ERLEADA® (apalutamide)
ERLEADA - Comparison of ERLEADA with ZYTIGA

SUMMARY

- Apalutamide is an androgen receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR. Apalutamide inhibits AR nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription.[1-3]
- Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17-α hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. Abiraterone acetate may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition.[4-6]
- No prospective, randomized, head-to-head studies comparing the efficacy and safety of ERLEADA with abiraterone acetate have been conducted.
- Results from a phase 2 evaluating androgen deprivation therapy (ADT) plus abiraterone acetate with prednisone (AAP), ERLEADA, and ERLEADA plus AAP in patients with multiple clinical states of prostate cancer, including newly diagnosed metastatic prostate cancer, have been reported (N=128).[7]
    - Primary and secondary endpoint results at week 25 are described in Table: Primary and Secondary Endpoints at Week 25. With a median follow-up of 14 months, prostate-specific antigen (PSA) ≤0.2 ng/mL was achieved by 75.6% (95% confidence interval [CI], 59.7-87.6) of patients in the ADT plus AAP arm, 60.0% (95% CI, 43.3-75.1) of patients in the ERLEADA arm, and 79.5% (95% CI, 63.5-90.7) of patients in the ERLEADA plus AAP arm.[7]
    - The estimated 2-year overall survival (OS) rate was 87.9% (95% CI, 77.9-97.8) with ERLEADA, 92.7% (95% CI, 84.8-100) with ERLEADA plus AAP, and 92.5% (95% CI, 84.3-100) with AAP plus ADT (*P*=0.5926).[8]
    - Grade 3-4 adverse events (AEs) occurred in 31.0%, 21.4% and 36.4% of patients in the ADT plus AAP, ERLEADA, and ERLEADA plus AAP arms, respectively (Table: Adverse Events). Treatment-related adverse events (TRAEs) of all grades were observed in 71.4% of patients in the ADT plus AAP arm, 81.0% of patients in the ERLEADA arm, and 81.8% of patients in ERLEADA plus AAP arm.[7]
- **Real-World, Retrospective Studies (Metastatic Castration-Sensitive Prostate Cancer [mCSPC]) - Survival**
    - Head-to-head, longitudinal study: compared OS at 24 months for patients who newly initiated ERLEADA (n=1879) vs abiraterone acetate (n=2073). Patients in the ERLEADA vs abiraterone acetate weighted cohort had a 26% reduction in the risk of death (88.7% vs 85.8%; hazard ratio [HR], 0.74; 95% CI, 0.59-0.93; *P*=0.010).[9]
    - ROMA study: unadjusted real-world survival rates were as follows for the ERLEADA (n=242) and abiraterone acetate (n=607) cohorts, respectively: 91.3% vs 88.4% by 12 months, 88.0% vs 82.9% by 18 months, and 85.7% vs 75.9% by 24 months. By 24 months postindex, patients in the ERLEADA cohort had a 40% lower mortality rate relative to patients initiated on abiraterone acetate (unadjusted HR, 0.60; 95% CI, 0.38-0.96; *P*=0.033).[10]
    - OASIS study: starting with ERLEADA plus ADT compared with abiraterone acetate plus ADT was associated with a statistically significant lower risk of death (adjusted HR, 0.51; 95% CI, 0.29-0.9; *P*<0.05).[11]
- **Real-World, Retrospective Studies/Analyses (mCSPC) – PSA & Other Results**
    - PROMPT-2 study: patients in the ERLEADA weighted cohort were 68% more likely to achieve ≥90% PSA reduction from baseline (PSA90) response compared with the abiraterone acetate weighted cohort (HR, 1.68; 95% CI, 1.42-2.00; *P*<0.001) by 6 months postindex. The median time to PSA90 of 3.6 months vs 10.3 months, respectively.[12]

- *De novo* study: 62.2% vs 41.6% of patients with *de novo* mCSPC in the ERLEADA and abiraterone acetate groups, respectively, achieved PSA90 at 6 months (HR, 1.64; 95% CI, 1.28-2.10; *P*<0.001). The median time to PSA90 was 3.6 months vs 10.3 months, respectively.[13]
- Summary of descriptive analyses for the rates of PSA90, undetectable PSA (≤0.2 ng/mL), progression to castration resistance (CR), castration resistance-free survival (CRFS), and/or OS in patients initiated on ERLEADA or enzalutamide are summarized in Tables: Clinical Outcome Results and Table: Clinical Outcomes.[14,15]
- Summary of PSA90 response was compared between patients initiated on ERLEADA or abiraterone acetate. Results are summarized in Table: PSA90 Response Results in ERLEADA vs Abiraterone Acetate Groups.[16] Additionally, PSA90 was assessed as well as undetectable PSA among patients initiated on ERLEADA or abiraterone acetate; results are summarized in Table: PSA Response Results in the ERLEADA and Abiraterone Acetate Groups.[17]

- Results from an interim analysis of a long-term, real-world registry study in Japanese patients with high-risk mCSPC who received ADT alone or combined androgen blockade (cohort 1) or ADT with ERLEADA, AAP, docetaxel, or enzalutamide (cohort 2) have been reported.[18]

PRODUCT LABELING

ERLEADA (apalutamide) [Prescribing Information]. Horsham, PA: Janssen Products, LP; https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ERLEADA-pi.pdf.

ZYTIGA (abiraterone acetate) [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.; https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ZYTIGA-pi.pdf.

CLINICAL DATA

Phase 2 Study

Maluf et al (2021)[7] reported results of a phase 2 study, LACOG-0415, that evaluated the efficacy and safety of ERLEADA, ERLEADA plus AAP, and AAP plus ADT in patients (N=128) with multiple clinical states of prostate cancer, including newly diagnosed metastatic prostate cancer (NCT02867020).

Study Design/Methods

- Phase 2, randomized, open-label, multicenter study
- Patients were randomized 1:1:1 to receive the following treatments:
  - ERLEADA 240 mg orally (PO) once daily (QD) alone
  - ERLEADA 240 mg PO QD plus abiraterone acetate 1,000 mg PO QD plus prednisone 5 mg PO twice daily
  - Abiraterone acetate 1,000 mg PO QD plus prednisone 5 mg PO twice daily plus ADT (goserelin 10.8 mg subcutaneously every 12 weeks)
- Patients were stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs 2) and metastatic disease (yes vs no).
- Patients were treated until week 25, disease progression (radiographic per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 and/or symptomatic +/- biochemical progression according to the Prostate Cancer Working Group Criteria 3), unacceptable toxicity, or consent withdrawal.
- **Select inclusion criteria**: locally advanced prostate cancer with positive lymph nodes, not candidates to radical surgery or radiotherapy and PSA ≥2 ng/mL; high-risk biochemical recurrence defined as PSA of ≥4 ng/mL and PSA doubling-time <10 months, or PSA ≥20 ng/mL; or mCSPC and PSA of ≥2 ng/mL; testosterone levels ≥230 ng/dL

- **Select exclusion criteria:** prior ADT (except in the context of local therapy with an ADT-free interval of ≥12 months prior to study entry); prostate adenocarcinoma with neuroendocrine differentiation or small cell histology; known or suspected brain or skull metastases, or leptomeningeal metastatic disease; prior hormonal therapy or chemotherapy, except if administered in the adjuvant/neoadjuvant setting for localized disease (must be completed ≥12 months before); prior radiation therapy for a primary tumor (within 3 months before study entry) or for metastases; active or asymptomatic viral hepatitis or chronic liver disease, or ascites or bleeding disorders secondary to hepatic dysfunction; surgical castration prior to study entry; impaired cardiac function; history of seizure or condition that may predispose to seizures[19]
- **Primary endpoint:** proportion of patients who achieved PSA ≤0.2 ng/mL at week 25
- **Secondary endpoints:** PSA decline of ≥50% and ≥80% at week 25; maximum PSA decline; overall PSA change from baseline up to week 25 and up to week 52; testosterone levels during treatment; radiographic progression-free survival (rPFS); health-related quality of life (HRQoL); PSA progression; and safety

Results

Patient Characteristics

- A total of 128 patients were randomized, and 120 of these patients were evaluable for the primary endpoint.
- The baseline demographics and disease characteristics were well balanced (Table: Select Patient Baseline Characteristics).
- A total of 74.2%, 17.2%, and 8.6% of patients had metastatic disease, high-risk biochemical recurrence disease, and locally advanced disease, respectively.

Select Patient Baseline Characteristics[7]

Characteristic	ADT Plus AAP (n=42)	ERLEADA (n=42)	ERLEADA Plus AAP (n=44)	Total (N=128)
Median age, year (range)	69 (51-85)	69.5 (53-88)	71 (49-87)	70 (49-88)
Median PSA, ng/mL (IQR)	16.7 (6.4-50.0)	19.9 (7.2-68.5)	32.4 (7.1-141.5)	22.5 (6.9-117.4)
Criteria for ADT indication, n (%)				
Biochemical recurrence	7 (16.7)	8 (19.0)	7 (15.9)	22 (17.2)
Locally advanced disease	6 (14.3)	2 (4.8)	3 (6.8)	11 (8.6)
Metastatic disease	29 (69.0)	32 (76.2)	34 (77.3)	95 (74.2)
Previous interventions, n (%)				
Radiotherapy	17 (40.5)	16 (38.1)	14 (31.8)	47 (36.7)
Prostatectomy	20 (47.6)	18 (42.9)	17 (38.6)	55 (43.0)
(Neo)adjuvant ADT	4 (9.5)	6 (14.3)	4 (9.1)	14 (10.9)

Abbreviations: AAP, abiraterone acetate plus prednisone; ADT, androgen deprivation therapy; IQR, interquartile range; PSA, prostate-specific antigen.

Efficacy

- With a median follow-up of 14 months, PSA ≤0.2 ng/mL was achieved in 75.6% (95% CI, 59.7-87.6) in the ADT plus AAP arm, 60.0% (95% CI, 43.3-75.1) in the ERLEADA arm, and 79.5% (95% CI, 63.5-90.7) in the ERLEADA plus AAP arm at week 25.
- Primary and secondary endpoint results are described in Table: Primary and Secondary Endpoints at Week 25.

- A total of 92.3%, 80.0%, and 87.5% of patients without metastatic disease achieved PSA ≤0.2 ng/mL in the ADT plus AAP, ERLEADA, and ERLEADA plus AAP arms, respectively.
- PSA progression at week 25 was observed in 3 patients in the ERLEADA arm, all of whom had metastatic disease at baseline.

Primary and Secondary Endpoints at Week 25[7]

	ADT Plus AAP (n=41)	ERLEADA (n=40)	ERLEADA Plus AAP (n=39)
Primary endpoint, n (%)			
PSA ≤0.2 ng/mL	31 (75.6)	24 (60.0)	31 (79.5)
Secondary endpoints			
PSA decline ≥50%, n (%)	41 (100)	37 (92.5)	39 (100)
PSA decline ≥80%, n (%)	41 (100)	36 (90.0)	39 (97.4)
Mean change in testosterone levels from baseline to week 25, % (SD)	-97.4 (31.8)	134.3 (110.6)	-73.8 (65.1)
Median testosterone level at week 25, ng/dL (IQR)	9.0 (3.6-12)	1022 (723-1260)	30.4 (9-139)
Radiographic progression[a], n (%)	1 (3.1)	1 (2.9)	0

Abbreviations: AAP, abiraterone acetate plus prednisone; ADT, androgen deprivation therapy; IQR, interquartile range; PSA, prostate-specific antigen; SD, standard deviation.
[a]Patients without evaluable images at week 25 or with overall response unable to assess were excluded.

2-year OS and Time-to-Treatment Failure (TTF) Analysis

- An additional analysis was conducted that evaluated the 2-year OS and TTF outcomes from the LACOG 0415 study.[8]
  - A total of 110 patients continued treatment after week 25.
  - At the 2-year visit, 80 (62.5%) patients remained on the study treatment.
  - The estimated 2-year OS rate was 87.9% (95% CI, 77.9-97.8) with ERLEADA, 92.7% (95% CI, 84.8-100) with ERLEADA plus AAP, and 92.5% (95% CI, 84.3-100) with AAP plus ADT (*P*=0.5926).
  - At week 25, the 2-year OS rate was 92.9% (95% CI, 85.3-96.2) in patients with PSA ≤0.2 ng/mL and 85.0% (95% CI, 72.9-97.1) in patients with PSA >0.2 ng/mL (*P*=0.1250).
  - Median TTF was 24.0 months (95% CI, not estimated [NE]) with ERLEADA, 24.0 months (95% CI, 13.0-24.0) with ERLEADA plus AAP, and 24.0 months (95% CI, 23.3-24.0) with AAP plus ADT.

Patient-Reported HRQoL

- In an analysis evaluating patient-reported outcomes (PROs) of HRQoL, there were no clinically significant changes in Functional Assessment of Cancer Therapy-Prostate (FACT-P) total and subscales scores from baseline to week 25 in the 3 treatment groups and no statistically significant difference between the groups in the time to FACT-P deterioration (*P*=0.3371).[20]

Safety

- A summary of AEs is shown in Table: Adverse Events.
- Grade 3-4 AEs occurred in 31.0%, 21.4% and 36.4% of patients in the ADT plus AAP, ERLEADA, and ERLEADA plus AAP arm, respectively.

- TRAEs of all grades were observed in 71.4% of patients in the ADT plus AAP arm, 81.0% of patients in the ERLEADA arm, and 81.8% of patients in ERLEADA plus AAP arm.
- Treatment interruptions due to toxicity occurred in 4.8%, 9.5% and 18.2% of patients in the ADT plus AAP, ERLEADA, and ERLEADA plus AAP arms, respectively.
- A total of 9 patients discontinued therapy before week 25, of which 6 due to toxicity (ADT plus AAP arm: stroke [n=1]; ERLEADA arm: grade 3 rash [n=1]; ERLEADA plus AAP: grade 3 rash and acute renal failure [n=1], grade 3 hypertension, grade 3 rash/pruritus, grade 3 pruritus [n=1 each]).
- In the additional analysis that evaluated the 2-year OS and TTF, the reasons for treatment discontinuation included disease progression (n=8 [6.3%]), toxicity (n=10 [7.8%]), death (n=6 [4.7%]), withdrawal (n=4 [3.1%]), and other (n=19 [14.8%]).[8]

Adverse Events[7]

Adverse Event, n (%)[a]	ADT Plus AAP (n=42)		ERLEADA (n=42)		ERLEADA Plus AAP (n=44)	
	All Grade	Grade 3, 4	All Grade	Grade 3, 4	All Grade	Grade 3, 4
Gynecomastia	3 (7)	0	23 (55)	0	9 (20)	0
Hot flashes	16 (38)	0	2 (5)	0	13 (30)	0
Fatigue	7 (17)	0	9 (21)	1 (2)	13 (30)	0
Hypertension	9 (21)	5 (12)	2 (5)	1 (2)	9 (20)	5 (11)
Rash	0	0	11 (26)	5 (12)	8 (18)	3 (7)
Back pain	8 (19)	0	5 (12)	0	4 (9)	1 (2)
Nausea	4 (10)	0	3 (7)	0	8 (18)	0
Pruritus	1 (2)	0	7 (17)	1 (2)	6 (14)	2 (5)
Diarrhea	5 (12)	0	2 (5)	0	6 (14)	2 (5)
Edema limbs	7 (17)	0	2 (5)	0	2 (5)	0
Headache	4 (10)	0	2 (5)	0	4 (9)	0
Hyperglycemia	4 (10)	2 (5)	1 (2)	0	5 (11)	2 (5)
Leg pain	5 (12)	0	3 (7)	0	1 (2)	0
Upper respiratory infection	4 (10)	0	1 (2)	0	4 (9)	0
Breast pain	0	0	6 (14)	0	2 (5)	0
Urinary infection	4 (10)	1 (2)	2 (5)	1 (2)	2 (5)	1 (2)
Vertigo	4 (10)	1 (2)	2 (5)	0	2 (5)	0
Myalgia	2 (5)	0	5 (12)	0	1 (2)	0
Anemia	4 (10)	1 (2)	1 (2)	0	1 (2)	0

Abbreviations: AAP, abiraterone acetate plus prednisone; ADT, androgen deprivation therapy.
[a]All events occurring in ≥10% of patients in any arm.

Efficacy and safety results were not delineated for patients with newly diagnosed metastatic prostate cancer.

ADDITIONAL DATA

Retrospective Real-World Studies in Patients with mCSPC

Lowentritt et al (2024)[9] conducted a head-to-head, real-world, retrospective, longitudinal study to evaluate OS at 24 months among US-based patients with mCSPC who initiated ERLEADA (n=1879) or abiraterone acetate (n=2073) using clinical data from Precision Point Specialty (PPS) Analytics linked with claims data from Komodo Research Database from September 2018 to December 2023. This analysis utilized propensity score-weighted cohorts of androgen receptor pathway inhibitors (ARPIs)-naïve patients newly initiated on ERLEADA or abiraterone acetate and followed an intent-to-treat design. The analysis used weighted Cox proportional hazards models to evaluate the causal relationship between index treatment and OS, weighted Kaplan-Meier analysis to assess the portion of patients surviving by 24 months postindex, and inverse probability of treatment weighting (IPTW) based on the propensity score to account for differences in baseline characteristics between both cohorts. Concurrent use of ADT was not required; 76.8% vs 74.0% of patients were receiving ADT at baseline in the ERLEADA vs abiraterone acetate weighted cohorts, respectively. Additionally, concurrent use of prednisone was not required for patients in the abiraterone acetate cohort.

Patients in the ERLEADA cohort had a 26% reduction in the risk of death compared with abiraterone acetate (88.7% vs 85.8%; HR, 0.74; 95% CI, 0.59-0.93; *P*=0.010). When evaluating OS using all available follow-up at 48 months postindex, results were 77.3% vs 69.4% in the ERLEADA vs abiraterone acetate weighted cohorts, respectively (HR, 0.72; 95% CI, 0.59-0.88; nominal *P*<0.001); this endpoint was not adjusted for multiple comparisons. Therefore, the P-value displayed is nominal, and statistical significance has not been established. The mean (median) follow-up period was 16.8 (19.5) months vs 16.3 (19.0) months and duration of continuous index ARPI use was 9.3 (6.6) months vs 10.7 (8.9) months in patients who initiated ERLEADA vs abiraterone acetate, respectively.

Bilen et al (2024)[10] conducted a real-world, retrospective, longitudinal cohort study to evaluate survival among US-based patients with mCSPC who initiated ERLEADA (n=242) or abiraterone acetate (n=607) using electronic health record data from the Flatiron Metastatic Prostate Cancer Core Registry from January 2013-May 2023 (ROMA study). Concurrent use of prednisone in the abiraterone acetate cohort and concurrent ADT in both cohorts was not required for inclusion however most patients (>84%) had prior use of ADT before treatment initiation. The median time between metastasis and index treatment initiation was 2.3 months in the ERLEADA cohort and 2.5 months in the abiraterone acetate cohort.

Using Kaplan-Meier analysis, unadjusted real-world survival rates were as follows for the ERLEADA and abiraterone acetate cohorts, respectively: 91.3% vs 88.4% by 12 months, 88.0% vs 82.9% by 18 months, and 85.7% vs 75.9% by 24 months. By 24 months postindex, patients in the ERLEADA cohort had a 40% lower mortality rate relative to patients initiated on abiraterone acetate (unadjusted HR, 0.60; 95% CI, 0.38-0.96; *P*=0.033). The median time on treatment and observation period was 11.4 months and 14.3 months in the ERLEADA cohort and 10.8 months and 14.0 months in the abiraterone acetate cohort.

Maughan et al (2024)[11] conducted a real-world, retrospective, observational cohort study to evaluate the impact of first-line treatment in US-based patients with mCSPC (OASIS study). Patients with a mCSPC diagnosis from January 2018-September 2022 in the ConcertAI database that started treatment with any androgen receptor signaling inhibitor (ARSI), docetaxel, or ADT alone were included. Enrollment included 4626 patients that started treatment with ERLEADA plus ADT (n=165), abiraterone acetate with prednisone plus ADT (n=1064), enzalutamide plus ADT (n=643), docetaxel plus ADT (n=293), and ADT alone (n=543).

Using multivariate Cox regression with IPTW method of risk of death, starting with ERLEADA plus ADT compared with abiraterone acetate plus ADT was associated with a statistically significant lower risk of death (adjusted HR, 0.51; 95% CI, 0.29-0.9; *P*<0.05). Results for ERLEADA plus ADT and AAP plus ADT compared to ADT alone for OS, time to CR, and time to undetectable PSA outomes are shown in Table: Adjusted HRs by Initial Treatment Compared to ADT Alone.

Adjusted HRs by Initial Treatment Compared to ADT Alone[11]

Adjusted HRs (95% CI)	ERLEADA + ADT	AAP + ADT
OS	0.4 (0.22-0.73)	0.77 (0.54-1.1)
TTCR	0.39 (0.23-0.67)	0.6 (0.43-0.84)
Time to undetectable PSA	2.79 (1.7-4.2)	1.3 (0.93-1.9)

Abbreviations: AAP, abiraterone acetate plus prednisone; ADT, androgen deprivation therapy; CI, confidence interval; HRs, hazard ratios; OS, overall survival; PSA, prostate-specific antigen; TTCR, time to castration resistance.

Brown et al (2024)[12] conducted a real-world, retrospective, longitudinal propensity score-weighted cohort study to evaluate PSA90 response by 6 months in patients with mCSPC newly initiated on ERLEADA (n=920) or abiraterone acetate (n=637) using data from the Komodo Research database from December 17, 2018-September 30, 2022 (PROMPT-2). Concurrent use of prednisone in the abiraterone acetate cohort and concurrent use of ADT in both cohorts was not required for inclusion however most patients (>86%) in the IPTW population had prior use of ADT before treatment initiation. Mean baseline PSA was 23.7 ng/mL and 25.0 ng/mL in the ERLEADA and abiraterone acetate weighted cohorts, respectively.

There were 82.1% of patients in the ERLEADA weighted cohort vs 74.3% of patients in the abiraterone acetate weighted cohort with a postindex PSA measurement. By 6 months postindex, patients in the ERLEADA weighted cohort were 68% more likely to achieve PSA90 response compared with the abiraterone acetate weighted cohort (HR, 1.68; 95% CI, 1.42-2.00; *P*<0.001). The same trend was observed over the entire observation period (*P*<0.001). At 6 months, 63.9% vs 41.7% of patients achieved PSA90 in the ERLEADA vs abiraterone acetate cohorts, with a median time to PSA90 of 3.6 months vs 10.3 months, respectively.

Brown et al (2024)[13] conducted a real-world causal analysis to evaluate PSA90 response by 6 months in patients with de novo mCSPC initiated on ERLEADA (n=356) or abiraterone acetate (n=324) using data from the Komodo Health Solutions Research Database from September 17, 2019 to September 30, 2022.

A weighted Kaplan-Meier analysis was used to compare the proportion of patients achieving a PSA90 response by 6 months and a weighted Cox proportional hazards model was used to compare the time to PSA90 response. IPTW was used to balance preindex covariates between cohorts (e.g., age, race, time from metastasis to index date, use of ADT, most recent PSA and testosterone levels).

The mean preindex PSA level was 33.3 ng/mL in both the ERLEADA and abiraterone acetate groups. By 6 months postindex, 82.0% of patients in the ERLEADA group and 73.5% of patients in the abiraterone acetate group had $\geq$1 PSA test. At 6 months, 62.2% vs 41.6% of patients achieved PSA90 in the ERLEADA vs abiraterone acetate groups (HR, 1.64; 95% CI, 1.28-2.10; *P*<0.001), with a median time to PSA90 of 3.6 vs 10.3 months, respectively.

Lowentritt et al (2023)[14] conducted a real-world, retrospective, longitudinal cohort study to evaluate PSA outcomes and disease progression in patients with mCSPC that were initiated on ERLEADA (n=589) or abiraterone acetate (n=553). The study also included data for patients who initiated treatment with enzalutamide; however, the results for this cohort are not summarized below.

Kaplan-Meier analyses were used to assess the rates of PSA90, PSA 0.2, progression to CR, and CRFS separately for each cohort. All analyses were descriptive and were not adjusted for potential baseline confounders. Patients were required to have ≥12 months of clinical activity prior to the index date. Concurrent use of ADT was not required for inclusion in either cohort and concurrent use of prednisone was not required for patients in the abiraterone acetate cohort. Among the exclusion criteria were prior use of an ARSI before the index date or the use of ≥2 ARSIs on the index date and prior use of any radiopharmaceuticals.

Most patients had prior use of ADT and concurrent use of ADT in the ERLEADA (90.5%, 96.3%) and abiraterone acetate (90.8%, 95.7%) cohorts, respectively. Concurrent prednisone use was observed among 94.6% patients in the abiraterone acetate cohort. Median baseline PSA was 19.2 ng/mL and 24.3 ng/mL in the ERLEADA and abiraterone acetate cohorts, respectively. The descriptive analyses are summarized in Table: Clinical Outcome Results.

Clinical Outcome Results[14]

Clinical Outcome, %	ERLEADA Group	Abiraterone Acetate Group
PSA90 response[a,b,c]		
	n=478	n=446
3 months	48.0	36.7
6 months	67.4	46.7
9 months	71.0	51.2
12 months	72.3	54.7
Undetectable PSA (0.2) response[a,b,d]		
	n=382	n=361
3 months	43.3	34.0
6 months	67.1	48.0
9 months	77.4	54.6
12 months	80.6	58.4
Progression to CR[a,e]		
	n=589	n=553
3 months	2.2	10.3
6 months	6.5	16.4
9 months	15.3	24.7
12 months	20.9	31.0
18 months	29.3	40.3
24 months	33.5	44.5
CRFS[a,e]		
	n=589	n=553
3 months	97.3	89.0
6 months	91.5	81.6
9 months	81.9	72.3
12 months	76.2	65.1
18 months	66.4	56.1
24 months	62.0	50.5

Abbreviations: CR, castration resistance; CRFS, castration resistance-free survival; mCSPC, metastatic castration-sensitive prostate cancer; PSA, prostate-specific antigen; PSA90, ≥90% PSA reduction from baseline.
[a]Reported as rates by Kaplan-Meier analysis.
[b]The median follow-up for PSA outcomes was 203 days in the ERLEADA group and 205 days in the abiraterone acetate group, respectively.
[c]Among patients with baseline PSA within 13 weeks prior to and including index date, the median time to PSA90 response was 3.2 months in the ERLEADA group and 7.6 months in the abiraterone acetate group, respectively.
[d]Among patients with most recent baseline PSA value >0.2 ng/mL within 13 weeks prior to and including index date, the median time to PSA 0.2 response was 3.5 months in the ERLEADA group and 7.1 months in the abiraterone acetate group, respectively.
[e]The median overall follow-up to assess progression to CR and CRFS was 341 days in the ERLEADA group and 520 days in the abiraterone acetate group, respectively.

Lowentritt et al (2023)[15] conducted retrospective real-world analyses to describe clinical outcomes in patients with mCSPC that were initiated on ERLEADA (n=155) or abiraterone acetate (n=711) using electronic medical record (EMR) data from the Flatiron Metastatic Prostate Cancer Core Registry. The study also included data for patients who initiated treatment with enzalutamide; however, the results for this cohort are not summarized below.

Kaplan-Meier analyses were used to assess the rates of progression to CR, OS, and CRFS separately for each cohort. All analyses were descriptive and were not adjusted for potential baseline confounders. Patients were required to have ≥12 months of clinical activity prior to the index date. Concurrent use of ADT was not required for inclusion in either cohort and use of prednisone was not required for the abiraterone acetate cohort. Among the exclusion criteria were prior use of an ARSI before the index date or the use of ≥2 ARSIs on the index date, and prior use of any advanced therapy for prostate cancer (ie, chemotherapy, immunotherapy, radiopharmaceuticals, estrogens, or PARP inhibitors).

Most patients had prior use of ADT before initiation of ERLEADA (83.2%) and abiraterone acetate (86.9%). The mean observation period was 12.7 months and 20.4 months in the ERLEADA and abiraterone acetate cohorts, respectively. The descriptive analyses are summarized in Table: Clinical Outcomes.

Clinical Outcomes[15]

Clinical Outcome, %	ERLEADA Group (n=155)	Abiraterone Acetate Group (n=711)
Progression to CR[a]		
3 months	2.1	7.7
6 months	8.0	12.8
9 months	10.0	17.6
12 months	12.4	22.4
18 months	23.5	29.5
24 months	26.2	32.8
OS[a]		
3 months	98.6	97.5
6 months	96.9	94.0
9 months	93.8	90.2
12 months	91.6	87.6
18 months	88.1	84.1
24 months	88.1	77.0
CRFS[a]		
3 months	96.5	90.2
6 months	89.9	82.8
9 months	86.0	76.1
12 months	82.6	69.9
18 months	70.1	62.0

24 months	67.6	56.9

Abbreviations: CR, castration resistance; CRFS, castration resistance-free survival; mCSPC, metastatic castration-sensitive prostate cancer; OS, overall survival.
[a]Reported as rates by Kaplan-Meier analysis.

Lowentritt et al (2023)[16] conducted a real-world analysis to retrospectively compare the proportion of patients with a PSA90 by 6 months postindex and time to PSA90 response from the date of index treatment initiation in patients with mCSPC that were initiated on ERLEADA or abiraterone acetate.

IPTW based on propensity score was used to account for differences in baseline characteristics and balancing of baseline characteristics after weighting was confirmed between both cohorts. The observation period spanned from the index date to either index treatment discontinuation, initiation of a different ARSI, use of radiopharmaceuticals, end of clinical activity (eg, death), or end of data availability, whichever occurred first.

Patients were required to have ≥12 months of clinical activity prior to the index date and ≥1 PSA test during the 13 weeks prior to and including index date. Among the exclusion criteria were prior use of an ARSI before the index date or the use of ≥2 ARSIs on the index date and evidence of CR prior to or on the index date. Concomitant use of ADT was not required for inclusion and concomitant use of prednisone was not required for patients to be included in the abiraterone acetate cohort.

Before applying IPTW, a total of 364 patients treated with ERLEADA and 147 patients treated with abiraterone acetate were identified and after applying IPTW, the reweighted cohort sizes were 260 patients and 251 patients, respectively. The mean baseline PSA level was 20.4 ng/mL vs 21.1 ng/mL in the ERLEADA weighted cohort vs the abiraterone acetate weighted cohort, respectively. A total of 97.3% patients vs 99.2% patients were taking concomitant ADT in the ERLEADA and abiraterone acetate cohorts, respectively, and 93.7% of patients in the abiraterone acetate cohort were taking concomitant glucocorticoid therapy.

In the IPTW population, 77.3% of patients treated with ERLEADA and 89.2% of patients treated with abiraterone acetate had ≥1 PSA test during the observation period, with nearly all (99.6% vs 99.4%, respectively) having their first PSA test within 6 months following treatment initiation. The PSA90 response and median time to PSA90 response results were significant in the ERLEADA vs abiraterone acetate cohorts at 6 months and beyond (Table: PSA90 Response Results in ERLEADA vs Abiraterone Acetate Groups). No safety data were reported.

PSA90 Response Results in ERLEADA vs Abiraterone Acetate Groups[16]

Efficacy Endpoint	ERLEADA Group[a] (n=260)	Abiraterone Acetate Group[b] (n=251)	Weighted HR (95% CI)	*P*-Value[c]
PSA90 response, %				
3 months	47.2	33.1	-	-
6 months	66.2	43.4	1.53 (1.08-2.16)	0.016
9 months	68.1	47.4	1.51 (1.08-2.11)	0.017
12 months	68.1	49.2	1.49 (1.07-2.09)	0.019
Median time to PSA90 response, months	3.47	Not reached	-	0.013

Abbreviations: CI, confidence interval; HR, hazard ratio; PSA90, ≥90% prostate-specific antigen reduction from baseline.
[a]Mean observation period was 236 days.
[b]Mean observation period was 218 days.
[c]Results significant at the 5% level.

Pilon et al (2021)[17] conducted a real-world analysis to retrospectively describe PSA responses (PSA90 and undetectable PSA [PSA <0.2 ng/mL]) among patients with mCSPC who initiated treatment with ERLEADA or abiraterone acetate. The study also included data for patients who initiated treatment with enzalutamide (not summarized).

The observation period was from the index date to index treatment discontinuation, initiation of a different next-generation androgen signaling inhibitor (ASI; ERLEADA or enzalutamide) or the use of radiopharmaceuticals, end of clinical activity including death, or end of data availability, whichever occurred first. A KM analysis was used to assess the proportion of patients who achieved each PSA response outcome at 3, 6, 9, and 12 months after the index date and median time to PSA response.

Patients were required to have ≥12 months of clinical activity prior to the index date and ≥1 medication dispensation of ERLEADA, abiraterone acetate or enzalutamide. Select exclusion criteria were prior use of a next-generation ASI before the index date or the use of >1 ASI on the index date and evidence of CR prior to or on the index date. PSA responses were assessed for patients who had ≥1 PSA measurement during the 13 weeks before the index date.

Overall, 45.0% and 70.0% of patients treated with ERLEADA, respectively, and 64.7% and 78.9% of patients treated with abiraterone acetate, respectively, had a PSA test on average every 3 and 6 months. Patients achieving PSA90 and undetectable PSA responses were observed by 3 months, with the proportion increasing at 6 months postindex (Table: PSA Response Results in the ERLEADA and Abiraterone Acetate Groups). No safety data were reported.

PSA Response Results in the ERLEADA and Abiraterone Acetate Groups[17]

PSA Outcomes	ERLEADA Group	Abiraterone Acetate Group
PSA90 response		
Total number of evaluable patients, n	212	270
Median time to PSA90 response, months	2.70	6.17
Number of patients achieving PSA90, n (%)	104 (49.1)	121 (44.8)
KM rates of patients achieving PSA90 response at specific time points, % (95% CI)		
3 months	52.9 (45.1-61.2)	39.5 (33.4-46.2)
6 months	70.2 (61.9-78.2)	49.1 (42.4-56.3)
9 months	71.4 (63.1-79.3)	55.7 (48.3-63.5)
12 months	71.4 (63.1-79.3)	59.5 (51.1-68.2)
Undetectable PSA (PSA <0.2 ng/mL) response		
Total number of evaluable patients, n	178	225
Median time to undetectable PSA response, months	3.53	9.70
Number of patients achieving undetectable PSA level, n (%)	90 (50.6)	96 (42.7)
KM rates of patients achieving undetectable PSA level at specific time points, % (95% CI)		
3 months	43.4 (35.3-52.5)	33.0 (26.7-40.2)
6 months	62.4 (53.4-71.4)	45.9 (38.6-53.9)
9 months	78.3 (68.8-86.5)	49.3 (41.5-57.6)
12 months	82.1 (72.5-89.9)	53.7 (45.2-62.7)

PSA Outcomes	ERLEADA Group	Abiraterone Acetate Group
Abbreviations: CI, confidence interval; KM, Kaplan-Meier; PSA, prostate-specific antigen; PSA90, ≥90% prostate-specific antigen reduction from baseline.		

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) was conducted on 31 May 2024. Summarized in this response are relevant data limited to patients with mCSPC. Due to methodological differences and other potential limitations including scope, timing, study designs and statistical approaches, network meta-analyses, and meta-analyses have been excluded in this response. Additional data beyond these parameters may be available in the literature.

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