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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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]
  - TITAN: apalutamide + ADT resulted in **35% reduction in risk of mortality** versus placebo + ADT[3,4]
  - ARCHES: enzalutamide + ADT resulted in **34% reduction in risk of mortality** versus placebo + ADT[5,6]

- No clinical trials or real-world studies have directly compared progression or survival outcomes between these agents approved in patients with mCSPC

1. U.S. Food and Drug Administration. FDA approves apalutamide for metastatic castration-sensitive prostate cancer. 2019; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-apalutamide-metastatic-castration-sensitive-prostate-cancer. Accessed January 13, 2022.
2. U.S. Food and Drug Administration. FDA approves enzalutamide for metastatic castration-sensitive prostate cancer. 2019; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-enzalutamide-metastatic-castration-sensitive-prostate-cancer. Accessed November 20, 2023.
3. Chi KN, et al. *N Engl J Med*. 2019;381(1):13-24.
4. Chi KN, et al. *J Clin Oncol*. 2021;39(20):2294-2303.
5. Armstrong AJ, et al. *J Clin Oncol*. 2019;37(32):2974-2986.
6. Armstrong AJ, et al. *J Clin Oncol*. 2022;40(15):1616-1622.

Objectives

- This real-world study **compared** the **proportion of patients surviving by 24 months** for patients with mCSPC who newly initiated **apalutamide** versus **enzalutamide**
  - Null hypothesis: In ARPI-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 ARPI-naïve patients with mCSPC, overall survival by 24 months post-apalutamide initiation **is different** than overall survival by 24 months post-enzalutamide initiation

Data sources

- This study **linked patient-level data** from two unique data sources:
  - Precision Point Specialty (PPS) is a clinical electronic medical records (EMR) database that contains **demographic and clinical data** collected from **urology practices** in the US, including **prostate-specific antigen** results, **dispensation information**, and additional **PC-specific medication and procedure** data
  - Komodo Research Database (KRD) is an insurance claims database of over **320 million US patients** across commercial, Medicaid, and Medicare insurers, and includes information on **diagnoses, procedures, and prescription fills**
- Mortality data from KRD were used to inform the overall survival analysis
  - These data are obtained from governments, public listings, private claims, and obituaries, and are therefore **not dependent on data supplied by healthcare providers**

Study design and analyses

- A retrospective longitudinal **causal analysis utilizing propensity score-weighted** cohorts of ARPI-naïve patients with mCSPC initiated on apalutamide or enzalutamide was conducted (1 January 2016 to 31 December 2023), 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 **(index date)**

- Weighted **Kaplan-Meier** analysis was used to assess the proportion of patients surviving by 24-months post-index

- A weighted **Cox proportional hazards model** was used to generate hazard ratios comparing overall survival between apalutamide and enzalutamide cohorts

- This study was designed to assess the effectiveness, not safety, of apalutamide versus enzalutamide

Weighted baseline characteristics

	Apalutamide (N=1,810)	Enzalutamide (N=1,909)
Age at index date, years, mean ± SD (median)	73.0 ± 9.2 (73.0)	73.0 ± 9.3 (73.0)
Race, n (%)		
White	1,083 (60)	1,135 (59)
Black or African American	407 (23)	432 (23)
Hispanic or Latino	135 (8)	146 (8)
Other/unknown	184 (10)	196 (10)
Medicare insurance coverage, n (%)	1,406 (78)	1,487 (78)
Index year, n (%)		
2019-2020	391 (22)	434 (23)
2021	488 (27)	524 (28)
2022	493 (27)	511 (27)
2023	438 (24)	440 (23)
Quan-Charlson comorbidity index, mean ± SD (median)	8.6 ± 3.0 (8.0)	8.6 ± 3.1 (9.0)
De novo PC, n (%)	1,017 (56)	1,072 (56)
Time between metastasis and index date, months, mean ± SD (median)	10.1 ± 18.2 (2.6)	10.6 ± 18.0 (2.7)
Time between PC diagnosis and index date, months, mean ± SD (median)	39.4 ± 46.6 (16.8)	39.8 ± 46.8 (17.8)
Metastasis in multiple sites, n (%)	485 (27)	498 (26)
ADT episode overlapping with index date, n (%)	1,434 (79)	1,486 (78)

Overall, 1,810 patients with mCSPC who **initiated apalutamide** and 1,909 patients with mCSPC who **initiated enzalutamide** were identified

Following IPTW, **baseline characteristics in both cohorts were similar** (i.e., standardized difference <10%)

Other baseline characteristics selected as **covariates to balance the cohorts include**: metastasis types (i.e., bone, nodal, visceral), prior use of first-generation ARPIs, prior use of chemotherapy, most recent PSA level, earliest Gleason score

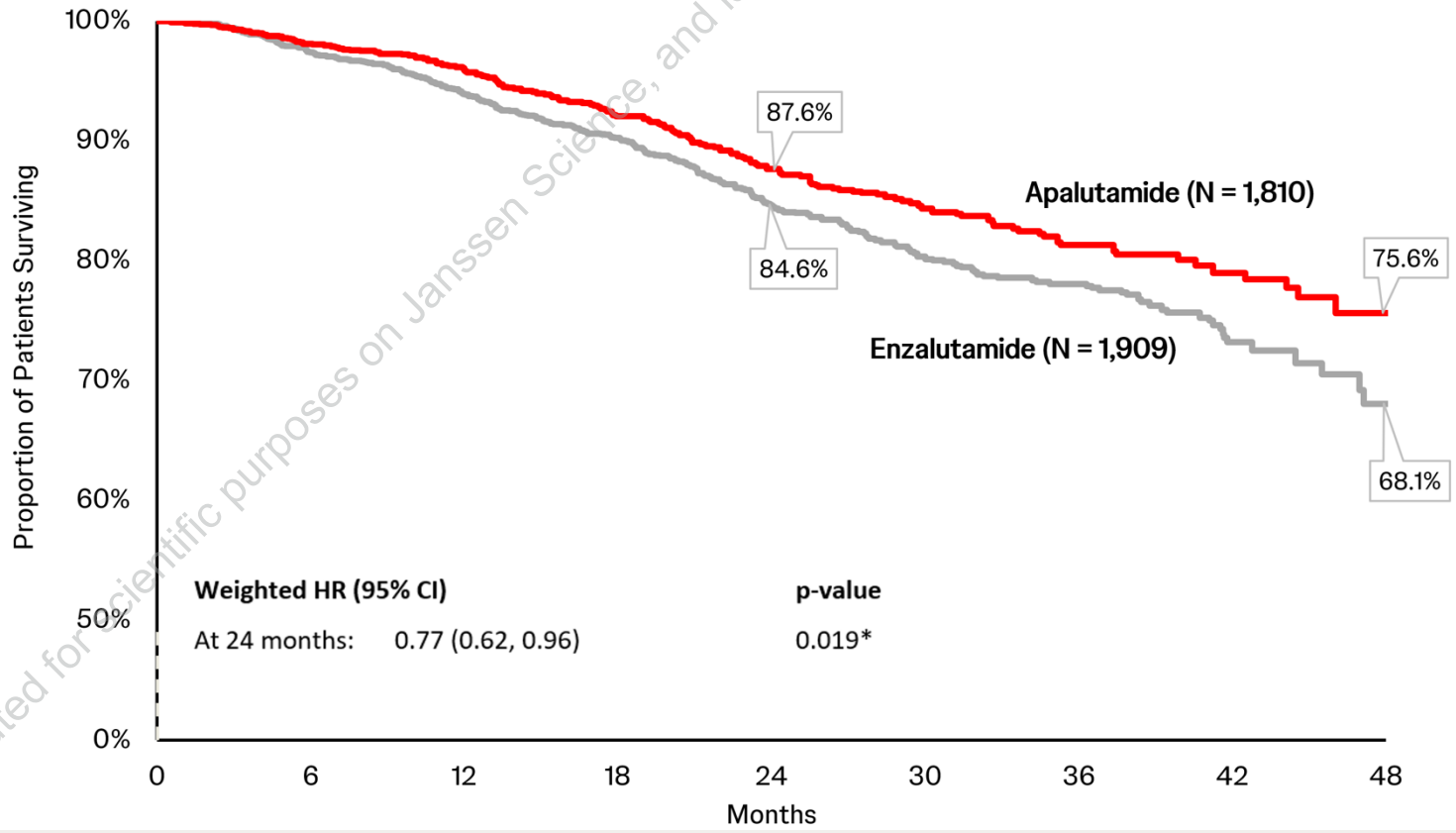
ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibitor; IPTW: inverse probability of treatment weighting; PC: prostate cancer; PSA: prostate-specific antigen; SD: standard deviation.

Results

- 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*)

- 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#)

Overall survival among patients initiating apalutamide versus enzalutamide



Number at Risk, n (%)									
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)

*Significant at the p<0.05 level
#Not adjusted for multiple comparisons. Statistical significance not established for time points beyond primary endpoint
CI: confidence interval; HR: hazard ratio.

Conclusions

- In patients with mCSPC, **those 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[1]

1. Chi KN, et al. *J Clin Oncol*. 2021;39(20):2294-2303.

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[1], 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[2,3], 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 patients may be needed to estimate the full magnitude of therapeutic effect for these agents

1. Komodo Health Inc. Komodo Mortality Data Version 238 User Guide.
2. Chi KN, et al. *J Clin Oncol*. 2021;39(20):2294-2303.
3. Armstrong AJ, et al. *J Clin Oncol*. 2022;40(15):1616-1622.

https://www.janssenscience.com/media/attestation/congresses/oncology/2024/ecop/realworld-headtohead-analysis-of-overall-survival-in-patients-with-metastatic-castration-slides.pdf

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