Cost-Effectiveness of Novel Androgen Receptor Inhibitors in Metastatic Castration-Sensitive Prostate Cancer: A U.S. Analysis Incorporating Two-Way Sensitivity Assessment

Poster Code: EE482

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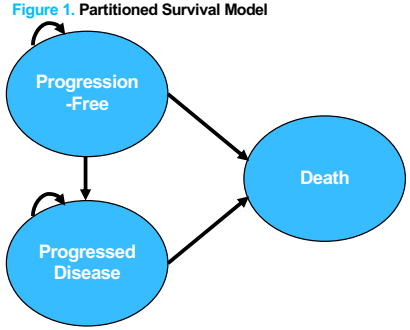
BACKGROUND

- Prostate cancer is the most commonly diagnosed malignancy among men and a leading cause of cancer-related death worldwide, with a substantial burden in the United States (U.S.) that contributes to a large and growing impact for health systems.[1]
- Metastatic castration sensitive prostate cancer (mCSPC) refers to advanced disease that remains responsive to androgen deprivation therapy (ADT), including both de novo and recurrent presentations, and represents a key opportunity for treatment intensification.[2]
- Pivotal trials demonstrated survival benefits for androgen receptor pathway inhibitor (ARPI) intensification of ADT, establishing these combinations as first-line standard of care for many patients, although comparative effectiveness among ARPI doublets remains uncertain in the absence of head-to-head trials.[3,4]
- Despite several economic evaluations of ARPI-based treatment strategies, comparative evidence for darolutamide plus ADT (DARO+ADT) without concomitant docetaxel versus other ARPI doublets in the U.S. setting remains limited, particularly in analyses that explicitly link discontinuation and downstream therapy use to long-term costs and outcomes.
- A cost-effectiveness analysis (CEA) showed DARO+ADT to be cost-effective against enzalutamide plus ADT (ENZ+ADT) and dominated apalutamide plus ADT in progression-free mCSPC (**Table 1**).[5]

OBJECTIVE

This analysis extended the CEA by evaluating cost-effectiveness under alternative assumptions for on-treatment and off-treatment utilities in mCSPC.

Figure 1. Partitioned Survival Model



METHODS

CEA Study Design

- A partitioned survival model (**Figure 1**) was developed from a U.S. healthcare sector perspective over a lifetime horizon.
- Progression-free (PFS) and overall survival (OS) informed health-state occupancy (mCSPC, progressed disease, death), with comparative outcomes derived from a network meta-analysis (NMA).[6]
- Direct medical costs (2025 USD) and quality-adjusted life years (QALYs) were discounted at 3% annually.
- Incremental cost-effectiveness ratios (ICERs) were evaluated at a $150,000/QALY threshold.

Model Inputs

- Clinical efficacy for DARO+ADT was sourced from the phase III ARANOTE trial, with comparative PFS and OS for ENZ+ADT and APA+ADT estimated using NMA-derived hazard ratios.
- Grade ≥3 adverse events (AEs), treatment discontinuation, and subsequent therapy use were informed by pivotal trials, NMA-based rate ratios, and real-world U.S. treatment patterns, respectively.
- Direct medical costs included drug acquisition and administration, AE management, subsequent therapy, and end-of-life care, with prices sourced from Red Book and published U.S. literature and inflated to 2025 USD.
- Health-state utilities for mCSPC and mCRPC were obtained from published sources, with per-cycle AE disutilities applied based on event frequency and severity. Disutilities were applied consistently and specifically across treatments.

Two-Way Sensitivity Analyses

- In the base case, off-treatment utility for the mCSPC state was assumed equal to on-treatment utility due to limited direct evidence.
- However, differences in treatment tolerability, AEs, and discontinuation, particularly when discontinuation leads to periods of untreated disease, may meaningfully affect patient quality of life.
- Two-way sensitivity analyses explored the impact of varying off-treatment mCSPC state utility alongside relative baseline utilities of ENZ+ADT and APA+ADT compared with DARO+ADT.

Table 1. Lifetime Cost-Effectiveness Results

Intervention	Cost ($)	Δ Cost ($)	QALYs	Δ QALYs	ICER ($/QALYs)	NMB ($150K WTP)
DARO + ADT	1,055,229	-	4.182	-	-	-
ENZ + ADT	1,042,666	12,564	4.035	0.148	**85,108**	9,579
APA + ADT	1,059,522	(4,293)	3.990	0.192	**Dominant**	33,153

ADT, Androgen Deprivation Therapy; **APA**, Apalutamide; **DARO**, Darolutamide; **ENZ**, Enzalutamide; **ICER**, Incremental Cost-Effectiveness Ratio; **NMB**, Net Monetary Benefit; **QALY**, Quality-Adjusted Life-Year; **ICER**, Incremental Cost-Effectiveness Ratio; **WTP**, Willingness-to-Pay

RESULTS

- DARO+ADT remained cost-effective across all plausible combinations of lower ENZ+ADT-treated utility values and increasing off-treatment disutility in mCSPC, with ICERs as low as $10,722 (**Table 2**) under plausible assumptions.
- DARO+ADT consistently dominated APA+ADT across all plausible scenarios that combined reduced utility while on APA with additional off-treatment disutility (**Table 3**).

LIMITATIONS

- This analysis relied on indirect treatment comparisons using hazard ratios from a NMA rather than head-to-head trial data, introducing uncertainty in relative efficacy estimates and reliance on proportional hazards assumptions.
- Parametric survival modeling and extrapolation beyond trial follow-up may not fully capture long-term outcomes, particularly for newer ARPIs with limited duration of follow-up.
- Model inputs were informed by clinical trial populations that may differ from patients treated in routine practice, as eligibility criteria can limit variability in comorbidities, disease burden, and performance, which may influence treatment effectiveness and cost-effectiveness outcomes.
- Post-progression therapies and associated costs were modeled using real-world treatment distributions; however, variation in treatment patterns and drug pricing across institutions and payers may limit generalizability of the findings.[7,8]
- Additional uncertainty arises from structural model assumptions, including independent parametric fitting of survival curves and capped background mortality.

CONCLUSIONS

- DARO+ADT was cost-effective versus ENZ+ADT and dominated APA+ADT in mCSPC across a range of plausible utility assumptions.
- Results were robust to variation in off-treatment utility and treatment-related differences in tolerability, discontinuation and AEs.
- These findings highlight the importance of incorporating treatment-specific utility differences, which may not be fully captured in conventional CEAs.
- DARO+ADT represents a clinically and economically favorable first-line ARPI option for patients with mCSPC.

Table 2. Two-way sensitivity analysis of ENZ vs DARO ICERs: mCSPC off-treatment utility and utility of other ARPIs relative to DARO

ICER vs. ENZ	mCSPC utility off-treatment, as a percentage of mCSPC utility						
$85,108	100%	90%	83%	70%	60%	50%	40%
mCSPC other ARPI utility: 100%	$85,108	$73,834	$67,569	$58,370	$52,837	$48,262	$44,416
98%	$53,120	$48,498	$45,714	$41,309	$38,459	$35,977	$33,795
95%	$38,609	$36,108	$34,542	$31,966	$30,232	$28,677	$27,274
93%	$30,325	$28,760	$27,758	$26,070	$24,905	$23,840	$22,862
90%	$24,968	$23,897	$23,201	$22,010	$21,174	$20,399	$19,679
88%	$21,219	$20,441	$19,929	$19,044	$18,415	$17,826	$17,274
85%	$18,449	$17,858	$17,466	$16,783	$16,292	$15,830	$15,392
83%	$16,319	$15,855	$15,545	$15,001	$14,608	$14,235	$13,881
75%	$12,121	$11,863	$11,688	$11,378	$11,151	$10,932	$10,722

Table 3. Two-way sensitivity analysis of APA vs DARO ICERs: mCSPC off-treatment utility and utility of other ARPIs relative to DARO

ICER vs. APA	mCSPC utility off-treatment, as a percentage of mCSPC utility						
-$22,313	100%	90%	83%	70%	60%	50%	40%
mCSPC other ARPI utility: 100%	-$22,313	-$19,025	-$17,246	-$14,695	-$13,193	-$11,970	-$10,955
98%	-$15,211	-$13,608	-$12,673	-$11,239	-$10,339	-$9,572	-$8,912
95%	-$11,538	-$10,592	-$10,017	-$9,099	-$8,500	-$7,975	-$7,511
93%	-$9,294	-$8,670	-$8,281	-$7,644	-$7,216	-$6,834	-$6,491
90%	-$7,781	-$7,339	-$7,058	-$6,590	-$6,270	-$5,979	-$5,715
88%	-$6,691	-$6,362	-$6,150	-$5,791	-$5,542	-$5,314	-$5,104
85%	-$5,870	-$5,614	-$5,448	-$5,165	-$4,966	-$4,783	-$4,612
83%	-$5,227	-$5,024	-$4,891	-$4,661	-$4,499	-$4,347	-$4,206
75%	-$3,936	-$3,819	-$3,742	-$3,606	-$3,508	-$3,415	-$3,327

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Presented at ISPOR 2026, Sunday, May 17 - Wednesday, May 20, 2026, Philadelphia, PA

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