Cost implications of adverse event profiles in second generation androgen receptor inhibitor (SGARI) treatments for non-metastatic castration resistant prostate cancer (nmCRPC)

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BACKGROUND

- Prostate cancer is the most commonly diagnosed cancer among men, with 1.4 million cases diagnosed worldwide in 2020.[1]
- 10-20% of prostate cancer patients develop castration-resistant prostate cancer (CRPC) within 5 years.[2]
- Non-metastatic CRPC (nmCRPC) is defined by rising levels of serum prostate-specific antigen and an absence of detectable metastases on conventional imaging in patients receiving androgen-deprivation therapy. [2]
- Patients with nmCRPC are at risk for progression to metastatic disease, which is associated with higher morbidity and mortality. [2]
- Second generation androgen receptor inhibitor (SGARI) treatments are the primary treatment options available for nmCRPC.
- In nmCRPC, treatment efficacy is a central factor when making treatment decisions, but adverse event profiles and costs are also important to consider for patients and physicians.

OBJECTIVE

- To compare adverse event (AE) profiles, costs, and metastasis-free life years (MFLY) gained for patients receiving SGARI therapies to treat nmCRPC.

Table 1. Model Overview

Category	Details
Population	• Adult men with nmCRPC
Interventions	• Darolutamide • Apalutamide • Enzalutamide
Clinical Inputs	• Metastasis-free survival (MFS) sourced from the respective clinical trial Kaplan-Meier (KM) curves[3-5] • Rates of GRADE 3-5 AEs from the respective clinical trials[3-5] • Treatment discontinuation rates from the respective clinical trials[3-5]
Economic Inputs	• Hospitalization costs for GRADE 3-5 AEs from 2018 Healthcare Cost and Utilization Project (HCUP) data,[6] inflated to 2021 USD
Outcomes	• Per-patient metastasis-free life years (MFLY) gained derived from clinical trials[3-5] • Per-patient AE costs derived from clinical trials and HCUP data
Setting	• United States
Time Horizon	• Three years
Discount Rate	• 3 percent

METHODS

Model Framework

- Cohort-based Markov model with three-year time horizon to simulate the treatment effects of darolutamide, enzalutamide, and apalutamide.
- Using a three-month cycle time, the model tracked the percent of patients still on treatment, discontinued due to AEs, and metastasized or died.
- The model calculated results for three AE scenarios (AS).
  - Baseline: grade 3-5 AEs reported in all 3 trials, minimum 1% incidence in one treatment arm.
  - AS1: grade 3-5 AEs reported in at least 2 trials, minimum 1% incidence in one treatment arm.
  - AS2: grade 3-5 AEs in all 3 trials, no incidence threshold.

Data Sources

- The data for MFS was obtained by digitizing the MFS KM curves from the following clinical trials: ARAMIS for darolutamide,[3] SPARTAN for apalutamide,[4] and PROSPER for enzalutamide.[5]
- Both the drug of interest and placebo arms were digitized to obtain the incremental MFS for each treatment, relative to its respective placebo.
- Incremental AE rates and MFLY were estimated from each treatment's pivotal trial,[3-5] compared to each respective placebo arm (Table 2).
- Grade 3-5 AE were selected as the AEs more likely to incur costs through associated hospitalizations.[3-5]
- Drug discontinuation rates were also extracted from each trial.[3-5]
- AE costs were calculated using hospitalization charges sourced from the Healthcare Cost and Utilization Project 2018 data[6], inflated to 2021 USD using the Consumer Price Index (Table 2).

Calculations

- Incremental AE rates and MFLY were estimated from each treatment's pivotal trial, compared to each respective placebo arm.
- Total MFLYs were calculated as the sum of all patients on treatment at the end of each quarter.
- Net MFLYs were calculated as the difference between the total MFLY of the treatment and placebo arms of each respective therapy.
- AEs were calculated by multiplying the AE rates by the number of patients on treatments to ascertain the simulated number of events.
- The rate of AEs was estimated from the trials per quarter.
  - Study length was 44 months,[3] 40 months,[4] and 39 months[5] for darolutamide, apalutamide, and enzalutamide respectively, resulting in study lengths of 14.67, 13.33, and 13.00 quarters respectively.
- The number of events was then multiplied with the HCUP unit costs. This resulted in the cost attributed to AEs. Costs were discounted at 3%. Net costs for each therapy were the difference between the intervention and placebo arm discounted AE costs.

RESULTS

- AEs included in the baseline scenario were diarrhea, fall, fatigue (excluding asthenia), hypertension, and weight loss.
- The highest incremental AE rate (compared to placebo) reported in each clinical trial was 0.9% (hypertension) for darolutamide, 3.0% (hypertension) for enzalutamide, and 4.9% (rash) for apalutamide (Table 2).
- Reflective of consistently lower rates of AEs, incremental per-patient AE costs over the 3-year time horizon were lowest for darolutamide in all three scenarios.
  - Baseline: darolutamide, $53; enzalutamide $432; apalutamide, $517.
  - AS1: darolutamide, $64; enzalutamide $670; apalutamide, $1,140.
  - AS2: darolutamide, $69; enzalutamide $506; apalutamide, $553 (Figure 1 and Table 3).
- MFLY gained were similar across the treatments, with darolutamide having the greatest per-patient at 0.41 compared to apalutamide (0.39) and enzalutamide (0.38) (Table 3).

Table 3. Net MFLY and AE costs (in 2021 USDs)

Treatment	Net MFLY	Net AE Cost Baseline	Net AE Cost AS1	Net AE Cost AS2
Darolutamide	0.41	$53	$64	$69
Apalutamide	0.39	$517	$1,140	$553
Enzalutamide	0.38	$432	$670	$506

Figure 1. Per-patient AE costs (by scenario) (in 2021 USD)

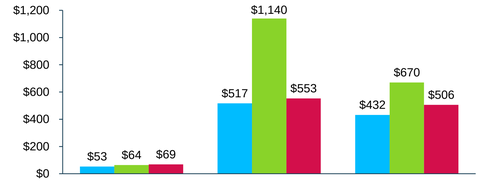

Table 2. AE rates, costs, and scenarios

Adverse Event	Darolutamide Intervention[3]	Darolutamide Placebo[3]	Apalutamide Intervention[4]	Apalutamide Placebo[4]	Enzalutamide Intervention[5]	Enzalutamide Placebo[5]	AE Cost (in 2021 USD)[6]	AE Scenario
Diarrhea	0.00%	0.20%	1.00%	0.50%	0.32%	0.43%	$8,096	Baseline, AS1, AS2
Fall	0.80%	0.70%	1.70%	0.80%	1.00%	1.00%	$13,647	Baseline, AS1, AS2
Fatigue (not including asthenia)	0.40%	0.90%	0.90%	0.30%	3.00%	1.00%	$13,169	Baseline, AS1, AS2
Hypertension	3.10%	2.20%	14.30%	11.80%	5.00%	2.00%	$8,923	Baseline, AS1, AS2
Weight loss	0.00%	0.00%	1.10%	0.30%	0.22%	0.00%	$10,941	Baseline, AS1, AS2
Bone fracture	0.90%	0.90%	2.70%	0.80%	--	--	$23,971	AS1
Fatigue (including asthenia)	0.60%	1.10%	--	--	4.00%	1.22%	$12,155	AS1
Rash	0.10%	0.00%	5.20%	0.30%	--	--	$8,611	AS1
Urinary retention	1.60%	2.00%	--	--	0.43%	1.00%	$7,615	AS1
Urinary tract infection	0.60%	0.50%	--	--	1.00%	1.00%	$8,092	AS1
Arthralgia	0.30%	0.40%	0.00%	0.00%	0.11%	0.22%	$7,766	AS2
Dizziness	0.20%	0.20%	0.60%	0.00%	0.43%	0.00%	$6,806	AS2
Memory/ Mental impairment	0.00%	0.00%	0.00%	0.00%	0.11%	0.00%	$9,674	AS2
Nausea	0.20%	0.00%	0.00%	0.00%	0.32%	0.00%	$7,647	AS2
Pneumonia	0.10%	0.00%	0.10%	0.00%	0.43%	0.00%	$11,310	AS2

CONCLUSIONS

- This study showed that darolutamide has the lowest rates of AEs causing hospitalization, regardless of how the AEs were selected for inclusion, resulting in significantly fewer per-patient AE costs than apalutamide or enzalutamide.
- Overall MFLY gained were similar across the three treatments, which increases the importance of examining the AE profiles across treatments.
- While having similar efficacy to the other drugs, darolutamide has a better AE profile than apalutamide and enzalutamide, thus reducing costs due to hospitalization in these patients.
- The lower costs may translate to significant savings for payers and improved patient quality of life due to avoidance of trips to the hospital.

STRENGTHS AND LIMITATIONS

- A strength of this study is the addition of MFLY as a measure of added benefit to patients.
- The AE scenarios also demonstrate that the selection of AEs for inclusion does not greatly impact the outcome of the per-patient AE costs.
- This study was limited by the lack of head-to-head data across all three treatments or an indirect treatment comparison linking all three treatments. As a result, the treatments cannot be directly compared to each other in this analysis.
- This study did not quality adjust the life year measure to serve as a simpler measure of benefit, so these results may underestimate the impact of these therapies on patient quality of life.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians. 2021;71(3):209-249.
2. Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. International Journal of Clinical Practice. 2011;65(11):1180-1192.
3. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2019;380(13):1235-1246.
4. Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med. 2018;378(15):1408-1418.
5. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018;378(26):2465-2474.
6. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project [Bayer data on file] 2018.
7. Grochtdreis T, König HH, Dobruschkin A, von Amsberg G, Dams J. Cost-effectiveness analyses and cost analyses in castration-resistant prostate cancer: A systematic review. PloS one. 2018;13(12):e0208063.
8. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value in Health. 2013;16(2):231-250.
9. Halabi S, Jiang S, Terasawa E, et al. Indirect Comparison of Darolutamide versus Apalutamide and Enzalutamide for Nonmetastatic Castration-Resistant Prostate Cancer. Journal of Urology. 2021;206(2):298-307.
10. Appukkuttan S, Tangirala K, Babajanyan S, Wen L, Simmons S, Shore N. A Retrospective Claims Analysis of Advanced Prostate Cancer Costs and Resource Use. PharmacoEconomics - Open. 2020;4(3):439-447.

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