Attainment of Early, Deep Prostate-Specific Antigen Response in Metastatic Castration-Sensitive Prostate Cancer: A Comparison of Patients Initiated on Apalutamide or Enzalutamide

Benjamin Lowentritt[1], Dominic Pilon[2], Ibrahim Khilfeh[3], Carmine Rossi[2], Erik Muser[3], Frederic Kinkead[2], Dexter Waters[3], Lorie Ellis[3], Patrick Lefebvre[2]

[1]Chesapeake Urology, Towson, MD, USA; [2]Analysis Group, Inc., Montréal, QC, Canada; [3]Janssen Scientific Affairs, LLC, Horsham, PA, USA

BACKGROUND

- Studies have shown that men with metastatic castration-sensitive prostate cancer (mCSPC) continue to be treated with ADT alone despite evidence for next-generation androgen receptor inhibitors (ARIs), including apalutamide (APA) and enzalutamide (ENZ), demonstrating superior outcomes when used in combination with ADT[1-4]
- Rapid, deep, and durable reduction of prostate-specific antigen (PSA) in clinical trials of next-generation ARIs is associated with increased probability of achieving progression-free and/or overall survival outcomes, with patients achieving a 90% or greater reduction in PSA from baseline having the greatest probability of long-term benefit[5-10]
- There is currently no data comparing real-world PSA outcomes among patients with mCSPC using next-generation ARIs, APA or ENZ, in the United States (US)

OBJECTIVE

- To compare the proportion of patients with a PSA reduction >90% from baseline (PSA90 response) by 6 months and beyond for patients with mCSPC who are new users of apalutamide (APA) versus enzalutamide (ENZ)

NULL HYPOTHESIS

- There is no difference in the proportion of patients with mCSPC achieving a rapid, deep PSA90 response (>90% reduction from baseline) when treated with APA or ENZ

METHODS

Data Source

- Clinical data from Precision Point Specialty (PPS) Analytics collected as part of routine clinical care from 69 urology sites in the US (study period: 1 February 2017 - 5 March 2021)
- Data are de-identified and Health Insurance Portability and Accountability Act (HIPAA) compliant

Study Design

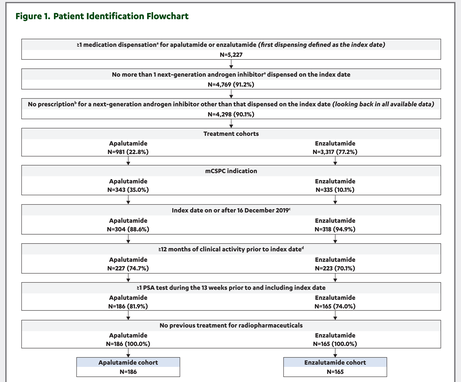
- A retrospective longitudinal propensity score-weighted cohort study in patients with mCSPC who were initiated on APA or ENZ
- Patients were assigned to mutually exclusive treatment cohorts based on the first dispensation of APA or ENZ
- Index date was defined as the first dispensation of APA or ENZ after 16 December 2019 (the US Food and Drug Administration approval date for ENZ which followed APA approval on 17 September 2019)
- Baseline patient characteristics were evaluated in the 12 months preceding the index date
- The observation period spanned from the index date to either index treatment discontinuation (using a 90-day treatment gap to define discontinuation), initiation of a different next-generation androgen inhibitor [i.e., APA, ENZ, darolutamide (DARO), or abiraterone acetate (ABI)] or the use of radiopharmaceuticals, end of clinical activity (including death), or end of data availability (5 March 2021), whichever occurred earliest

Patient Selection Criteria

- Patients were included in the study if they met the following inclusion criteria:
  - Male sex
  - ≥1 medication dispensation for APA or ENZ
  - Had evidence of metastatic prostate cancer defined by the presence of bone, nodal, or visceral metastasis prior to or on the index date
  - ≥18 years of age on the index date
  - ≥12 months of clinical activity prior to the index date
  - ≥1 PSA test during the 13 weeks prior to and including index date
- Patients were excluded from the study if they met any of the following exclusion criteria:
  - Index date prior to the US Food and Drug Administration approval for ENZ on 16 December 2019 (APA approved by US Food and Drug Administration on 17 September 2019)
  - Prior use of a next-generation androgen inhibitor before the index date or the use of ≥2 next-generation androgen inhibitors on the index date
  - Prior use of radiopharmaceuticals
  - Evidence of castration resistance (CR) prior to or on the index date, based on an algorithm utilizing presence of ADT and PSA levels[5] or an indicator for CR as reported in the clinical data

METHODS (cont'd)

Figure 1. Patient Identification Flowchart



mCSPC: metastatic castration-sensitive prostate cancer; PSA: prostate-specific antigen.

Notes:

[a]Agent identified at index date was based on medication dispensation only.

[b]To confirm that patients were newly initiated on a next-generation androgen inhibitor as identified through dispensations, prescription information was examined to exclude patients with prescriptions for next-generation androgen inhibitors prior to the index date.

[c]The Food and Drug Administration (FDA) approved enzalutamide as treatment for mCSPC on 16 December 2019.

[d]Continuous clinical activity was defined as the period from the first to last record in the clinical database. Patients with no observation period after the index date were excluded.

Study Outcomes

- Proportion of patients who achieved at least a 90% reduction in PSA (PSA90) from the baseline value by 6 months post-index
- Time to PSA90 response from the date of index treatment 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 APA and ENZ cohorts[11]
- The PS was obtained from a logistic regression model for APA or ENZ treatment assignment with the following baseline characteristics: age, race, index year, ADT use ±6 months, first-generation ARI use, most recent PSA level, most recent testosterone level, Gleason score, and time between metastasis and the index date
- Each patient was attributed a weight that was defined as follows: 1/PS for the APA cohort and 1/(1-PS) for the ENZ cohort. Weights were then normalized by using the mean weight and stabilized by truncating the weights to the 95th percentile of the distribution
- Consequently, the weighted sample sizes (i.e., post-IPTW) were different from the original sample sizes although the same patients contributed to the analysis
- 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 achieving PSA90 by 3-, 6-, 9-, and 12-months post-index, as well as the median time to PSA90
- Weighted Cox proportional hazards models were used to evaluate the causal relationship between index treatment and the likelihood of achieving PSA90
- Standard errors were estimated from a conventional variance estimator whose empirical coverage rates result in non-nominal 95% confidence intervals (CIs) and p-values. The conventional variance estimator does not account for the additional variability when estimating the IPTW[12]

RESULTS

Baseline Characteristics

- Before applying IPTW, a total of 351 (unweighted) patients were identified (186 APA patients and 165 ENZ patients) [**Figure 1**]
- After applying IPTW, the reweighted cohort sizes were 174 patients for APA and 177 patients for ENZ (total population 351)
- Baseline patient characteristics were generally well-balanced between the weighted cohorts, with standardized differences <10% [**Table 1**]
  - In both weighted cohorts, the mean age was 76 years, 71% were white, and the mean baseline PSA level was 18 ng/mL
  - The mean time between diagnosis of metastasis and index treatment initiation was 7 months in the APA cohort and 8 months in the ENZ cohort

Table 1. Baseline Characteristics

	Non-weighted Population			IPTW Population[a]		
	APA N=186	ENZ N=165	Standardized Difference[b]	APA Weighted N=174	ENZ Weighted N=177	Standardized Difference[b]
Age, mean ± SD [median]	76.2 ± 8.0 [76.0]	76.1 ± 7.7 [75.0]	1.4	76.1 ± 7.8 [76.0]	76.3 ± 8.0 [75.0]	2.5
Age group, n (%)						
≤60	3 (1.6)	2 (1.2)	3.4	3 (1.5)	2 (1.3)	1.3
61-70	49 (26.3)	38 (23.0)	7.7	44 (25.1)	43 (24.2)	2.0
71-80	78 (41.9)	83 (50.3)	16.9	79 (45.5)	82 (46.4)	1.8
≥81	56 (30.1)	42 (25.5)	10.4	49 (28.0)	50 (28.1)	0.2
Race, n (%)						
White	135 (72.6)	106 (64.2)	18.0	123 (71.0)	125 (70.5)	1.1
Black	32 (17.2)	35 (21.2)	10.2	31 (17.6)	32 (18.0)	1.0
Other	3 (1.6)	1 (0.6)	9.6	2 (1.0)	1 (0.5)	5.9
Unknown	16 (8.6)	23 (13.9)	16.9	18 (10.3)	19 (11.0)	2.1
Year of treatment initiation (index date), n (%)						
2019-2020	140 (75.3)	135 (81.8)	16.0	134 (77.2)	137 (77.1)	0.1
2021	46 (24.7)	30 (18.2)	16.0	40 (22.8)	41 (22.9)	0.1
Time between metastasis and treatment initiation, months, mean ± SD [median]	6.3 ± 12.7 [1.6]	8.4 ± 14.7 [2.2]	15.5	7.4 ± 14.0 [1.6]	7.6 ± 13.9 [1.9]	1.5
Prior use of ADT[c], n (%)	172 (92.5)	147 (89.1)	11.7	159 (91.4)	162 (91.2)	0.7
Time between ADT initiation and index date, months, mean ± SD [median]	16.1 ± 24.6 [2.9]	21.4 ± 30.5 [8.5]	19.4	18.9 ± 25.9 [4.2]	19.3 ± 30.4 [5.1]	1.4
≤6 months, n (%)	66 (38.4)	84 (57.1)	38.3	73 (45.9)	77 (47.6)	3.6
Prior use of first-generation ARI[c], n (%)	23 (12.4)	26 (15.8)	9.8	23 (13.3)	25 (14.2)	2.5
Baseline PSA level[d], ng/mL, mean ± SD [median]	19.0 ± 45.1 [3.4]	18.9 ± 44.7 [2.0]	0.2	18.4 ± 45.2 [3.3]	18.3 ± 42.1 [2.6]	0.3
Reported baseline testosterone tests[e], n (%)	120 (64.5)	91 (55.2)	19.2	107 (61.3)	106 (60.0)	2.7
Testosterone <50 ng/dL, n (%)	86 (71.7)	75 (82.4)	25.8	81 (75.9)	82 (77.5)	3.7
Baseline Gleason score[f], n (%)						
≤6	19 (10.2)	10 (6.1)	15.2	14 (8.0)	13 (7.1)	3.5
7	49 (26.3)	35 (21.2)	12.1	44 (25.3)	45 (25.4)	0.1
8	18 (9.7)	22 (13.3)	11.5	20 (11.7)	22 (12.5)	2.4
9	47 (25.3)	32 (19.4)	14.1	40 (22.7)	37 (21.1)	3.9
10	4 (2.2)	9 (5.5)	17.3	6 (3.3)	7 (3.9)	3.2
Not available	49 (26.3)	57 (34.5)	17.9	50 (28.9)	53 (30.1)	2.5

ADT: androgen deprivation therapy; APA: apalutamide; ARI: androgen receptor inhibitor; ENZ: enzalutamide; IPTW: inverse probability of treatment weight; PSA: prostate-specific antigen; SD: standard deviation.

Notes:

[a]Propensity scores were generated using probability estimates from a logistic regression model using the following predictors: age group, race, index year, previous ADT use, baseline duration of ADT +6 months, baseline first-generation ARI, baseline PSA level (continuous), baseline testosterone level (categorized as <50 ng/dL, >50 ng/dL and missing), categorized Gleason score, and time between metastasis and the index date. Each patient was attributed an inverse-probability of treatment weight that was defined as follows: 1/(propensity score) for the APA cohort and 1/(1-propensity score) for the ENZ cohort.

[b]Standardized differences <10% indicate that the variable was balanced between the APA and ENZ cohorts.

[c]Prior use of ADT medication was defined as any ADT administration at any time prior to (and excluding) the index date.

[d]Prior use of first-generation ARI was defined as any prescription for bicalutamide, nilutamide, or flutamide, at any time prior to (and excluding) the index date.

[e]Baseline PSA was evaluated as the most recent value from 13 weeks pre-index up to, and including, the index date.

[f]Testosterone testing was evaluated during the 12-month baseline period and included the index date, with the most recent value reported.

[g]Gleason score was evaluated at any time prior to and including the index date, with the most recent value reported.

PSA-related Measurements

- Despite the potential for variation in real-world PSA testing patterns following treatment initiation, PSA testing frequency was similar between the APA and ENZ cohorts [**Table 2**]
  - By 6 months, 73.6% of APA patients and 69.5% of ENZ patients had a post-index PSA measurement

Table 2. Follow-up PSA Testing

	Unweighted Population		IPTW Population[a]	
	APA N=186	ENZ N=165	APA Weighted N=174	ENZ Weighted N=177
Patients with ≥1 PSA test, n (%)	136 (73.1)	119 (72.1)	128 (73.6)	125 (70.5)
Within 3 months of observation	127 (68.3)	97 (58.8)	120 (69.0)	103 (58.2)
Within 6 months of observation	136 (73.1)	117 (70.9)	128 (73.6)	123 (69.5)
Number of follow-up PSA tests per year, mean ± SD [median]	4.5 ± 4.6 [3.9]	4.2 ± 5.4 [3.3]	4.4 ± 4.4 [3.8]	4.5 ± 6.1 [3.3]
Patients with PSA test on average every 3 months, n (%)	89 (47.8)	66 (40.0)	81 (46.6)	74 (41.5)
Patients with PSA test on average every 6 months, n (%)	131 (70.4)	114 (69.1)	124 (71.2)	120 (67.8)

APA: apalutamide; ENZ: enzalutamide; PSA: prostate-specific antigen; SD: standard deviation.

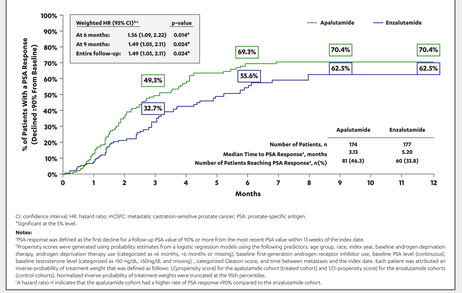
Note:

[a]Propensity scores were generated using probability estimates from a logistic regression model using the following predictors: age group, race, index year, baseline ADT use, baseline duration of ADT +6 months, baseline first-generation antiandrogen use, baseline PSA level (continuous), baseline testosterone level (categorized as <50 ng/dL, >50 ng/dL and missing), categorized Gleason score, and time between metastasis and the index date. Each patient was attributed an inverse-probability of treatment weight that was defined as follows: 1/(propensity score) for the APA cohort and 1/(1-propensity score) for the ENZ cohort.

PSA Outcomes

- By 6 months and beyond, significantly more APA patients attained a PSA90 response compared to ENZ patients (all p<0.024; **Figure 2**)
- PSA90 response was attained significantly earlier in patients treated with APA than for those treated with ENZ (all p<0.024; **Figure 2**)
  - The median time to PSA90 was 3.1 months for APA patients and 5.2 months for ENZ patients

Figure 2. Comparison of Time to PSA90 Response Among Patients with mCSPC[a]



CI: confidence interval; HR: hazard ratio; mCSPC: metastatic castration-sensitive prostate cancer; PSA: prostate-specific antigen.

*Significant at the 5% level.

Notes:

[a]PSA response was defined as the first decline for a follow-up PSA value of 90% or more from the most recent PSA value within 13 weeks of the index date.

[b]Propensity scores were generated using probability estimates from a logistic regression models using the following predictors: age group, race, index year, baseline androgen deprivation therapy, androgen deprivation therapy use (categorized as ≤6 months, >6 months or missing), baseline first-generation androgen receptor inhibitor use, baseline PSA level (continuous), baseline testosterone level (categorized as <50 ng/dL, >50ng/dL and missing), categorized Gleason score, and time between metastasis and the index date. Each patient was attributed an inverse-probability of treatment weight that was defined as follows: 1/(propensity score) for the apalutamide cohort (treated cohort) and 1/(1-propensity score) for the enzalutamide cohorts (control cohorts). Normalized inverse-probability of treatment weights were truncated at the 95th percentiles.

[c]A hazard ratio >1 indicates that the apalutamide cohort had a higher rate of PSA response >90% compared to the enzalutamide cohort.

LIMITATIONS

- This study relied upon clinical data that may contain inaccuracies or omissions (e.g., diagnosis dates, treatment start dates) and does not capture any diagnoses, medical services, or prescription fills obtained outside of the urology practice
- Miscoding or misclassification in the clinical record may introduce selection and information biases despite efforts to match the study populations
- While robust methodology was applied to this analysis, this study did not address whether these findings represent a clinically meaningful difference or whether they translate into differences in longer-term outcomes (e.g., overall survival)
- 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

CONCLUSIONS

- In this real-world study of patients with mCSPC, significantly more patients attained an early and deep PSA90 response when treated with APA relative to ENZ
- PSA90 response was attained significantly earlier in patients treated with APA than with ENZ
- The proportions of patients attaining a PSA90 response by 6 and 12 months following initiation of APA are consistent with those observed in the Phase III study of APA in mCSPC (TITAN)[9]
- The clinical implications of these observations warrant further consideration given existing evidence on the association between attainment of rapid, deep, and durable PSA response with survival-related endpoints in patients treated with these medications[5-10]

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Disclosures

B. Lowentritt is an employee of Chesapeake Urology Associates and has received consulting fees from Janssen Scientific Affairs, LLC. D. Pilon, C. Rossi, F. Kinkead, and P. Lefebvre are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Janssen Scientific Affairs, LLC. I. Khilfeh, E. Muser, D. Waters, and L. Ellis are employees of Janssen Scientific Affairs, LLC.

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