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Real-World Head-to-Head Analysis of Overall Survival in Patients with Metastatic Castration-Sensitive Prostate Cancer Initiated on Apalutamide versus Enzalutamide in the United States

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Key Takeaway

By 24 months post-treatment initiation, patients with mCSPC initiating apalutamide had a statistically significant 23% reduction in the risk of death when compared to patients initiating enzalutamide

Conclusions

In patients with mCSPC, patients treated with apalutamide were 23% less likely to have died by 24 months post-treatment initiation compared to those treated with enzalutamide

Overall survival observed in the apalutamide cohort of this real-world study by 24 months is consistent with overall survival observed in the Phase 3 TITAN study[3]

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Poster

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Disclosures

N. Shore is an employee of Carolina Urologic Research Center and has received consulting fees from Janssen Scientific Affairs, LLC, a Johnson & Johnson company. B. Lowentritt is an employee of Chesapeake Urology Associates and has received consulting fees from Janssen Scientific Affairs, LLC, a Johnson & Johnson company. I. Khilfeh, S. Du, and L. Ellis are employees of Janssen Scientific Affairs, LLC, a Johnson & Johnson company and stockholders of Johnson & Johnson. C. Rossi, F. Kinkead, L. Diaz, and D. Pilon are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Janssen Scientific Affairs, LLC, a Johnson & Johnson company. M. Bilen is an employee of the Winship Cancer Institute of Emory University and has received consulting fees from Janssen Scientific Affairs, LLC, a Johnson & Johnson company.

Background

- Apalutamide and enzalutamide are androgen receptor pathway inhibitors (ARPIs), approved for use in combination with androgen deprivation therapy (ADT) for the treatment of metastatic castration-sensitive prostate cancer (mCSPC)[1,2]
- Phase 3 trials of apalutamide (TITAN) and enzalutamide (ARCHES) demonstrated statistically significant reduction in disease progression and death as compared to ADT alone in patients with mCSPC[3-6]
- To date, however, no clinical trials or real-world studies have directly compared progression or survival outcomes between these agents approved in patients with mCSPC

Objectives

- To compare the proportion of patients surviving by 24 months for patients with mCSPC who newly initiated apalutamide versus enzalutamide
- Null hypothesis: In ARSI-naïve patients with mCSPC, overall survival by 24 months post-apalutamide initiation is not different than overall survival by 24 months post-enzalutamide initiation
- Alternative hypothesis: In ARSI-naïve patients with mCSPC, overall survival by 24 months post-apalutamide initiation is different than overall survival by 24 months post-enzalutamide initiation

Methods

- This study attempted to apply best practices from the US Food and Drug Administration guidance document entitled "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry"[7]

Data sources

- Clinical data from Precision Point Specialty (PPS) Analytics collected as part of routine clinical care from community-based urology practices in the US linked with administrative claims data from the Komodo Research Database (KRD; study period: 16 December 2018 - 31 December 2023)
- Electronic medical record (EMR) data from PPS were robust and captured longitudinal laboratory data including prostate-specific antigen (PSA) test results, and castration resistance, which were not available in administrative claims data, and necessary to identify mCSPC patients
- Mortality data from the KRD were updated monthly and captured >90% of all oncology-specific US deaths as identified by the US Centers for Disease Control and Prevention.[8] These data are curated from multiple third-party sources that aggregate their data from national and state governments, public listings (e.g., cemetery, funeral home), private claims and obituary data
- Data were de-identified and Health Insurance Portability and Accountability Act (HIPAA) compliant

Study design

- A power calculation was performed to verify that the sample size was sufficient to detect statistically significant differences in survival between the apalutamide and enzalutamide cohorts
- A retrospective longitudinal causal analysis utilizing propensity score-weighted cohorts of ARPI-naïve patients with mCSPC initiated on apalutamide or enzalutamide was conducted, following an intention-to-treat design
- Patients were assigned to mutually exclusive treatment cohorts based on the first dispensation or paid pharmacy claim for apalutamide or enzalutamide
- The index date was defined as the first dispensation or paid pharmacy claim for apalutamide or enzalutamide on or after 16 December 2019 (the US Food and Drug Administration approval date for enzalutamide[2] which followed apalutamide approval on 17 September 2019[1])
- Baseline patient characteristics were evaluated in the 12 months preceding the index date
- The observation period spanned from the index date to the latter of end of clinical activity (in PPS) or claims activity (in KRD), both no later than 31 December 2023
- Treatment patterns were observed from the index date for a period spanning up to 24 months

Patient selection criteria

- Patients were assessed as having mCSPC if they had a diagnosis code or clinical indicator for bone, nodal, or visceral metastasis, in the absence of castration resistance prior to or on the index date. Castration resistance was assessed based on a previously published algorithm incorporating presence of ADT (as identified in both PPS and KRD)[9] and PSA levels and clinical notes abstracted from the EMR by PPS
- Concurrent use of ADT was not required for patients to be included in either the apalutamide or enzalutamide cohort

Figure 1: Patient Flowchart

ARPI: androgen receptor pathway inhibitor; mCSPC: metastatic castration-sensitive prostate cancer; PARP: poly ADP ribose polymerase.

Study outcome

- The primary outcome was the proportion of patients who survived by 24-months post-index ARPI initiation

Statistical analysis

- Inverse probability of treatment weighting (IPTW), based on the propensity score (PS), was used to account for differences in baseline characteristics between the apalutamide and enzalutamide cohorts[10]
- The PS was obtained from a logistic regression model where index treatment was the dependent variable and with the following baseline characteristics as independent variables: age, race, geographic region, payer type, index year, time between metastasis and index date, time between initial PC diagnosis and index date, metastasis type, Quan Charlson Comorbidity index, *de novo* PC diagnosis, ADT use overlapping index date, prior first-generation antiandrogens, prior chemotherapy, baseline PSA level, and initial Gleason score
- Balancing of baseline characteristics between treatment cohorts after weighting was confirmed by standardized differences <10% which indicates balance[11]
- Weighted Kaplan-Meier analysis was used to assess the proportion of patients surviving by 24-months post-index
- Weighted Cox proportional hazards models were used to evaluate the causal relationship between index treatment and overall survival

Results

Baseline characteristics

- Overall, 1,810 patients with mCSPC who initiated apalutamide and 1,909 patients with mCSPC who initiated enzalutamide were identified (**Figure 1**)
- Baseline patient characteristics were generally well-balanced between the weighted cohorts, with standardized differences <10% (**Table 1**)

Table 1: Baseline Characteristics

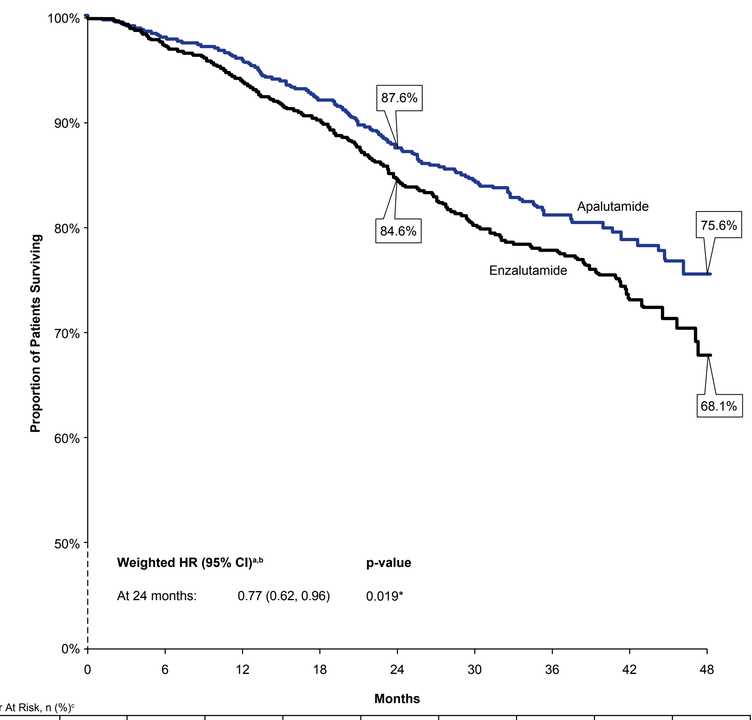
	Non-Weighted Population			Weighted Population[a]		
	Apalutamide N=1,810	Enzalutamide N=1,909	Standardized Difference, %	Apalutamide N=1,810	Enzalutamide N=1,909	Standardized Difference, %
Age, mean ± SD [median]	72.9 ± 9.2 [73.0]	73.0 ± 9.4 [73.0]	0.9	73.0 ± 9.2 [73.0]	73.0 ± 9.3 [73.0]	0.1
Race, n (%)						
White	1,096 (60.6)	1,107 (58.0)	5.2	1,083 (59.8)	1,135 (59.4)	0.8
Black or African American	400 (22.1)	449 (23.5)	3.4	407 (22.5)	432 (22.7)	0.3
Hispanic or Latino	133 (7.3)	150 (7.9)	1.9	135 (7.5)	146 (7.6)	0.6
Other	68 (3.8)	101 (5.3)	7.4	79 (4.4)	88 (4.6)	1.2
Unknown	113 (6.2)	102 (5.3)	3.9	105 (5.8)	108 (5.7)	0.7
Geographic region, n (%)						
South	1,031 (57.0)	975 (51.1)	11.8	986 (54.5)	1,021 (53.5)	2.0
Midwest	409 (22.6)	472 (24.7)	5.0	429 (23.7)	458 (24.0)	0.6
Northeast	200 (11.0)	288 (15.1)	12.0	225 (12.4)	250 (13.1)	1.9
West	170 (9.4)	174 (9.1)	1.0	170 (9.4)	181 (9.5)	0.3
Index year, n (%)						
2019-2020	336 (18.6)	510 (26.7)	19.6	391 (21.6)	434 (22.7)	2.7
2021	447 (24.7)	562 (29.4)	10.7	488 (27.0)	524 (27.5)	1.2
2022	519 (28.7)	469 (24.6)	9.3	493 (27.3)	511 (26.7)	1.2
2023	508 (28.1)	368 (19.3)	20.8	438 (24.2)	440 (23.1)	2.7
Time between metastasis and index date, months, mean ± SD [median]	9.2 ± 18.2 [2.3]	12.1 ± 18.8 [3.4]	15.8	10.1 ± 18.2 [2.6]	10.6 ± 18.0 [2.7]	2.7
Time between PC diagnosis and index date, months, mean ± SD [median]	39.5 ± 47.1 [15.4]	40.9 ± 46.7 [21.9]	3.0	39.4 ± 46.6 [16.8]	39.8 ± 46.8 [17.8]	1.0
Metastasis type[b], n (%)						
Bone	1,258 (69.5)	1,448 (75.9)	14.3	1,301 (71.9)	1,390 (72.8)	2.1
Nodal	936 (51.7)	856 (44.8)	13.8	887 (49.0)	918 (48.1)	1.8
Visceral	324 (17.9)	453 (23.7)	14.4	356 (19.7)	398 (20.8)	2.9
Metastasis in multiple sites	521 (28.8)	445 (23.3)	12.5	485 (26.8)	498 (26.1)	1.6
Quan-CCI, mean ± SD [median]	8.5 ± 3.0 [8.0]	8.7 ± 3.1 [9.0]	7.2	8.6 ± 3.0 [8.0]	8.6 ± 3.1 [9.0]	1.1
***De novo* PC[c], n (%)**	1,004 (55.5)	1,073 (56.2)	1.5	1,017 (56.2)	1,072 (56.2)	0.1
Concurrent use of ADT with index ARPI[d], n (%)	1,480 (81.8)	1,411 (73.9)	19.0	1,434 (79.2)	1,486 (77.8)	3.3
Duration of ADT episode overlapping with index date, months, mean ± SD [median]	4.4 ± 8.6 [1.8]	5.9 ± 9.4 [2.4]	15.7	4.5 ± 8.6 [1.8]	5.5 ± 9.3 [2.2]	9.6
Prior use of first-generation ARPI[e], n (%)	279 (15.4)	470 (24.6)	23.2	350 (19.4)	393 (20.6)	3.0
Prior use of chemotherapy[f], n (%)	29 (1.6)	64 (3.4)	11.3	41 (2.3)	49 (2.6)	2.0
Most recent PSA level, ng/mL, n (%)						
≤0.2	309 (17.1)	242 (12.7)	12.4	281 (15.5)	283 (14.8)	2.0
>0.2 to ≤2	298 (16.5)	285 (14.9)	4.2	291 (16.1)	302 (15.8)	0.8
>2 to ≤5	206 (11.4)	156 (8.2)	10.8	180 (9.9)	181 (9.5)	1.5
>5 to ≤10	186 (10.3)	138 (7.2)	10.8	165 (9.1)	165 (8.6)	1.6
>10	541 (29.9)	544 (28.5)	3.1	541 (29.9)	563 (29.5)	0.8
Unknown	270 (14.9)	544 (28.5)	33.4	352 (19.5)	415 (21.7)	5.6
Initial Gleason score[g], n (%)						
≤6	107 (5.9)	101 (5.3)	2.7	101 (5.6)	108 (5.7)	0.3
7	357 (19.7)	282 (14.8)	13.1	323 (17.8)	326 (17.1)	2.1
8	251 (13.9)	259 (13.6)	0.9	256 (14.2)	267 (14.0)	0.4
9	388 (21.4)	403 (21.1)	0.8	383 (21.1)	405 (21.2)	0.1
10	52 (2.9)	68 (3.6)	3.9	60 (3.3)	64 (3.3)	0.1
Unknown	655 (36.2)	796 (41.7)	11.3	687 (37.9)	739 (38.7)	1.6

ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibitor; CCI: Charlson Comorbidity Index; PC: prostate cancer; PSA: prostate-specific antigen; SD: standard deviation.
Notes:
[a]Of note, the number of patients reported in this weighted population represents the sum of weights for the corresponding non-weighted patients, rounded to the nearest integer. The proportions displayed were calculated before the rounding and may be slightly different than if they were calculated based on rounded numbers.
[b]Types of metastases were defined at any time prior to (and including) the index date. Types of metastases were not mutually exclusive.
[c]*De novo* PC was defined as ≤180 days between first observed PC diagnosis and date of metastasis.
[d]Concurrent ADT use was defined as an episode of continuous ADT use overlapping with the index date (using a 60-day gap to define discontinuation).
[e]Prior use of first-generation ARPI was defined as any prescription for bicalutamide, nilutamide, or flutamide in the 12 months preceding the index date.
[f]Prior chemotherapy use was defined as administration at any time prior to (and excluding) the index date.
[g]Gleason score was evaluated at any time prior to and including the index date.

Overall survival

- By 24 months post-index, apalutamide patients had a statistically significant 23% reduction in their risk of death compared with patients initiated on enzalutamide (hazard ratio [HR]=0.77, 95% confidence interval [CI]: 0.62, 0.96; p=0.019; **Figure 2**)
- This result was consistent when evaluating overall survival using all available follow-up (HR=0.77, 95% CI: 0.64, 0.93; nominal p=0.008 [not adjusted for multiple comparison and statistical significance not established for time points beyond primary endpoint])

Figure 2: Comparison of Overall Survival among Patients with mCSPC



Number At Risk, n (%)[c]

Apalutamide	1,810 (100)	1,594 (88.1)	1,322 (73.0)	1,025 (56.6)	748 (41.3)	504 (27.8)	309 (17.1)	159 (8.8)	35 (1.9)
Enzalutamide	1,909 (100)	1,711 (89.6)	1,369 (71.7)	1,083 (56.7)	766 (40.2)	511 (26.8)	321 (16.8)	151 (7.9)	23 (1.2)

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; mCSPC: metastatic castration-sensitive prostate cancer; PC: prostate cancer; PSA: prostate-specific antigen.
*Significant at the 5% level.
Notes:
[a]Propensity scores were generated using probability estimates from a logistic regression models using the following predictors: age (continuous), race, geographic region, payer, year of index date, time between metastasis and index date (continuous and categorical), time between PC diagnosis and index date (continuous), *de novo* PC, ADT use overlapping with index date, first-generation antiandrogen use, chemotherapy use, types of metastases (bone, nodal, visceral, and metastasis in multiple sites), Quan-Charlson comorbidity index (continuous), most recent PSA level (categorical), and earliest Gleason score (categorical). Each patient was attributed an inverse-probability of treatment weight that was defined as follows: 1/(propensity score) for the apalutamide cohort and 1/(1-propensity score) for the enzalutamide cohort. Normalized inverse-probability of treatment weights were truncated at the 95th percentiles.
[b]A hazard ratio <1 indicates that the apalutamide cohort had a lower rate of death compared to the enzalutamide cohort.
[c]Of note, the number of patients reported in this weighted population represents the sum of weights for the corresponding non-weighted patients, rounded to the nearest integer. The proportions displayed were calculated before the rounding and may be slightly different than if they were calculated based on rounded numbers.

Treatment patterns

- The mean (median) follow-up period was 17.2 (20.1) months in patients who initiated apalutamide and 17.2 (20.1) months in patients who initiated enzalutamide
- The mean (median) duration of continuous index ARPI use, using a 90-day gap in treatment to define discontinuation, was 9.6 (6.9) months in patients who initiated apalutamide and 8.6 (6.4) months in patients who initiated enzalutamide

Limitations

- Miscoding or misclassification in the clinical record or through the administrative claims may introduce selection and information biases despite efforts to balance the study populations
- The database represents the community urology perspective and may not be representative of the entire population of patients with mCSPC in the US, which may limit the generalizability of the study in certain settings
- While comparisons with US Centers for Disease Control (CDC) estimates of overall survival has demonstrated that KRD captured >90% of all deaths in oncology settings between 2018 and 2023[8], it is possible that not all deaths are captured in the data
- Regression analyses could only adjust for documented covariates and unknown confounders may be present
- In phase 3 trials[4,6], overall survival was assessed at pre-specified numbers of events. In this study, survival was assessed by 24 months for evaluation of statistical comparison. Studies assessing longer follow-up in these patient cohorts may be needed to estimate the full magnitude of therapeutic effect for these agents

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