

The definition of PFS applied in this study, initiation of a subsequent systemic therapy from a predefined list of later-line agents or death, represents a pragmatic proxy for disease progression rather than the imaging-based rPFS employed in randomized trials. This claims-based surrogate captures both time on treatment and the interval to next-line therapy, which may differ systematically between the two treatments. Accordingly, direct comparisons of PFS estimates with imaging-based rPFS from clinical trials should be made with caution.

4.6. Conclusion

In this large retrospective cohort study of 2,843 patients with mCRPC previously treated with docetaxel and at least one ARPI, real-world evidence suggests that patients treated with Lu-PSMA have superior overall and progression-free survival compared to those treated with cabazitaxel. The PFS benefit was consistently large across analytical approaches and concordant with evidence from both randomized trials as well as comparative real-world analyses from European and international cohorts. The OS advantage, while more modest in magnitude, was statistically significant. These findings address a critical evidence gap in the US real-world literature by providing the largest head-to-head comparison of Lu-PSMA versus cabazitaxel in this patient population.

Table 1. Baseline characteristics

Characteristics	Unweighted population				Weighted population[a]			
	Overall (n=2,843)	Lu-PSMA (n=954)	CABA (n=1,889)	SMD	Overall (n=2,834)	Lu-PSMA (n=954)	CABA (n=1,889)	SMD
Age, mean (SD)	71.0 (8.2)	72.4 (7.8)	70.3 (8.3)	0.27	72.1 (7.7)	72.4 (7.8)	72.0 (7.7)	0.046
Region, n (%)								
Midwest	862 (30.3)	347 (36.4)	515 (27.3)	0.189	1,029 (36.2)	347.0 (36.4)	682.3 (36.1)	0.0015
Northeast	671 (23.6)	210 (22.0)	461 (24.4)	0.058	643.7 (22.6)	210.0 (22.0)	433.7 (23.0)	0.021
South	820 (28.8)	241 (25.3)	579 (30.7)	0.12	730.3 (25.7)	241.0 (25.3)	489.3 (25.9)	0.018
West	489 (17.2)	156 (16.4)	333 (17.6)	0.035	440 (15.5)	156.0 (16.4)	283.6 (15.0)	0.047
Territories	1 (0.0)	0 (0.0)	1 (0.1)	0.028	0.2 (0.0)	0.0 (0.0)	0.2 (0.0)	0.0041
Insurance type, n (%)								
Commercial	542 (19.1)	153 (16.0)	389 (20.6)	0.12	460.8 (16.2)	153.0 (16.0)	307.8 (16.3)	0.0062
Medicaid	185 (6.5)	39 (4.1)	146 (7.7)	0.18	125.0 (4.4)	39.0 (4.1)	86.0 (4.6)	0.026
Medicare	2,104 (74.0)	759 (79.6)	1,345 (71.2)	0.21	2,243 (78.9)	759.0 (79.6)	1,484 (78.6)	0.024
Unknown	12 (0.4)	3 (0.3)	9 (0.5)	0.029	14.2 (0.5)	3.0 (0.3)	11.2 (0.6)	0.040
Index treatment year, n (%)								
2022	953 (33.5)	165 (17.3)	788 (41.7)	0.65	498.6 (17.5)	165.0 (17.3)	333.6 (17.7)	0.021
2023	1,325 (46.6)	497 (52.1)	828 (43.8)	0.17	1,512 (53.2)	497.0 (52.1)	1,015 (53.7)	0.033
2024	565 (19.9)	292 (30.6)	273 (14.5)	0.35	832.7 (29.3)	292.0 (30.6)	540.7 (28.6)	0.052
De novo metastasis[b], n (%)	1,146 (40.3)	361 (37.8)	785 (41.6)	0.077	1,089 (38.3)	361.0 (37.8)	728 (38.5)	0.0012
Location of metastasis, n (%)								
Bone	2,619 (92.1)	866 (90.8)	1,753 (92.8)	0.070	2,587 (91.0)	866.0 (90.8)	1,721 (91.1)	0.0010
Visceral	947 (33.3)	241 (25.3)	706 (37.4)	0.28	747 (26.3)	241.0 (25.3)	505.5 (26.8)	0.034
Lymph	1,108 (39.0)	392 (41.1)	716 (37.9)	0.065	1,15 (40.3)	392.0 (41.1)	752.5 (39.8)	0.035
Bone + Visceral	894 (31.4)	227 (23.8)	667 (35.3)	0.27	699.9 (24.6)	227.0 (23.8)	472.9 (25.0)	0.028
ADT use, n (%)	2,547 (89.6)	847 (88.8)	1,700 (90.0)	0.038	2,540 (89.4)	847 (88.8)	1,693 (89.6)	0.021
CCI score, mean (SD)[c]	2.2 (2.3)	2.1 (2.2)	2.2 (2.3)	0.019	2.1 (2.2)	2.1 (2.2)	2.1 (2.2)	0.019
CCI category, n (%)[c]								
None: 0	823 (28.9)	270 (28.3)	553 (29.3)	0.14	799.0 (28.1)	270.0 (28.3)	529.0 (28.0)	0.0083
Mild: 1-2	994 (35.0)	350 (36.7)	644 (34.1)	0.13	1,060 (37.3)	350.0 (36.7)	710.1 (37.6)	0.0003
Moderate: 3-4	565 (19.9)	184 (19.3)	381 (20.2)	0.002	563.7 (19.8)	184.0 (19.3)	379.7 (20.1)	0.030
Severe: ≥5	461 (16.2)	150 (15.7)	311 (16.5)	0.007	420.2 (14.8)	150.0 (15.7)	270.2 (14.3)	0.042
ECI score, mean (SD)	8.3 (9.2)	8.1 (9.1)	8.3 (9.2)	0.013	8.1 (9.0)	8.1 (9.1)	8.0 (9.0)	0.018
Select comorbidities, n (%)								
Myocardial infarction	160 (5.6)	59 (6.2)	101 (5.3)	0.034	174.1 (6.1)	59.0 (6.2)	115.1 (6.1)	0.012
CHF	331 (11.6)	125 (13.1)	206 (10.9)	0.065	378.7 (13.3)	125.0 (13.1)	253.7 (13.4)	0.0002
PVD	607 (21.4)	222 (23.3)	385 (20.4)	0.068	668.1 (23.5)	222.0 (23.3)	446.1 (23.6)	0.0017
CVD	265 (9.3)	103 (10.8)	162 (8.6)	0.072	300.5 (10.6)	103.0 (10.8)	197.5 (10.5)	0.019
Dementia	39 (1.4)	13 (1.4)	26 (1.4)	0.001	40.2 (1.4)	13.0 (1.4)	27.2 (1.4)	0.015
CPD	485 (17.1)	168 (17.6)	317 (16.8)	0.022	506.4 (17.8)	168.0 (17.6)	338.4 (17.9)	0.0047
Mild liver disease	511 (18.0)	144 (15.1)	367 (19.4)	0.12	432.1 (15.2)	144.0 (15.1)	288.1 (15.3)	0.014
Diabetes	810 (28.5)	266 (27.9)	544 (28.8)	0.020	801.5 (28.2)	266.0 (27.9)	535.5 (28.4)	0.0043
Renal Disease	463 (16.3)	151 (15.8)	312 (16.5)	0.019	440.8 (15.5)	151.0 (15.8)	289.8 (15.3)	0.0002
Hypertension	1,896 (66.7)	648 (67.9)	1,248 (66.1)	0.040	1,912 (67.3)	648.0 (67.9)	1,264 (66.9)	0.028
Prior treatments[d], n (%)								
Docetaxel	2,137 (75.2)	689 (72.2)	1,448 (76.7)	0.099	2,042 (71.8)	689.0 (72.2)	1,353 (71.6)	0.019
ARPI	1,841 (64.8)	587 (61.5)	1,254 (66.4)	0.10	1,756 (61.8)	587.0 (61.5)	1,169 (61.9)	0.0018
Docetaxel + ARPI	1,368 (48.1)	425 (44.5)	943 (49.9)	0.11	1,255 (44.1)	425.0 (44.5)	829.8 (43.9)	0.019
Opioid use	2,012 (70.8)	638 (66.9)	1,374 (72.7)	0.12	1,937 (68.1)	638.0 (66.9)	1,299 (68.8)	0.030
First-generation antiandrogen	190 (6.7)	50 (5.2)	140 (7.4)	0.097	149.0 (5.2)	50.0 (5.2)	99.0 (5.2)	0.0031
Bone health agents	2,218 (78.0)	703 (73.7)	1,515 (80.2)	0.15	2,123 (74.7)	703.0 (73.7)	1,420 (75.2)	0.016
ED visit, n (%)	921 (32.4)	277 (29.0)	644 (34.1)	0.11	839.3 (29.5)	277.0 (29.0)	562.3 (29.8)	0.0037
Time (months) to index treatment, Mean (SD)								
Initial PCa diagnosis	57.5 (56.7)	62.0 (27.8)	55.2 (25.9)	0.24	61.5 (27.5)	62.0 (27.8)	61.2 (27.4)	0.011
Initial metastasis	42.3 (25.4)	45.5 (27.3)	40.8 (24.3)	0.17	45.1 (26.6)	45.5 (27.3)	44.9 (26.3)	0.015

ADT: androgen deprivation therapy, **CCI**: Charlson comorbidity index, **CHF**: congestive heart failure, **CPD:** chronic pulmonary disease, **CVD**: cerebrovascular disease, **PVD**: peripheral vascular disease, **ED**: emergency department, **ECI**: elixhauser comorbidity index, **SMD**: standardized mean difference, **SD**: standard deviation

[a]Overlapping weights normalized to sum up to 1 within each treatment group and scaled to original population.

[b]De novo metastasis defined as having evidence of metastasis within 30 days of initial prostate cancer diagnosis

[c]CCI and ECI computations excluded prostate cancer and associated metastasis

[d]Drugs listed in **Table S3**

Figure 1. Prisma Flow Diagram for Study Population

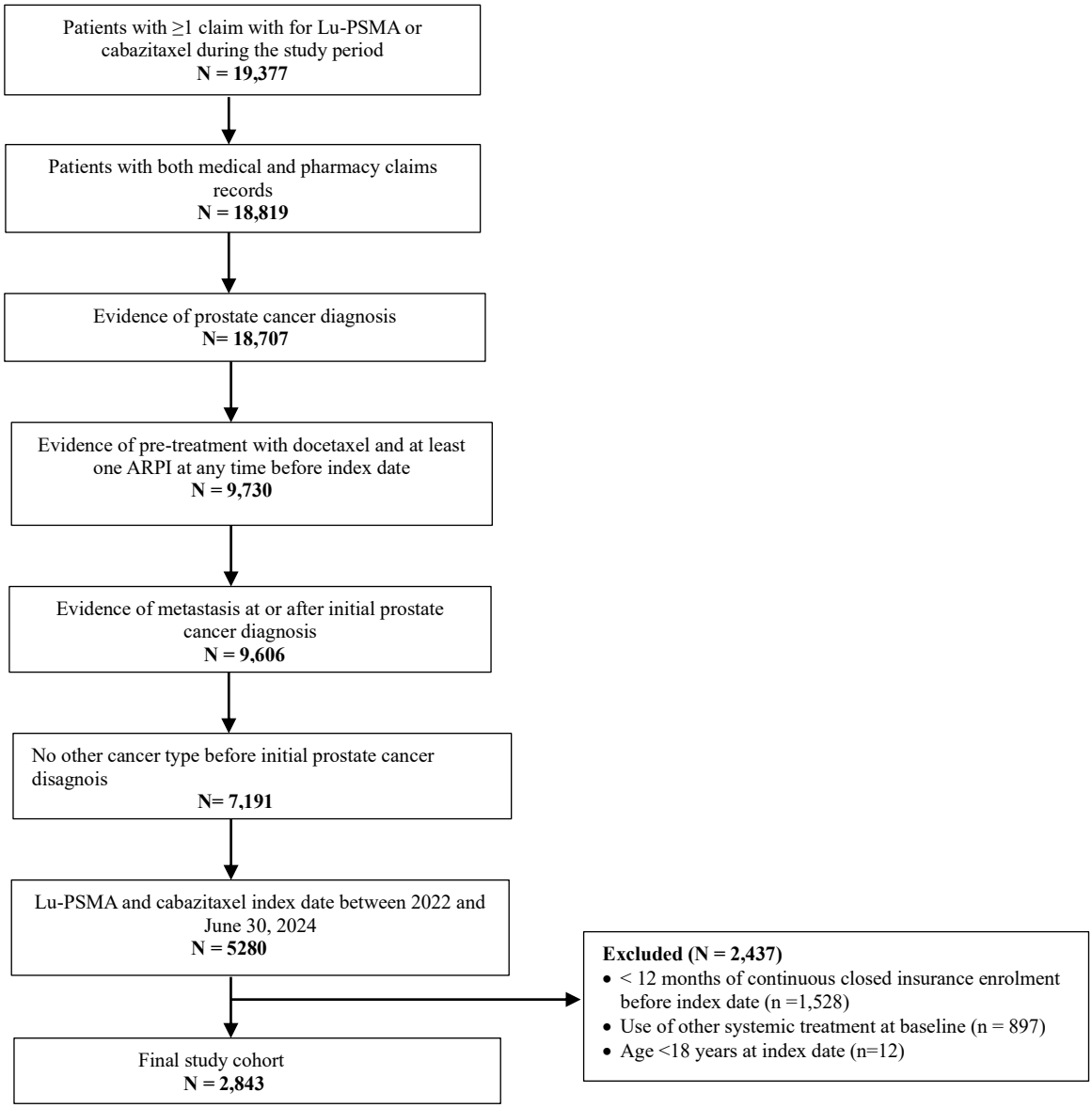
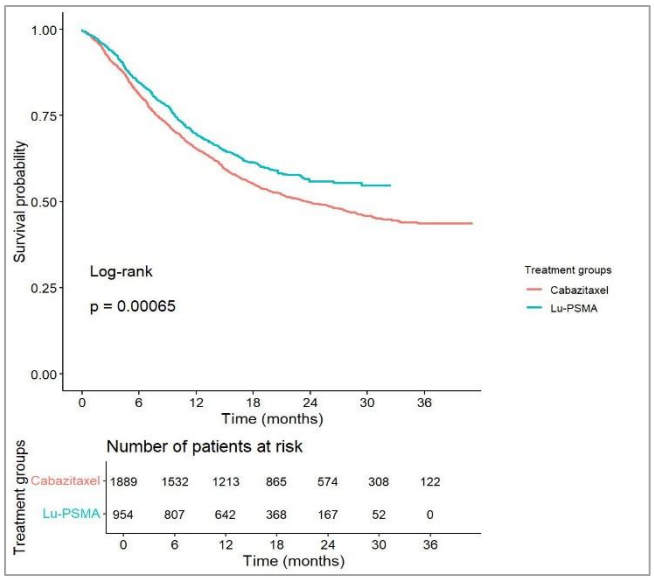
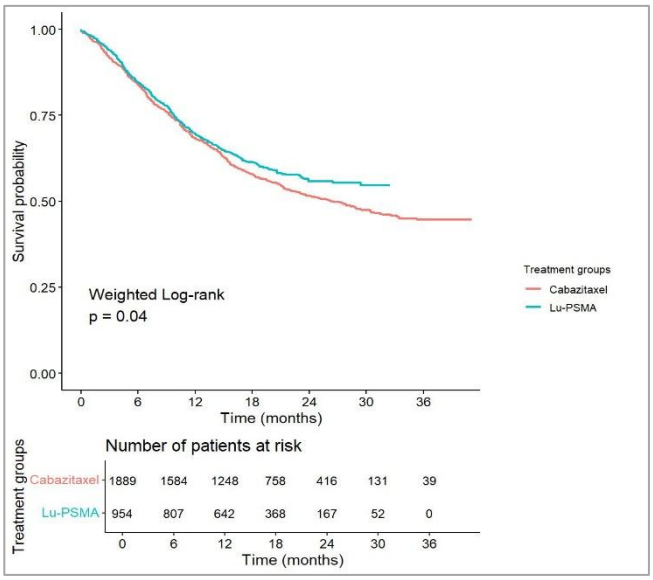


Figure 2. Kaplan-Meier Overall Survival

A. Unweighted OS



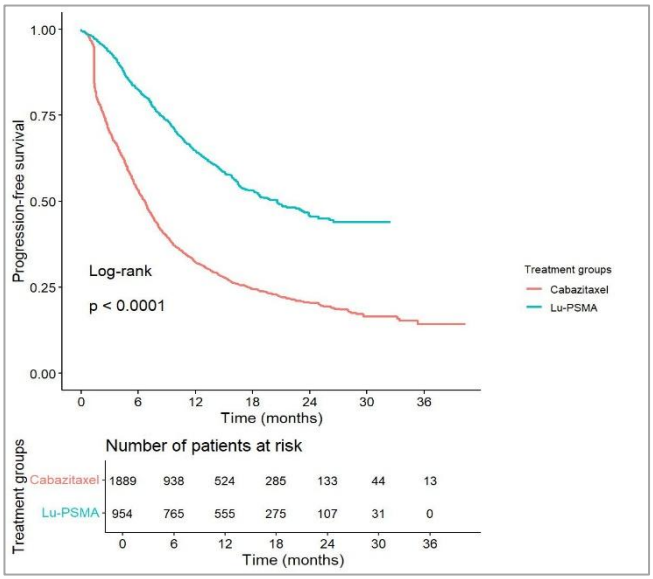
B. Weighted OS



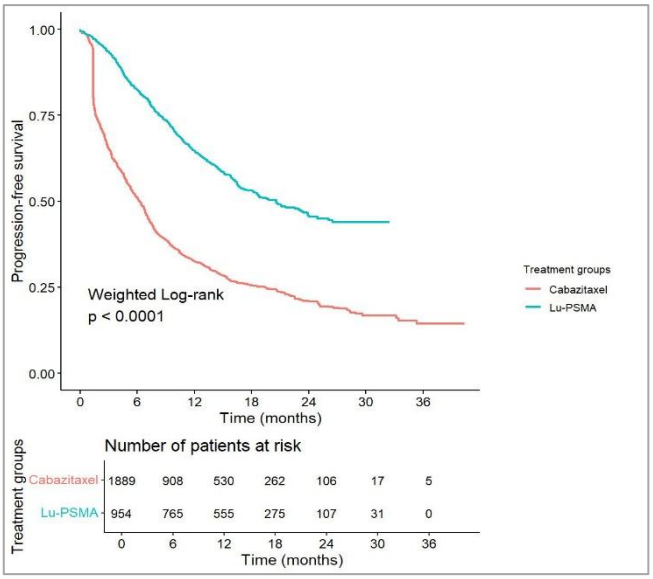
OS: overall survival, **Lu-PSMA**: Lutetium-177-PSMA-617

Figure 3. Kaplan-Meier Progression-free survival

A. Unweighted PFS curve



B. Weighted PFS curve



PFS: progression-free survival, **Lu-PSMA**: Lutetium-177-PSMA-617

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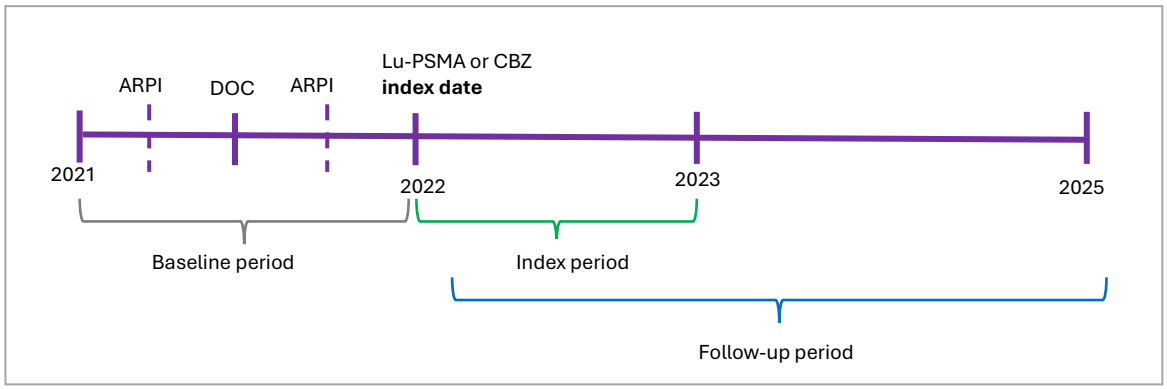
Supplementary Materials

Figure S1. Study design schematic



ARPI: androgen receptor pathway inhibitor, **DOC**: docetaxel

Followed through June 6, 2025
Index period from January 2022 to June 30, 2023

Table S1. Summary of target trial protocol

Protocol components	Description
Eligibility criteria	Eligible patients will be adult men with progressive mCRPC who had experienced disease progression after previous treatment on at least one ARPI (abiraterone or enzalutamide) and docetaxel. Patients will be included if they have PSMA-positive mCRPC defined by having at least one PSMA-positive metastatic lesion confirmed by centrally assessed PSMA-PET imaging at baseline.
Treatment strategies	Lu-PSMA versus cabazitaxel
Assignment procedure	Men will be randomly assigned to receive Lu-PSMA-617 (6·0–8·5 GBq intravenously every 6 weeks for up to six cycles) or cabazitaxel (20 mg/m^2 intravenously every 3 weeks for up to ten cycles)
Outcomes	**Primary outcome**: Imaging-based progression-free survival, defined as time from randomization to independently centrally reviewed disease progression based on the Prostate Cancer Clinical Trials Working Group 3 criteria. **Secondary outcome**: Overall survival (time from randomization to death from any cause.)
Follow-up	Patients will be followed from randomization to outcome, loss to follow-up, or end of study period.
Causal contrasts of interest	Intention-to-treat effect
Analysis plan	Time-to-event analysis using Cox proportional hazards model to hazard ratios and estimated 95% confidence interval. Intention-to-treat effect analysis will estimate treatment effects among individuals assigned to each treatment strategy regardless of adherence or treatment changes.

Table S2. Prostate cancer medications assessed during the study period

Medications	HCPSC code	mHSPC and mCRPC	mCRPC only
Chemotherapy			
Cabazitaxel	C9276, J9043		X
Medical castration (ADT)			
GnRH Agonist			
Leuprolide	J1950, J9217, J9218, J9219, J1951, J1952, Q0057, C9430	X	
Goserelin	J902	X	
Histrelin	J9225, J9226, J1675, S0133, Q2020	X	
Triptorelin	J3315, J3316, J3320, J3321, C9016	X	
GnRH antagonist			
Relugolix		X	
Degarelix	J9155	X	
Radiopharmaceuticals			
Lutetiu-177 vipivotide tetraxtan	A9607		X
Radium-223	A9606		X
PARP inhibitors			
Olaparib			X
Rucaparib			X
Immunotherapy			
Pembrolizumab	C9027, J9271		X
Sipeleucel-T	C9273, Q2043		X

Table S3. Prior treatments

Medications	HCPCS code
ARPIs	
Abiraterone	
Apalutamide	
Enzalutamide	
Darolutamide	
Chemotherapy	
Docetaxel	J9170, J1971, J9172
Opioid analgesics	
Morphine	J2270, J2271, J2274
Codeine sulfate	J0745
Hydrocodone	
Fentanyl	J3010
Alfentanil	
Opium/belladonna alkaloids	
Hydromorphone	J1170
Levorphanol tartrate	
Meperidine	J2175
Methadone	J1230
Oxycodone	
Oxymorphone	
Remifentanil	
Tramadol	
Tapentadol	
Sufentanil	
Bone health agents	
Denosumab	J0897, C9272
Etidronate	J1436
Ibandronate	C9229, J1740
Pamidronate	C9411, J2430
Risedronate	
Alendronate	
Zoledronic acid	C9115, J3487, J3488, J3489, Q2051, Q4095, J3487, J3488, J3489, Q2051
First-generation antiandrogens	
Bicalutamide	
Flutamide	
Nilutamide	

Table S4. Procedure codes for surgical castration

Procedure	CPT	ICD-10-PCS	ICD-10-CM
Surgical castration	54520, 54522, 54530, 54533, 54535, 54690	0VT90ZZ, 0VT94ZZ, 0VTB0ZZ,0VTB4ZZ, 0VTC0ZZ, 0VTC4ZZ, 0VB90ZZ, 0VBB0ZZ, 0VBC0ZZ	Z9079

Table S5. Medical conditions (ICD-10-CM) assessed during the study period

Medical Condition	**ICD-10-CM**
Prostate cancer	C61
Other Cancer types	
Lip, oral cavity, and pharynx	C00-C14
digestive organs	C15-C26, R18.0
respiratory and intrathoracic organs	C30-C39
bone, connective tissue, skin (bone connective tissue skin)	C40-C49
Malignant neoplasm of the breast	C50
genitourinary organ (excluding prostate cancer)	C51-C58, C60, C62-C68
lymphatic and hematopoietic tissue	C81-C96
Eye, brain, and other parts of the central nervous system	C69-C72
Thyroid and other endocrine glands	C73-C75, C7A, C7B, E31.20- E31.23
Other specified	C76
Other unspecified	C80
Metastasis	
Any	C77.0 to C80.0, C7B
Bone	C79.5
Lymph node	C77.0 to C77.9
Visceral	C78.0 to C79.4; C79.6 to C79.9; C80.0; C7B

Generalized boosted model (GBM)

Table S6. GBM specifications (WeightIt package in R)

Parameter	Specification	Comments
Number of trees	5,000	This represents the maximum number of regression trees or iterations to be used. It controls model complexity and the risk of overfitting.
Estimand	ATT	Estimates average treatment effect in the treated population
Focal	1	Specifies that estimand should consider the treated group (1) rather than control (0)
Criterion	smd.mean	Minimizes the average absolute standardized mean difference among covariates across all treatment groups. The goal is to ensure overall balance by minimizing the average imbalance (preferred choice)
Interaction depth	3	Determines the complexity of interactions between variables in the model. Higher values indicate a better ability to capture nonlinear and nonadditive relationships.
Shrinkage	0.01	This denotes the learning rate of the model and is applied to the trees. The lower the shrinkage, the more trees one may have to include to achieve the optimum.

ATT: average treatment effect in the treated, **SMD**: standaradized mean difference

Number of trees, interaction depth, and shrinkage were fine-tuned iteratively before arriving at the combination that yielded the most balance in balance characteristics across all treatment groups (i.e., lowest SMD)

Figure S2. Plot of average SMD against number of trees (GBM)

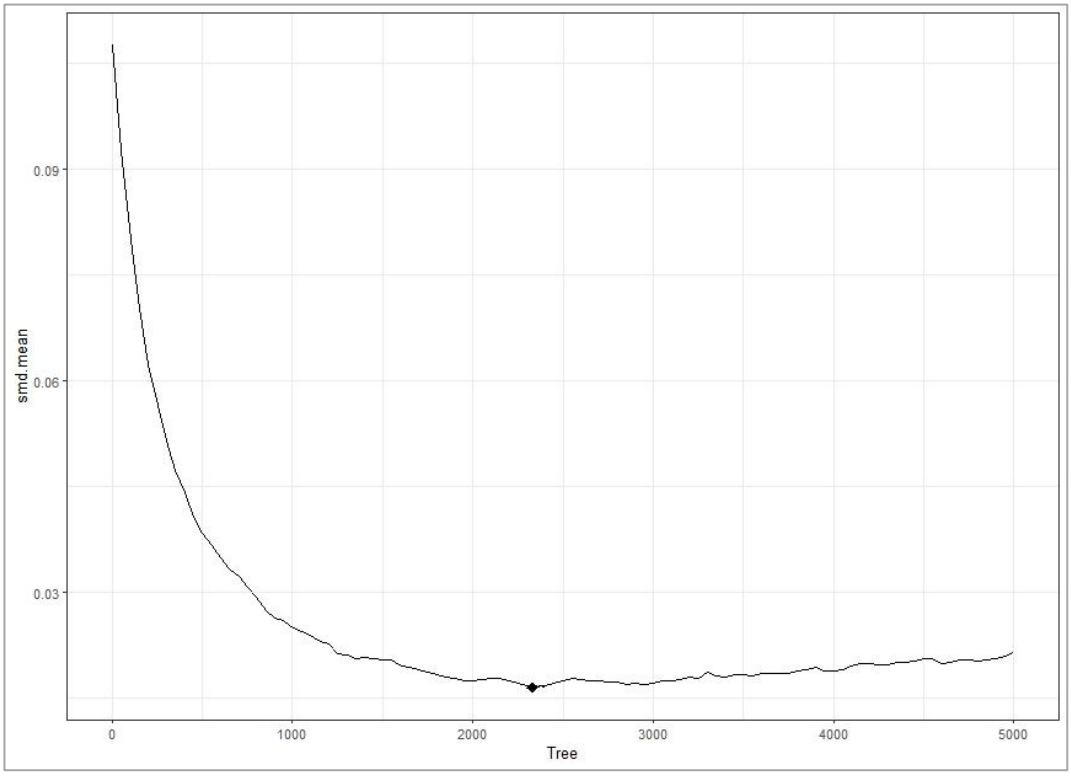
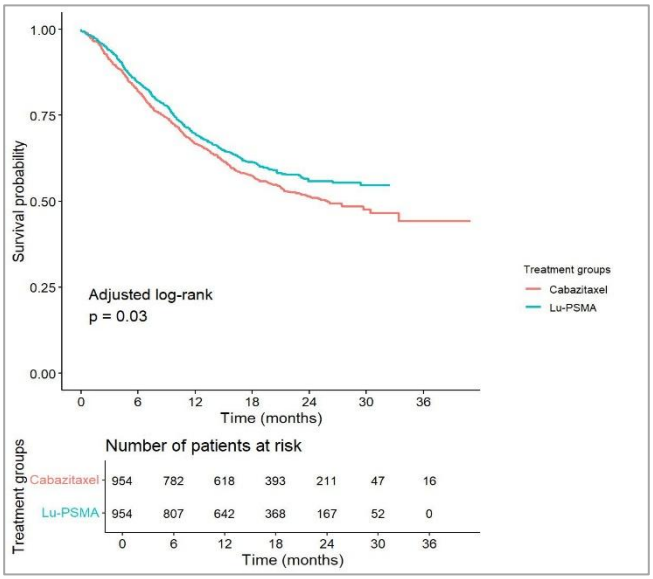
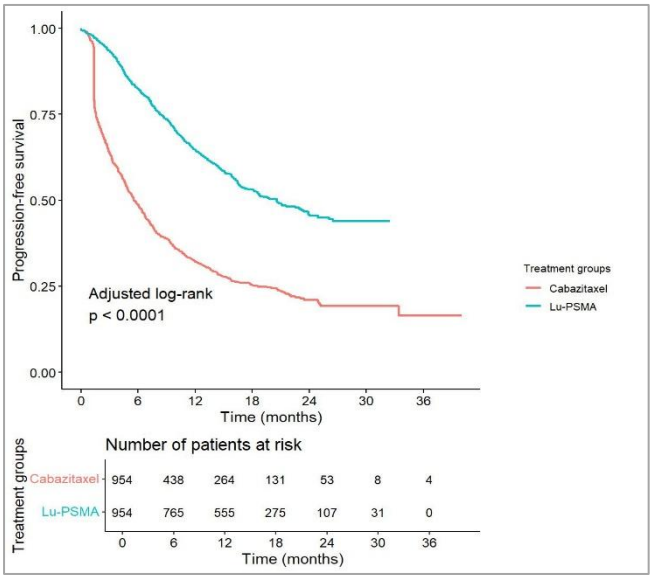


Figure S3. Adjusted OS (matched cohort)



OS: overall survival, **Lu-PSMA**: Lutetium-177-PSMA-617

Figure S4. Adjusted PFS (matched cohort)



PFS: progression-free survival, **Lu-PSMA**: Lutetium-177-PSMA-617

CHAPTER 5: Synthesis, Implications, and Future Directions

5.1 Summary of Findings

This dissertation generated the first most comprehensive, US-based real-world comparative effectiveness and value evidence across the modern treatment continuum for advanced prostate cancer. In Aim 1, all three androgen receptor pathway inhibitor (ARPI) doublets were associated with superior progression-free survival, time to mCRPC progression, and time to next treatment compared with docetaxel doublet, while overall survival was statistically comparable across all four regimens. No clinically meaningful differences were detected among the three ARPIs. In Aim 2, despite the longer survival projected for enzalutamide and apalutamide, abiraterone was the most cost-effective first-line strategy across every evaluated willingness-to-pay threshold, driven primarily by the availability of generic abiraterone; docetaxel was dominated by abiraterone, and apalutamide was dominated by enzalutamide. In Aim 3, lutetium-177 PSMA-617 was associated with significantly longer overall and progression-free survival than cabazitaxel in mCRPC patients previously treated with docetaxel and at least one ARPI, providing the first US real-world evidence to address a comparison that the pivotal VISION trial did not.

Together, these three studies address key treatment decisions across the metastatic prostate cancer continuum: ARPIs deliver clinical benefit at the front line, generic abiraterone delivers that benefit at the lowest cost, and Lu-PSMA delivers a meaningful survival advantage over cabazitaxel for patients who progress through that front-line care.

5.2 Clinical Implications

For practicing oncologists and urologists, the findings reinforce that ARPI doublets may be considered over docetaxel as first-line choice for most patients with mHSPC. The absence of detectable differences among individual ARPIs is a clinically reassuring result, supporting treatment selection based on tolerability, cost, dosing convenience, and patient preference

rather than differential effectiveness. For patients in whom oral therapy is undesirable or contraindicated, docetaxel remains a reasonable option, but its inferior progression-free survival should be communicated. In the post-docetaxel, post-ARPI mCRPC setting, the Aim 3 findings support Lu-PSMA as a preferred option over cabazitaxel for patients with PSMA-avid disease, particularly those for whom cabazitaxel toxicity is a meaningful concern.

5.3. Methodological Contributions

Methodologically, this dissertation demonstrates the feasibility and value of applying the target trial emulation framework with overlap and ATT propensity score weighting to high-dimensional administrative claims data for comparative oncology questions where head-to-head trials are unlikely to be conducted. Overlap weighting in the four-arm mHSPC analysis achieved exact covariate balance and emphasized the subpopulation in clinical equipoise, addressing a recurring criticism of inverse-probability weighting in multi-treatment comparisons. The decision to anchor the cost-effectiveness model in propensity-weighted real-world survival rather than trial-derived efficacy estimates illustrates how observational evidence and decision-analytic modelling can be productively integrated when the policy question concerns routine-care effectiveness rather than ideal-conditions efficacy.

5.4. Policy Implications

The policy implications are immediate. The Inflation Reduction Act requires the Centers for Medicare and Medicaid Services to consider comparative clinical effectiveness and unmet medical need when negotiating maximum fair prices, and enzalutamide has already been selected for negotiation with prices effective January 2027. The Aim 1 finding that enzalutamide does not meaningfully outperform generic abiraterone on overall survival in routine US practice, combined with the Aim 2 finding that enzalutamide is dominated on cost-effectiveness grounds at any plausible willingness-to-pay threshold, provides directly relevant evidence for the negotiation process and for downstream value-assessment bodies such as the

Institute for Clinical and Economic Review. As Lu-PSMA utilization expands and future negotiation cycles approach, the Aim 3 findings will similarly inform the evidence base on which negotiated pricing is determined.

5.5. Limitations

Several limitations should be considered when interpreting this work. Administrative claims data lack direct clinical measures such as PSMA-PET imaging characteristics, performance status, Gleason score, and PSA kinetics, and residual confounding by unmeasured prognostic factors cannot be fully excluded despite extensive propensity score adjustment. Disease progression in claims is necessarily defined by surrogate events (treatment change, new systemic therapy initiation) rather than radiographic or biochemical criteria, which may underestimate or misclassify true progression. The Komodo Health database, although large and nationally distributed, may not be fully representative of the US Medicare population, and follow-up duration limits the maturity of overall survival estimates for the most recently approved regimens. The cost-effectiveness analysis adopted a US healthcare sector perspective and did not capture indirect costs, productivity losses, or caregiver burden. Finally, the rapidly evolving treatment landscape, including emerging triplet regimens, novel PSMA-targeted agents, and PARP inhibitors for biomarker-defined subgroups, means that today's comparative evidence will require periodic updating.

5.6. Future Directions

Several extensions follow naturally from this work. First, longer-term follow-up may be considered to refine overall survival estimates and capture late-emerging differences between regimens. Second, subgroup analyses by molecular features such as homologous recombination repair mutation status, by PSMA-PET expression, and by metastatic volume and timing would help identify patients most likely to benefit from specific regimens. Third, comparative effectiveness and value of triplet therapies (ADT plus docetaxel plus an ARPI)

not evaluated here represents an important next question as triplet regimens diffuse into clinical practice. Fourth, linking claims data to electronic health records, registries, or PSMA-PET imaging databases would address several of the residual confounding limitations and enable richer subgroup analyses. Finally, prospective monitoring of utilization, outcomes, and prices in the post-IRA negotiation environment will be essential to evaluate the real-world impact of federal price negotiation on access, adherence, and outcomes for patients with advanced prostate cancer.

5.7. Concluding Remarks

Advanced prostate cancer remains a leading cause of cancer mortality among US men, but the past decade has produced a remarkable expansion of effective therapies. Translating that scientific progress into optimal care requires evidence not only that new agents work under trial conditions, but that clinicians, payers, and policymakers can choose wisely among them in routine practice. By generating real-world comparative effectiveness and value evidence across the modern mHSPC and mCRPC treatment continuum, this dissertation contributes evidence directly applicable to the clinical, economic, and policy decisions.