ERLEADA® (apalutamide)
Sequencing of ERLEADA With ZYTIGA

SUMMARY

- No prospective, randomized trials have been conducted to evaluate sequencing of ERLEADA and ZYTIGA (abiraterone acetate) plus prednisone (AAP).
- In SPARTAN, patients in both the ERLEADA and placebo groups who progressed to metastatic castration-resistant prostate cancer (mCRPC) during the study were eligible to receive subsequent approved therapy for mCRPC, including sponsor-provided AAP.[1-3] In the final analysis for overall survival (OS), which occurred after a median follow-up of 52 months, of patients who received first subsequent systemic therapy for prostate cancer, 73% (282 out of 386) of patients in the ERLEADA group and 72% (206 out of 285) of patients in the placebo group received AAP as the first subsequent therapy. AAP was the most commonly administered first subsequent treatment.[4,5] Subsequent therapy results, including number of patients treated with ZYTIGA, were also previously reported in the primary analysis and in the second interim analysis for OS.[1,6]
    - A post-hoc analysis evaluated efficacy outcomes in patients receiving first subsequent therapy, including ZYTIGA, following progression to mCRPC after initial treatment with ERLEADA. Results are summarized in Table: Efficacy Outcomes of Subsequent Treatment in 1L mCRPC After Progression on ERLEADA.[7]
- In TITAN, patients in both the ERLEADA and placebo groups who progressed during the study were eligible to receive subsequent systemic therapy for prostate cancer, including AAP.[8-10] In the final analysis for OS, which occurred after a median follow-up of 44.0 months, of the patients who were alive at treatment discontinuation, 10.9% (27 out of 247) of patients in the ERLEADA group and 18.8% (65 out of 345) of patients in the placebo group received first subsequent therapy with AAP, which was the most common first subsequent hormonal therapy received by patients in both groups.[11,12] Subsequent therapy results, including number of patients treated with ZYTIGA, were also previously reported in the primary analysis for OS.[8,9]
    - Two post-hoc analyses evaluated second progression-free survival (PFS2) by first subsequent therapy (specifically hormonal compared to taxane therapy) following discontinuation of study treatment as well as in patients with baseline high- and low-risk disease. PFS2 results were reported in aggregate for the ERLEADA and placebo groups and were not stratified by first subsequent therapy received.[13,14]
- The ARN-509-001 phase 2, open-label, multicenter study evaluated the efficacy and safety of ERLEADA in patients with mCRPC who either received or did not receive prior therapy with AAP (N=46). The proportion of patients with prostate-specific antigen (PSA) decline ≥50% at 12 weeks was 88% (95% CI, 69-97) and 22% (95% CI, 6-48) in patients who had not received prior therapy with AAP (AAP-naïve cohort) and in those who had received prior therapy (post-AAP cohort), respectively. The most common treatment-emergent adverse events (TEAEs) were fatigue (60%), nausea (56%), and abdominal pain (48%) in the AAP-naïve cohort, and fatigue (52%), diarrhea (38%), and nausea (33%) in the post-AAP cohort.[15]

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

No prospective, randomized trials have been conducted to evaluate sequencing of ERLEADA and AAP. However, information on subsequent therapy reported in the phase 3 SPARTAN study (NCT01946204) conducted in patients with non-metastatic castration-resistant prostate cancer (nmCRPC) and in the phase 3 TITAN study (NCT02489318) conducted in patients with metastatic castration-sensitive prostate cancer (mCSPC) is summarized in this section.

In addition, results from the phase 2 ARN-509-001 study conducted in patients with mCRPC who either did or did not receive prior therapy with AAP is summarized in this section. Information from a phase 1b study in patients with mCRPC has also been reported.

Phase 3 SPARTAN Study

In SPARTAN, the phase 3, randomized, double-blind, placebo-controlled, multicenter study (N=1207) conducted in patients with high-risk nmCRPC (defined as PSA doubling time [PSADT] ≤10 months), patients were excluded if they had received prior therapy with a cytochrome P450 (CYP) 17 inhibitor (eg, ZYTIGA).[1,2] A total of 806 patients were randomized to receive ERLEADA 240 mg orally once daily and 401 patients received placebo. All patients in the study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy.[1,2] The final OS analysis included a total of 1201 patients: 803 patients in the ERLEADA group and 398 patients in the placebo group. The median treatment duration was 32.9 months in the ERLEADA group, 11.5 months in the placebo group, and 26.1 months in the placebo to ERLEADA crossover group.[4] Following detection of distant metastasis, patients were eligible to receive treatment with sponsor-provided AAP. After study drug discontinuation, the administration of AAP or any other treatment for mCRPC was at the discretion of the treating physician.[1]

In the final OS analysis, which occurred at a median follow-up of 52 months, 70% (566 out of 803) of patients in the ERLEADA group, 100% (322 out of 322) of patients in the placebo group, and 39% (30 out of 76) of patients in the crossover group had discontinued study treatment. A total of 48% (386 out of 806) and 71% (285 out of 401) of patients in the ERLEADA and placebo groups, respectively, received first subsequent systemic therapy for prostate cancer. Of patients who received first subsequent therapy for prostate cancer, 73% (282 out of 386) of patients in the ERLEADA group and 72% (206 out of 285) of patients in the placebo group received AAP as the first subsequent therapy. AAP was the most commonly administered first subsequent treatment.[4,5]

Results were reported for the exploratory endpoint of PFS2, which was defined as the time from randomization to investigator-assessed disease progression (PSA progression, detection of metastatic disease on imaging, symptomatic progression, or any combination) during the first subsequent treatment for mCRPC or death from any cause. However, PFS2 results were reported in aggregate for the ERLEADA and placebo groups and were not stratified by first subsequent therapy received.[1,2,4]

Additional information regarding the SPARTAN study, including the clinical study report, protocol, and statistical analysis plan, can be found: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/Erleada_210951_toc.cfm (scroll to the "Sponsor Clinical Study Reports ARN-509-003 SPARTAN NCT # 01946204" section at the bottom of the web page).

A post hoc analysis of patients in the ERLEADA group described the relative efficacy outcomes of subsequent therapies in patients who progressed to mCRPC. At SPARTAN study completion, 237 patients remained on ERLEADA without progression, while 311 progressed following initial treatment with ERLEADA plus androgen deprivation therapy (ADT) and received subsequent treatment with ZYTIGA, docetaxel, enzalutamide, or other. Compared to the ERLEADA intent-to-treat population (N=806), the subsequent first mCRPC treatment cohort had a higher PSA value at baseline and proportion of patients with PSADT ≤6 months at the point of randomization, experienced poorer deep PSA response to ERLEADA in terms of undetectable PSA and ≥90% reduction in PSA from baseline, and had poorer median metastasis-free survival (25.8 months vs 40.5 months) and OS (52.8 months vs 73.9 months) from randomization.[7] A summary of the efficacy outcomes in patients who received subsequent therapy after progression on ERLEADA are outlined in Table: Efficacy Outcomes of Subsequent Treatment in 1L mCRPC After Progression on ERLEADA.

Efficacy Outcomes of Subsequent Treatment in 1L mCRPC After Progression on ERLEADA[7]

	AAP (n=241)	Overall[a] (n=311)
Median sPFS, months (95% CI)	6.7 (5.4-7.8)	6.8 (5.8-7.9)
Median sOS, months (95% CI)	20.2 (16.7-23.3)	20.0 (17.0-22.6)

Abbreviations: 1L, first-line; AAP, ZYTIGA (abiraterone acetate) plus prednisone**;** mCRPC, metastatic castration-resistant prostate cancer; sOS, subsequent overall survival; sPFS, subsequent progression-free survival.
[a]Additional subsequent therapies included in this analysis: docetaxel, n=29; enzalutamide, n=20; other, n=21.

Phase 3 TITAN Study

In TITAN, the phase 3, randomized, double-blind, placebo-controlled, multicenter study (N=1052) conducted in patients with mCSPC, patients were excluded if they had received prior therapy with a CYP17 inhibitor (eg, ZYTIGA).[8,10] A total of 525 patients were randomized to receive ERLEADA 240 mg orally once daily and 527 patients received placebo. All patients in the study received a concomitant GnRH analog or had a prior bilateral orchiectomy.[8-10] The final OS analysis included 1052 patients: 525 patients in the ERLEADA group and 527 patients in the placebo group. The median treatment duration was 39.3 months in the ERLEADA group, 20.2 months in the placebo group, and 15.4 months in the placebo to ERLEADA crossover group.[11]

In the final OS analysis, which occurred at a median follow-up of 44.0 months, 49.0% (257 out of 525) of patients in the ERLEADA group and 67.9% (358 out of 527) of patients in the placebo group had discontinued study treatment. At treatment discontinuation, 247 (47.0%) patients in the ERLEADA group and 345 (65.5%) patients in the placebo group were alive.[11] A total of 48.6% (120 out of 247) of patients in the ERLEADA group and 64.1% (221 out of 345) of patients in the placebo group received first subsequent systemic therapy for prostate cancer. Of the patients who were alive at treatment discontinuation, 10.9% (27 out of 247) of patients in the ERLEADA group and 18.8% (65 out of 345) of patients in the placebo group received first subsequent systemic therapy with AAP, which was the most common first subsequent hormonal therapy received by patients in both groups.[12] There were 138 patients in the ERLEADA group and 261 patients in the placebo group who discontinued treatment for progressive disease and remained alive, of whom 20 (14.5%) and 56 (21.5%) received AAP as first life-prolonging subsequent therapy for prostate cancer, respectively.[11]

Results were reported for the exploratory endpoint of PFS2, which was defined as the time from randomization to the first occurrence of investigator-assessed disease progression (PSA progression, progression on imaging, or clinical progression) while the patient was receiving first subsequent therapy for prostate cancer or death due to any cause, whichever occurred first. However, PFS2 results were reported in aggregate for the ERLEADA and placebo groups and were not stratified by first subsequent therapy received.[8,10,11]

Phase 2 ARN-509-001 Study

Rathkopf et al (2017)[15] evaluated the efficacy and safety of ERLEADA in patients with mCRPC who either received or did not receive prior therapy with AAP (N=46).

Study Design/Methods

- Phase 2, open-label, multicenter study
- Patients with mCRPC were enrolled in 1 of 2 cohorts:
  - AAP-naïve cohort (n=25): patients who were not treated previously with AAP and who had disease progression, defined by a rising PSA ≥2 ng/mL within 2 weeks of study enrollment or measurable disease (new or progressive tissue disease on computed tomography/magnetic resonance imaging or ≥2 new bone lesions on radiographic scans)
  - Post-AAP cohort (n=21): patients who received ≥6 months of AAP therapy prior to disease progression
- Results from a third cohort of patients with nmCPRC were reported separately.[16]
- Results from an *AR* mutations analysis for patients with nmCRPC and mCRPC enrolled in the study were reported separately.[17]
- Patients received ERLEADA 240 mg orally once daily until evidence of both PSA progression and radiographic progression or clinical progression alone, development of unacceptable toxicity, or withdrawal of consent.
- All patients had pathologically proven prostate adenocarcinoma, received continuous ADT with a GnRH analogue or orchiectomy, had castrate levels of serum testosterone (≤50 ng/dL) within 4 weeks of study enrollment, and had Eastern Cooperative Oncology Group performance status of 0 to 1.
- Patients were excluded if they received previous treatment with enzalutamide, ketoconazole, or chemotherapy for mCRPC, or had a history of seizure or conditions that predispose to seizures.
- **Primary endpoint:** proportion of patients with a ≥50% decline in PSA from baseline at 12 weeks (or earlier for those who discontinued therapy)
- **Secondary endpoints:** time to PSA progression, progression-free survival, and objective response rate

Results

Patient Characteristics

- Patient baseline characteristics are shown in Table: Select Patient Baseline Demographics below.

Select Patient Baseline Demographics[15]

	AAP-Naïve mCRPC (n=25)	Post-AAP mCRPC (n=21)
Age, years, median (range)	68 (53-91)	67 (48-83)
Baseline PSA, ng/mL, median (range)	14.7 (1.1-2552.1)	58.4 (1.1-6074.3)
ECOG PS, n (%)		
0	13 (52)	13 (62)
1	12 (48)	8 (38)
Gleason score at initial diagnosis, n (%)		

	AAP-Naïve mCRPC (n=25)	Post-AAP mCRPC (n=21)
≤7	7 (28)	14 (67)
8-10	18 (72)	6 (29)
Missing	0	1 (5)
Time since initial diagnosis, months, median (range)	61 (10-191)	107 (16-236)
Primary treatment, n (%)		
Prostatectomy ± salvage radiation	10 (40)	13 (62)
Primary radiation	11 (44)	12 (57)
No primary or salvage radiation	13 (52)	5 (24)
Metastases, n (%)		
Bone	11 (44)	8 (38)
Soft tissue	9 (36)	5 (24)

Abbreviations: AAP, ZYTIGA (abiraterone acetate) plus prednisone; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

Efficacy

- Three patients in the post-AAP cohort were excluded from the efficacy analysis for either failing to meet criteria for progressive metastatic disease (n=1) or not receiving ZYTIGA for ≥6 months (n=2).
- Median time on treatment was 21 months (range, 2.6-37.5 months) for the AAP-naïve cohort and 4.9 months (range, 1.3-23.2 months) for the post-AAP cohort.
- The proportion of patients with PSA decline ≥50% at 12 weeks was 88% (95% CI, 69-97) and 22% (95% CI, 6-48) in the AAP-naïve and post-AAP cohorts, respectively (Table: Efficacy Outcomes).
- Eighty percent and 64% of AAP-naïve patients and 43% and 10% of post-AAP patients remained on treatment for ≥6 months and ≥12 months, respectively.

Efficacy Outcomes[15]

	AAP-Naïve mCRPC (n=25)	Post-AAP mCRPC (n=18)
PSA response rate[a], n (%)		
12 weeks	22 (88)	4 (22)
24 weeks	20 (80)	1 (6)
36 weeks	17 (68)	0
Maximal PSA response[b], n (%)	23 (92)	5 (28)
Median time to PSA progression, months (95% CI)	18.2 (8.3-NR)	3.7 (2.8-5.6)
Median PFS[c], months (95% CI)	NR (16.7-NR)	NR (NR-NR)
ORR[d], n/N (%)	4/8 (50)	0/10 (0)

Abbreviations: AAP, ZYTIGA (abiraterone acetate) plus prednisone; mCRPC, metastatic castration-resistant prostate cancer; NR, not reported; ORR, objective response rate; PFS, progression-free survival; PSA, prostate-specific antigen.
[a]≥50% decline in PSA from baseline from Prostate Cancer Working Group 2 criteria.
[b]Maximal percent reduction postbaseline for the individual patient at any time point (ie, ≥50% decline at any time).
[c]Per protocol, patients who had progressive disease that was not confirmed prior to subsequent therapy were censored back to their last assessment prior to subsequent therapy.
[d]Eight patients in the AAP-naïve cohort and 10 patients in the post-AAP cohort had measurable disease at baseline; a partial response was observed in 4/8 AAP-naïve patients.

Safety

- The most common TEAEs were fatigue, nausea, and abdominal pain in the AAP-naïve cohort, and fatigue, diarrhea, and nausea in the post-AAP cohort (Table: TEAEs).
- Serious adverse events (AEs) were reported in 8 (32%) AAP-naïve patients and 6 (29%) post-AAP patients; no seizures were reported.

- Seven (28%) patients in the AAP-naïve cohort and 8 (38%) patients in the post-AAP cohort required dose modifications, mostly due to AEs.
- Treatment discontinuation due to an AE occurred in 3 patients in the AAP-naïve cohort and 1 patient in the post-AAP cohort.

TEAEs[15]

TEAE[a]	AAP-Naïve mCRPC (n=25)		Post-AAP mCRPC (n=21)	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Fatigue	15 (60)	0	11 (52)	1 (5)
Nausea	14 (56)	0	7 (33)	0
Abdominal pain	12 (48)	1 (4)	2 (10)	0
Diarrhea	11 (44)	0	8 (38)	0
Dyspnea	7 (28)	1 (4)	3 (14)	0
Rash	7 (28)	0	0	0
Arthralgia	6 (24)	0	6 (29)	0
Back pain	6 (24)	0	4 (19)	2 (10)
Cough	6 (24)	0	2 (10)	0
Anemia	5 (20)	2 (8)	3 (14)	0
Hot flush	5 (20)	0	0	0
Decreased appetite	4 (16)	0	5 (24)	0
Dizziness	4 (16)	0	2 (10)	0
Insomnia	4 (16)	0	1 (5)	0
Peripheral edema	4 (16)	0	1 (5)	0
Upper respiratory tract infection	4 (16)	0	1 (5)	0
Musculoskeletal chest pain	4 (16)	0	3 (14)	1 (5)
Vomiting	4 (16)	0	4 (19)	1 (5)
Headache	3 (12)	0	4 (19)	0
Constipation	2 (8)	1 (4)	5 (24)	1 (5)
Flatulence	4 (16)	0	0	0
Musculoskeletal pain	2 (8)	0	6 (29)	1 (5)

Abbreviations: AAP, ZYTIGA (abiraterone acetate) plus prednisone; mCRPC, metastatic castration-resistant prostate cancer; TEAE, treatment-emergent adverse event.
[a]Based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0, reported in >15% of patients in either cohort.

Phase 1b Study

A phase 1 study that evaluated the antitumor activity, pharmacokinetics, and safety of ERLEADA in combination with AAP in patients with mCRPC (N=57) included patients who were previously treated with AAP, enzalutamide, docetaxel, and/or cabazitaxel. Results were stratified by patients who had received prior therapy with AAP (n=19), enzalutamide (n=13), AAP and enzalutamide (n=10), and those who had not received prior therapy with either (n=15). A total of 21%, 15%, 0%, and 80% of patients who had received prior therapy with AAP, enzalutamide, AAP and enzalutamide, and those who had not received prior therapy with either had a ≥50% reduction in PSA from baseline, respectively. A total of 0%, 0%, 0%, and 40% of patients who had received prior therapy with AAP, enzalutamide, AAP and enzalutamide, and those who had not received prior therapy with either had a ≥90% reduction in PSA from baseline, respectively. The most commonly reported (≥40%) AEs were fatigue (56.1%), nausea (40.4%), and vomiting (40.4%).[18,19]

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 21 November 2024. Summarized in this response are relevant data limited to the phase 3 SPARTAN study in patients with nmCRPC and phase 3 TITAN study in patients with mCSPC, as well as a phase 2 study and a phase 1b study in patients with mCRPC.

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