ERLEADA® (apalutamide)
Use of ERLEADA in Combination with ZYTIGA

SUMMARY

- ACIS, a phase 3, randomized, double-blind, placebo-controlled, multicenter study, evaluated the efficacy and safety of ERLEADA plus abiraterone acetate with prednisone (AAP) and androgen deprivation therapy (ADT) compared to placebo plus AAP and ADT in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC; N=982). The primary endpoint was radiographic progression-free survival (rPFS), and secondary endpoints included overall survival (OS), time to initiation of cytotoxic chemotherapy, time to pain progression, and time to chronic opioid use.[1]
    - Prespecified endpoints are described in Table: Prespecified Primary, Secondary, and Exploratory Endpoints. At the final analysis for rPFS, after a median follow-up of 54.8 months, a statistically significant improvement in median rPFS was observed in the ERLEADA plus AAP group vs the placebo plus AAP group (24.0 months vs 16.6 months, respectively; HR, 0.70; 95% CI, 0.60-0.83; *P*<0.0001).
    - Similar median OS was observed in both groups: 36.2 months in the ERLEADA plus AAP group vs 33.7 months in the placebo plus AAP group (HR, 0.95; 95% CI, 0.81-1.11; *P*=0.50).
    - The incidences of any treatment-emergent adverse events (TEAEs) and serious TEAEs were similar between the ERLEADA plus AAP group and the placebo plus AAP group (Table: Summary of Adverse Events).
    - Additional analyses evaluating health-related quality of life (HRQoL)[2], association of blood biomarkers with clinical outcomes[3], metastatic stage at presentation,[4] and subgroup analyses of patients aged ≥75 years or with visceral disease[5,6] have been reported.
    - On April 19, 2021, the Janssen Pharmaceutical Companies of Johnson & Johnson announced that regulatory submissions based on the Phase 3 ACIS Study will not be pursued.[7]
- In a phase 2 study, the efficacy and safety of ERLEADA and AAP with or without ipilimumab or cabazitaxel and carboplatin (CABCARB) in patients with mCRPC based on initial response to 8 weeks of ERLEADA and AAP therapy was evaluated. After a median follow-up of 48 months, the median OS (95% CI) for patients receiving ERLEADA and AAP (Mod2A), ERLEADA and AAP with ipilimumab (Mod2B), and ERLEADA and AAP with CABCARB (Mod3) was 44.3 months (38.1-47.7), 41.4 months (33.3-not reached [NR]), and 18.7 months (14.3-36.3), respectively. Serious adverse events (SAEs) occurred in 3 patients (4.7%), 21 patients (33%), and 6 patients (10.2%) in Mod2A, Mod2B, and Mod3, respectively. In Mod3, 1 death due to neutropenic sepsis was reported.[8,9]
    - Additionally, results from an assessment of aggressive variant prostate cancer molecular signature and androgen indifference have been reported.[10]
- Efficacy results have been reported for the ongoing, phase 2, prospective PANTHER study (NCT03098836) evaluating the use of ERLEADA and abiraterone acetate plus prednisone (AAP) in Black (n=43) and White (n=50) patients with metastatic castration-resistant prostate cancer (mCRPC) (Table: Efficacy Outcomes in Black and White Patients in the PANTHER Study).[11,12]
- A phase 1b study reported results on the antitumor activity, pharmacokinetics (PK), and safety of ERLEADA in combination with AAP in patients with mCRPC (N=57). A ≥50% decline in prostate-specific antigen (PSA) from baseline was reported in 12 of the 15 patients (80%) who did not receive prior AAP or enzalutamide therapy vs 6 of the 42 patients (14%) who received prior therapy. The most commonly reported TEAEs were fatigue (56%), nausea (40%), vomiting (40%), back pain (33%), decreased appetite (32%), constipation (30%), arthralgia (28%), diarrhea (26%), and hypokalemia (25%).[13]
- SATURN (NCT03902951), a prospective, phase 2, single-arm, single-center study, evaluated the efficacy and safety of adding apalutamide, AAP, and prostate-specific

membrane antigen positron emission tomography (PSMA-PET)/computed tomography (CT)-guided metastasis-directed stereotactic body radiotherapy (SBRT) to intermittent ADT for patients with oligorecurrent metastatic hormone-sensitive prostate cancer after prior radical prostatectomy (RP; N=28). The primary endpoint was the percentage of patients with PSA <0.05 ng/mL 6 months after serum testosterone recovery to ≥150 ng/dL following androgen annihilation therapy (AAT).[14]
    - At 6 months after testosterone recovery, PSA was maintained at <0.05 ng/mL in 13 of 26 (50%) evaluable patients (95% CI, 32-67).
    - The rates of grade 2 and 3 AAT toxicity were 21% each.
- Study descriptions of ongoing phase 2-3 studies and results from additional phase 2 studies in multiple clinical states of prostate cancer have been published, however, results were not delineated in studies that included patients with metastatic castration-sensitive prostate cancer (mCSPC).[15-27]

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 3 Study

ACIS Study

Saad et al (2021)[1] reported the efficacy and safety of ERLEADA plus AAP compared to placebo plus AAP in patients with chemotherapy-naïve mCRPC (N=982; NCT02257736).

Study Design/Methods

- Phase 3, randomized, double-blind, placebo-controlled, multicenter study
- Patients were randomized 1:1 to receive either:
    - ERLEADA 240 mg orally (PO) once daily (QD) and abiraterone acetate 1,000 mg PO QD with prednisone 5 mg PO twice daily (BID)
    - Placebo and abiraterone acetate 1,000 mg PO QD with prednisone 5 mg PO BID
- All patients received ongoing ADT.
- Patients received 28-day treatment cycles until unequivocal clinical disease progression, unacceptable toxicity, death, or withdrawal of consent.
- Select inclusion and exclusion criteria are described in the Table: Select Inclusion and Exclusion Criteria in the ACIS Study.
- Patients were stratified by presence or absence of visceral metastases, Eastern Cooperative Oncology Group performance status (ECOG PS; 0 or 1), and geographical region (Europe, USA and Canada, or the rest of world).

Select Inclusion and Exclusion Criteria in the ACIS Study[1,28]

Inclusion Criteria	Exclusion Criteria
• Men (≥18 years) with mCRPC ○ If lymph nodes were the only evidence of metastasis, these had to be ≥2 cm in diameter at the longest point. • mCRPC progression defined by PCWG2 or modified RECIST, version 1.1 • ECOG PS 0 or 1 • Pain score on BPI-SF ≤3	• Small cell (neuroendocrine) carcinoma of the prostate • Known brain metastases • Previous chemotherapy for prostate cancer, except if administered in the adjuvant/neoadjuvant setting • Prior treatment with androgen biosynthesis inhibitors and/or AR inhibitor • Prior treatment with ketoconazole for prostate cancer for >7 days • Current treatment with spironolactone
Abbreviations: AR, androgen receptor; BPI-SF, Brief Pain Inventory-Short Form; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRPC, metastatic castration-resistant prostate cancer; PCWG2, Prostate Cancer Working Group 2; RECIST, Response Evaluation Criteria in Solid Tumors.	

- **Primary endpoint:** rPFS (by investigator), defined as the time from date of randomization to date of radiographic progression or death, whichever occurred first
- **Secondary endpoints:** OS; time to initiation of cytotoxic chemotherapy; time to pain progression; time to chronic opioid use
- **Key Exploratory endpoints:** time to clinical progression; time to first subsequent anticancer therapy; time to second progression-free survival; confirmed decline of at least 50% in PSA concentration (PSA50); time to PSA progression; patient-reported outcomes (measured by the Functional Assessment on Cancer Therapy-Prostate [FACT-P] and the Brief Pain Inventory-Short Form [PI-SF]); safety[2]

Results

Patient Characteristics

- Patient baseline characteristics were comparable between treatment groups (Table: Select Patient Baseline Characteristics).

Select Patient Baseline Characteristics[1]

	ERLEADA Plus AAP Group (n=492)	Placebo Plus AAP Group (n=490)
Age, median (IQR), years	71 (66-78)	71 (65-77)
≥75 years, n (%)	188 (38)	165 (34)
Baseline PSA, median (IQR), ng/mL	32.3 (11.5-91.4)	31.2 (12.2-106.5)
Gleason score at initial diagnosis, n (%)	n=491	n=489
<7	47 (10)	42 (9)
7	162 (33)	161 (33)
>7	260 (53)	258 (53)
Unknown	22 (4)	28 (6)
ECOG PS score at baseline, n (%)		
0	336 (68)	333 (68)
1	156 (32)	157 (32)
Previous prostate cancer therapy, n (%)		
Prostatectomy	127 (26)	149/489 (30)

	ERLEADA Plus AAP Group (n=492)	Placebo Plus AAP Group (n=490)
Radiotherapy	265 (54)	238/489 (49)
Hormonal	491 (100)	488/489 (100)
Adjuvant or neoadjuvant chemotherapy	8 (2)	11/489 (2)
Other	68 (14)	78/489 (16)
Site of disease at baseline, n (%)	n=488	n=487
Bone	406 (83)	423 (87)
Bone only	207 (42)	205 (42)
Lymph node	235 (48)	230 (47)
Soft tissue	60 (12)	66 (14)
Visceral	74 (15)	69 (14)
Adrenal gland	6 (1)	5 (1)
Liver	21 (4)	20 (4)
Lung	53 (11)	50 (10)
Metastasis stage at diagnosis, n (%)	n=490	n=487
M0	229 (47)	204 (42)
M1	164 (33)	171 (35)
Unknown	97 (20)	112 (23)

Abbreviations: AAP, abiraterone acetate with prednisone; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; PSA, prostate-specific antigen.

Efficacy

- A summary of efficacy results is provided in Table: Prespecified Primary, Secondary, and Exploratory Endpoints.
- At the primary analysis for rPFS, after a median follow-up of 25.7 months, a statistically significant improvement in median rPFS was observed: 22.6 months in the ERLEADA plus AAP group vs 16.6 months in the placebo plus AAP group (HR, 0.69; 95% CI, 0.58-0.83; *P*<0.0001).
    - A blinded independent central review showed 75% concordance in radiographic progression determination with the investigator review, with high positive correlation coefficients in both treatment groups (R=0.833; 95% CI, 0.77–0.88 for ERLEADA plus AAP and R=0.80; 95% CI, 0.75–0.85 for placebo plus AAP).
- At the updated analysis for rPFS, after a median follow-up of 54.8 months, consistent improvement in median rPFS was observed with ERLEADA plus AAP compared with placebo plus AAP (24.0 months vs 16.6 months, respectively; HR, 0.70; 95% CI, 0.60-0.83; *P*<0.0001).
- At the final analysis for OS, after a median follow-up of 54.8 months, the median OS was 36.2 months in the ERLEADA plus AAP group and 33.7 months in the placebo plus AAP group (HR, 0.95; 95% CI, 0.81-1.11; *P*=0.50).
- A total of 391 patients (79%) in the ERLEADA plus AAP group and 357 patients (73%) in the placebo plus AAP demonstrated PSA50 (RR, 1.09; 95% CI, 1.02-1.17; *P*=0.015). Additionally, 121 patients (25%) in the ERLEADA plus AAP group and 94 patients (19%) in the placebo plus AAP group reached an undetectable PSA level (<0.2 ng/mL) at any time during treatment (RR, 1.28; 95% CI, 1.01-1.62; *P*=0.040).
- Of the patients who were alive at the time of treatment discontinuation, 273 of 437 patients (62%) in the ERLEADA plus AAP group and 282 of 435 patients (65%) in

the placebo plus AAP group received life-prolonging subsequent therapy for prostate cancer.

- The most common subsequent life-prolonging therapy was chemotherapy, including cabazitaxel or docetaxel (69% [189/273] in the ERLEADA plus AAP group and 71% [200/282] in the placebo plus AAP group). Additionally, 22% of patients (61/273) in the ERLEADA plus AAP group and 20% (56/282) in the placebo plus AAP group received hormonal therapy, including enzalutamide or darolutamide.[28]

Prespecified Primary, Secondary, and Exploratory Endpoints[1]

Median (95% CI)	ERLEADA Plus AAP Group (n=492)	Placebo Plus AAP Group (n=490)	Hazard Ratio[a] (95% CI; *P*-Value[b])
Primary Endpoint (primary analysis)[c]			
rPFS, months	22.6 (19.5-27.4)	16.6 (13.9-19.3)	0.69 (0.58-0.83; <0.0001)
Primary Endpoint (final analysis)[d]			
rPFS, months	24.0 (19.7-27.5)	16.6 (13.9-19.3)	0.70 (0.60-0.83; <0.0001)
Secondary Endpoints			
OS, months	36.2 (32.8-38.8)	33.7 (31.2-38.3)	0.95 (0.81-1.11; 0.50)
Time to initiation of cytotoxic chemotherapy, months	36.1 (32.2-42.6)	34.2 (29.5-39.2)	0.94 (0.78-1.13; 0.51)
Time to chronic opioid use, months	47.0 (39.2-NE)	53.3 (42.0-NE)	1.07 (0.87-1.32; 0.50)
Time to pain progression, months	21.8 (18.0-25.7)	26.5 (22.6-29.5)	1.12 (0.95-1.33; 0.19)
Exploratory Endpoints			
Time to clinical progression, months	16.0 (14.3-17.3)	18.1 (16.4-19.8)	1.10 (0.96-1.27; 0.18)
Time to first subsequent anticancer therapy, months	25.6 (22.6-28.6)	23.5 (20.4-27.3)	0.96 (0.82-1.13; 0.63)
Time to PFS2, months	31.8 (28.4-36.9)	30.2 (27.2-34.9)	0.92 (0.78-1.08; 0.31)
Time to PSA progression, months	13.8 (12.0-5.6)	12.0 (10.2-13.8)	0.87 (0.74-1.02; 0.076)

Abbreviations: AAP, abiraterone acetate with prednisone; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not estimable; OS, overall survival; PFS2, second progression-free survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.
[a]Stratified proportional hazards model where HR<1 favors ERLEADA plus AAP
[b]Long-rank test stratified by ECOG PS at screening, presence of visceral metastases at screening, and geographic region.
[c]After a median follow-up of 25.7 months.
[d]After a median follow-up of 54.8 months.

Safety

- A summary of AEs is described in Table: Summary of Adverse Events.
- The most common TEAEs leading to death were myocardial infarction (n=3), pneumonia (n=2), and pulmonary embolism (n=2) in the ERLEADA plus AAP group and myocardial infarction (n=3), cardiac failure (n=3), cardiorespiratory arrest (n=3), multiple organ dysfunction syndrome (n=2), and sudden death (n=5) in the placebo plus AAP group.[28]

Summary of Adverse Events[1]

n (%)	ERLEADA Plus AAP Group (n=490)				Placebo Plus AAP Group (n=489)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Any TEAE	173 (35)	268 (55)	26 (5)	17 (3)	187 (38)	214 (44)	36 (7)	37 (8)
Drug-related TEAEs	228 (47)	132 (27)	6 (1)	3 (1)	228 (47)	93 (19)	6 (1)	5 (1)
Serious TEAEs	9 (2)	151 (31)	18 (4)	17 (3)	11 (2)	110 (22)	22 (4)	37 (8)
Drug-related serious TEAEs	1 (<1)	23 (5)	3 (1)	3 (1)	5 (1)	18 (4)	3 (1)	5 (1)
TEAEs leading to discontinuation	28 (6)	38 (8)	8 (2)	9 (2)	7 (1)	22 (4)	9 (2)	23 (5)
Drug-related TEAEs leading to discontinuation	21 (4)	19 (4)	1 (<1)	2 (<1)	2 (<1)	4 (1)	2 (<1)	3 (1)
TEAEs associated with death[a]	17 (3)				37 (8)			
Drug-related TEAEs leading to death	3 (1)				5 (1)			
TEAEs reported in ≥15% of patients in the ERLEADA plus AAP group								
Fatigue	150 (31)	15 (3)	0	0	122 (25)	12 (2)	0	0
Back pain	140 (29)	16 (3)	0	0	117 (24)	17 (3)	0	0
Hypertension	62 (13)	82 (17)	0	0	73 (15)	49 (10)	0	0
Weight decreased	128 (26)	8 (2)	0	0	78 (16)	6 (1)	0	0
Arthralgia	114 (23)	14 (3)	0	0	115 (24)	6 (1)	0	0
Fall	90 (18)	16 (3)	0	0	90 (18)	3 (1)	0	0
Constipation	96 (20)	0	0	0	94 (19)	2 (<1)	0	0
Diarrhea	85 (17)	7 (1)	0	0	71 (15)	3 (1)	0	0
Nausea	76 (16)	8 (2)	0	0	72 (15)	5 (1)	0	0
Pain in extremity	72 (15)	9 (2)	0	0	56 (11)	1 (<1)	0	0
Headache	75 (15)	4 (1)	0	0	61 (12)	2 (<1)	0	0
Hypokalemia	62 (13)	14 (3)	3 (1)	0	54 (11)	17 (3)	3 (1)	0
Peripheral oedema	76 (16)	0	0	0	70 (14)	3 (1)	0	0
Hot flush	74 (15)	0	0	0	56 (11)	0	0	0
TEAEs of special interest								
Hypertension	57 (12)	100 (20)	1 (<1)	0	69 (14)	61 (12)	0	0
Fall	90 (18)	16 (3)	0	0	90 (18)	3 (1)	0	0
Skin rash	79 (16)	21 (4)	1 (<1)	0	47 (10)	2 (<1)	0	0
Cardiac disorders[b]	43 (9)	38 (8)	6 (1)	6 (1)	48 (10)	26 (5)	2 (<1)	18 (4)
Hypokalemia[c]	62 (13)	14 (3)	3 (1)	0	54 (11)	17 (3)	3 (1)	0
Peripheral edema	90 (18)	1 (<1)	0	0	89 (18)	4 (1)	0	0
Fracture[d] and osteoporosis	54 (11)	20 (4)	0	0	52 (11)	7 (1)	0	0

n (%)	ERLEADA Plus AAP Group (n=490)				Placebo Plus AAP Group (n=489)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Ischemic CV disorders	5 (1)	3 (1)	0	1 (<1)	7 (1)	2 (<1)	4 (1)	1 (<1)
Seizures	2 (<1)	1 (<1)	0	0	0	0	0	1 (<1)

Abbreviations: AAP, abiraterone acetate with prednisone; CV, cardiovascular; DC, discontinuation; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Included cardiac disorders (n=6 [1%] in the ERLEADA plus AAP group and n=13 [3%] in the placebo plus AAP group).
[b]Cardiac disorders included cardiac arrhythmia, ischemic heart disease, cardiac failure, and other cardiac disorders.
[c]Includes only one term.
[d]Excluding fractures related to bone metastasis.

Phase 2 Studies

Viscuse et al (2022)[8] reported results from the DynAMo study evaluating the efficacy and safety of ERLEADA and AAP with or without ipilimumab or CABCARB in patients with mCRPC based on initial response to 8 weeks of ERLEADA and AAP therapy (N=195; NCT02703623).

Study Design/Methods

- Phase 2, open-label study
- All patients received ERLEADA and AAP for 8 weeks (Mod1). Patients who achieved PSA50 from baseline and circulating tumor cell (CTC) ≤5/7.5 mL at week 8 were considered satisfactory (S) responders; patients who did not were considered unsatisfactory (US) responders.
- S patients were then randomized to receive one of two treatments:
  - ERLEADA PO QD, abiraterone acetate PO QD, and prednisone PO BID (Mod2A)[9]
  - ERLEADA PO QD, abiraterone acetate PO QD, prednisone PO BID, and ipilimumab IV, up to 4 cycles (Mod2B)[9]
- US patients continued ERLEADA and AAP with up to 10 cycles of CABCARB (Mod3).
- All patients received ERLEADA and AAP until progression.
- **Select exclusion criteria:** any prior treatment with ipilimumab; treatment with any other systemic therapy for prostate cancer within 28 days of cycle 1 day 1, including investigational products (exceptions were luteinizing hormone-releasing hormone [LHRH] agonists, LHRH antagonists, bisphosphonates, and RANK-ligand inhibitors); treatment within 12 months of cycle 1 day 1 with any CYP17-lyase inhibitor, any second generation androgen receptor (AR) antagonist, cabazitaxel, or carboplatin; patients who experienced disease progression while on treatment or within 3 months of discontinuation of any CYP17-lyase inhibitor, any second generation AR antagonist, cabazitaxel, or carboplatin
- OS was calculated from entry into Mod2 or Mod3.

Results

Patient Characteristics

- Of 195 enrolled patients, 128 (67%) patients were allocated to S and randomized to Mod2A (n=64) and Mod2B (n=64).
- In Mod3 (n=64), 59 patients were treated with CABCARB on study.
- In Mod1, 3 patients went off study without clinical decline.
- US patients were more likely than S patients to have had de novo metastases (33% vs 59%; *P*<0.001), Response Evaluation Criteria in Solid Tumor (RECIST) measurable disease (23% vs 42%; *P*=0.01), and liver metastases (3% vs 42%; *P*=0.01).

- Based on historical data, the estimated median OS for patients in Mod2 and Mod3 were 36 months and 16 months, respectively.

Efficacy

- After a median follow-up of 48 months, the median OS (95% CI) for patients in Mod2A, Mod2B, and Mod3 was 44.3 months (38.1-47.7), 41.4 months (33.3-NR), and 18.7 months (14.3-36.3), respectively.

Safety

- SAEs occurred in 3 patients (4.7%), 21 patients (33%), and 6 patients (10.2%) in Mod2A, Mod2B, and Mod3, respectively.
- In Mod3, 1 death due to neutropenic sepsis was reported.

George et al (2024)[11] and **(2023)**[12] reported results of the ongoing PANTHER study evaluating the efficacy and safety of ERLEADA and AAP in patients with mCRPC stratified by race (Black, n=43; White, n=50).

Study Design/Methods

- Phase 2, prospective, open-label, multicenter, parallel cohort study
- All patients were treated with ERLEADA 240 mg PO QD, abiraterone acetate 1000 mg PO QD, and prednisone 5 mg PO BID until unacceptable toxicity, disease progression, or 2 years,[29] at which point patients were switched to standard of care.
- **Select inclusion criteria**: mCRPC, prior docetaxel allowed in the mCSPC setting, adequate lab function, evaluable disease by Response Evaluation Criteria in Solid Tumors (RECIST)/Prostate Cancer Working Group 3 (PCWG3), self-reported race as either Black/African American or White
- **Select exclusion criteria**: prior treatment with an androgen receptor pathway inhibitor (ARPI), prior treatment with ketoconazole for prostate cancer >7 days
- **Primary endpoint:** rPFS
- **Secondary endpoints:** time to PSA progression, OS, PSA response
- **Exploratory endpoints:** safety, correlative biomarkers of outcome by race and ancestry

Results

Patient Demographics

- Key baseline characteristics for each cohort are summarized in Table: Select Baseline Patient Characteristics.

Select Baseline Patient Characteristics[11]

Characteristic	Black Patients (n=43)	White Patients (n=50)
Median age, years	67	72
Gleason score 8-10, %	56	56
Karnofsky performance status, 70-80%, %	26	18
Median PSA, ng/mL	15.20	17.56
Median time from diagnosis to enrollment, years	4.6	3.3
Visceral metastases, %	23.7	18.0
Prior docetaxel, %	33	44

Characteristic	Black Patients (n=43)	White Patients (n=50)
Abbreviation: PSA, prostate-specific antigen.		

Efficacy

- Efficacy outcomes for both cohorts are summarized in Table: Efficacy Outcomes in Black and White Patients in the PANTHER Study. In the long-term efficacy analysis, the median follow-up was 56 months and 62 months for the Black and White cohort, respectively.

Efficacy Outcomes in Black and White Patients in the PANTHER Study[11,12]

Rate	Black Patients (n=43)	White Patients (n=50)
Long Term Efficacy Outcomes		
24-month rPFS, % (95% CI)	61 (49-78)	38 (27-54)
rPFS events	22	40
36-month OS, % (95% CI)	68 (55-83)	50 (37-66)
OS events	20	35
Interim Efficacy Outcomes		
12-month rPFS, % (95% CI)	79 (68-92)	51 (39-67)
24-month rPFS, % (95% CI)	63 (50-80)	38 (26-55)
rPFS events	18	36
12-month TTP, % (95% CI)	81 (69-94)	59 (43-80)
24-month TTP, % (95% CI)	59 (46-77)	39 (25-60)
12-month OS, % (95% CI)	95 (89-100)	84 (73-97)
24-month OS, % (95% CI)	83 (74-95)	65 (52-80)
OS events	15	30
n (%)		
≥50% PSA decline	40 (93)	34 (68)
PSA <0.1	21 (49)	14 (28)
No PSA decline	1 (2.3)	7 (14)
Abbreviations: CI, confidence interval; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; TTP, time to PSA progression.		

Safety

- Safety results were not reported.

Phase 1 Studies

Posadas et al (2020)[13] reported results for a phase 1b study that evaluated the antitumor activity, PK, and safety of ERLEADA in combination with AAP in patients with mCRPC (N=57). PK results for the dose-escalation portion of the study were reported previously.[30]

Study Design/Methods

- Phase 1b, open-label, multicenter study

- Patients ≥18 years of age with progressive mCRPC and ECOG PS ≤2 received therapy with abiraterone acetate 1,000 mg PO QD plus prednisone 5 mg PO BID on treatment cycle 1 day 1 with the addition of ERLEADA 240 mg PO QD on cycle 1 day 8 over 28-day treatment cycles.
- Surgical castration or continuous ADT with a gonadotropin-releasing hormone analog (GnRHa) was required to maintain castrate levels of testosterone (<50 ng/dL).
- Patients could have received any number of prior hormonal therapies, including abiraterone acetate and enzalutamide, and prior chemotherapy was allowed.
- Antitumor activity was primarily assessed using PSA data, including the proportion of patients with PSA50 and a PSA decline of ≥90% (PSA90).

Results

Patient Characteristics

- Median patient age was 70 years (range, 49-89 years), ECOG PS was 0 or 1 for 96% of patients, and median baseline PSA was 111 µg/L (range, 4-2597 µg/L).
- Bone, nodal, and visceral disease were present in 50 (88%), 31 (54%), and 17 (30%) patients, respectively.
- A total of 42 patients (74%) received prior therapy with abiraterone acetate and/or enzalutamide (AAP only, n=19; enzalutamide only, n=13; both, n=10), while 15 patients (26%) did not receive prior therapy with either agent.

Efficacy

- Median treatment durations were 36.0 weeks (range, 8-92 weeks) for patients who did not receive prior therapy with AAP or with enzalutamide, 28.0 weeks (range, 3-88 weeks) for those who received prior AAP only, 15.9 weeks (range, 8-40 weeks) for those who received prior enzalutamide only, and 10.4 weeks (range, 4-31 weeks) for those who received both agents previously.
- The overall median treatment duration among patients who received ERLEADA plus AAP was 17 weeks (range, 3-92 weeks).
- Eighteen (32%) patients had a PSA50 from baseline at any time, and 6 (11%) patients had PSA90 from baseline at any time.
- Patients who did not receive prior AAP or enzalutamide therapy were more likely to have a reduction in PSA from baseline than those who received prior therapy and were also more likely to have a greater mean decrease in PSA level.
    - Twelve of the 15 patients (80%) who did not receive prior AAP or enzalutamide therapy reached PSA50 compared with 6 of the 42 patients (14%) who received prior therapy.
    - PSA90 was achieved by 6 of the 15 patients (40%) who did not receive prior AAP or enzalutamide therapy and by none of patients who did receive prior therapy.

PK

- Administration of apalutamide in combination with AAP resulted in approximate decreases of 23% in abiraterone maximum plasma concentration (C_{max}), 14% in abiraterone area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}), and 5% in abiraterone minimum plasma concentration (C_{min}).
- Exposures to prednisone and its metabolite prednisolone were reduced by 51% to 61% and 26% to 42%, respectively, when administered with apalutamide.
- The PK parameters of apalutamide and N-desmethyl apalutamide observed with the administration of apalutamide 240 mg QD in combination with AAP were similar to those previously reported for apalutamide alone.

Safety

- Forty-seven patients (83%) discontinued treatment, with the most common reason being clinical progression (with or without PSA progression, 68%), followed by patient withdrawal (7%), PSA progression (without clinical progression, 3.5%), physician decision (n=1), and death (n=1).
- The most commonly reported (≥25% of patients) TEAEs were fatigue (56%), nausea (40%), vomiting (40%), back pain (33%), decreased appetite (32%), constipation (30%), arthralgia (28%), diarrhea (26%), and hypokalemia (25%).
- Grade 3 TEAEs reported in >1 patient included fatigue (8.8%), hypokalemia (5.3%), anemia (5.3%), and back pain (3.5%) along with pneumonia, hyponatremia, hypertension, and fall (incidence not reported); grade 4 TEAEs were reported in 3 patients (5.3%) and included hypokalemia, pyrexia, and septic shock and fall (reported in 1 patient each).
- One patient discontinued treatment due to grade 3 fatigue.
- Serious AEs were reported in 22 patients (39%) and those reported in >1 patient included pneumonia (n=4); back pain (n=3); constipation, pyrexia, and fall (n=2 each); majority of these events were not considered related to study drugs.
- Six deaths were reported in the study; however, none were considered related to study treatment.

Phase 1 Study in Patients with mCRPC

In a phase I trial that evaluated the safety and efficacy of ERLEADA in combination with AAP and docetaxel in patients with mCRPC (N=16), Cohort 1 had 4 patients that received ERLEADA 120 mg QD and cohort 2 had 12 patients that received ERLEADA 240 mg QD. Both cohorts also received abiraterone acetate 1,000 mg PO QD plus prednisone 5 mg PO BID and docetaxel 75 mg/m^2 every 3 weeks. Following initial combination therapy, ERLEADA plus AAP could be continued without docetaxel. A study expansion added men at full doses of all medications.[31,32]

During dose escalation, there was one dose-limiting toxicity of grade 3 hypertension. In the overall study, including expansion, non-hematologic AEs included grade 3 hypertension, hyperglycemia, and rash, and grade 2 hypertension, fatigue, rash, neuropathy, and nausea. Hematologic AEs included grade 3 anemia and grade 4 neutropenia with one case of febrile neutropenia. A total of 15 patients (93.8%) had PSA50, of which 12 patients achieved PSA90 and 4 patients a PSA decline of >99%. Median rPFS was not reached with a median follow-up of 22.8 months. The 2-year rPFS was 70.1% (95% CI, 32.3-89.5).[32] Interim results have been previously reported.[33]

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 May 2024. Summarized in this response are relevant data limited to patients with mCRPC. No studies were identified that evaluated ERLEADA in combination with abiraterone acetate in patients with non-metastatic castration-resistant prostate cancer (nmCRPC).

REFERENCES

1. Saad F, Efstathiou E, Attard G, et al. Apalutamide plus abiraterone acetate and prednisone versus placebo plus abiraterone and prednisone in metastatic, castration-resistant prostate cancer (ACIS): a randomised, placebo-controlled, double-blind, multinational, phase 3 study. *Lancet Oncol*. 2021;22(11):1541-1559.

2. Oudard S, Bevans KB, Attard G, et al. Health-related quality of life in ACIS: a phase 3 trial of apalutamide with abiraterone acetate and prednisone (APA + AAP) vs AAP in metastatic castration-resistant prostate cancer (mCRPC). Poster presented at: European Society for Medical Oncology (ESMO) Congress; September 16-21, 2021; Virtual.

3. Efstathiou E, Attard G, Lucas J, et al. Blood biomarkers and association with clinical outcomes in metastatic castration-resistant prostate cancer: longitudinal analysis from the ACIS study of apalutamide or placebo combined

with abiraterone acetate plus prednisone. Poster presented at: American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium; February 17-19, 2022; San Francisco, CA.

4. Roy S, Wallis CJD, Morgan SC, et al. Implications of metastatic stage at presentation in docetaxel naive metastatic castration resistant prostate cancer. *Prostate*. 2023;83(10):912-921.

5. Saad F, Efstathiou E, Attard G, et al. Analysis of two prespecified subgroups in ACIS evaluating apalutamide + abiraterone acetate plus prednisone (APA + AAP) vs placebo (PBO) + AAP in metastatic castration-resistant prostate cancer (mCRPC). Poster presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 4-8, 2021; Virtual.

6. Saad F, Efstathiou E, Attard G, et al. Analysis of two poor prognosis subgroups in ACIS evaluating apalutamide + abiraterone acetate plus prednisone (APA + AAP) versus placebo (PBO) + AAP in metastatic castration-resistant prostate cancer (mCRPC) [abstract]. *J Clin Oncol*. 2021;150(Suppl. 15):Abstract 5037.

7. Johnson & Johnson. Janssen Provides Update on Phase 3 ACIS Study in Patients with Metastatic Castration-Resistant Prostate Cancer Treated with ERLEADA® (apalutamide) and ZYTIGA® (abiraterone acetate) Plus Prednisone Combination. Accessed May 21, 2024. Available at: https://www.jnj.com/janssen-provides-update-on-phase-3-acis-study-in-patients-with-metastatic-castration-resistant-prostate-cancer-treated-with-erleada-apalutamide-and-zytiga-abiraterone-acetate-plus-prednisone-combination

8. Viscuse PV, Tidwell R, Liu J, et al. DynAMo: a dynamic allocation modular sequential trial of approved and promising therapies in men with metastatic CRPC [abstract]. *J Clin Oncol*. 2022;40(Suppl. 16):Abstract 5059.

9. M.D. Anderson Cancer Center. A dynamic allocation modular sequential trial of approved and promising therapies in men with metastatic castrate resistant prostate cancer. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2024 May 21]. Available from: https://clinicaltrials.gov/ct2/show/NCT02703623. NLM Identifier: NCT02703623.

10. Viscuse PV, Zhang M, Liu J, et al. Linking the aggressive variant prostate cancer (AVPC) molecular signature (-ms) to androgen indifference in a prospective clinical trial. *J Clin Oncol*. 2020;38((suppl 6)):Abstract 156.

11. George DJ, Halabi S, Fleming MT, et al. Overall survival from PANTHER: a multicenter trial of apalutamide, abiraterone acetate plus prednisone in Black and White patients with metastatic castration-resistant prostate cancer (mCRPC) [abstract]. *J Clin Oncol*. 2024;42(Suppl. 16):Abstract 5072.

12. George DJ, Halabi S, Fleming M, et al. A prospective trial of apalutamide and abiraterone acetate plus prednisone in Black and White men with metastatic castrate-resistant prostate cancer [abstract]. *J Clin Oncol*. 2023;41(Suppl. 16):Abstract 5015.

13. Posadas EM, Chi KN, de Wit R, et al. Pharmacokinetics, safety, and antitumor effect of apalutamide with abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: phase Ib study. *Clin Cancer Res*. 2020;26(14):3517-3524.

14. Nikitas J, Rettig M, Shen J, et al. Systemic and tumor-directed therapy for oligorecurrent metastatic prostate cancer (SATURN): primary endpoint results from a phase 2 clinical trial. *Eur Urol*. 2024;85(6):517-520.

15. McKay RR, Xie W, Ye H, et al. Results of a randomized phase II trial of intense androgen deprivation therapy prior to radical prostatectomy in men with high-risk localized prostate cancer. *J Urol*. 2021;206(1):80-87.

16. McKay RR, Xie W, Yang X, et al. Postradical prostatectomy prostate-specific antigen outcomes after 6 versus 18 months of perioperative androgen-deprivation therapy in men with localized, unfavorable intermediate–risk or high-risk prostate cancer: results of part 2 of a randomized phase 2 trial. *Cancer*. 2024;130(9):1629-1641.

17. Sterling J, Chua K, Patel H, et al. Interim analysis of phase 2 randomized prospective study of neoadjuvant apalutamide/abiraterone acetate with prednisone and the feasibility of performing nerve-sparing radical prostatectomy in men with high-risk prostate cancer (NCT02949284) [abstract]. *J Urol*. 2020;203(Suppl. 4):Abstract PD10-09.

18. Efstathiou E, Boukovala MA, Spetsieris N, et al. Neoadjuvant apalutamide (APA) plus leuprolide (LHRHa) with or without abiraterone (AA) in localized high-risk prostate cancer (LHRPC). *J Clin Oncol*. 2020;38(Suppl. 15):5504-5504.

19. Maluf FC, Schutz FA, Cronemberger EH, et al. A phase 2 randomized clinical trial of abiraterone plus ADT, apalutamide, or abiraterone and apalutamide in patients with advanced prostate cancer with non-castrate testosterone levels (LACOG 0415). *Eur J Cancer*. 2021;158:63-71.

20. Teo MY, Taplin M, Eastham JA, et al. Metacure: multi-arm multimodality therapy for very high risk localized and low volume metastatic prostatic adenocarcinoma [abstract]. *J Clin Oncol*. 2019;37(Suppl. 7):Abstract TPS349.

21. Teo MY, McBride SM, Gopalan A, et al. Biochemical response (PSA0) and testosterone (T) recovery in Metacure, a multi-arm multi-modality (MM) therapy (tx) for very high risk localized (HRL) and low volume metastatic (LVM) prostatic adenocarcinoma [abstract]. *Ann Oncol*. 2021;32(Suppl. 5):Abstract 637P.

22. Graham LS, True LD, Gulati R, et al. Targeting backdoor androgen synthesis through AKR1C3 inhibition: a presurgical hormonal ablative neoadjuvant trial in high-risk localized prostate cancer. *Prostate*. 2021;81(7):418-426.

23. McBride SM, Spratt DE, Kollmeier M, et al. Interim results of AASUR: a single arm, multi-center phase 2 trial of apalutamide (A) + abiraterone acetate + prednisone (AA+P) + leuprolide with stereotactic ultrahypofractionated radiation (UHRT) in very high risk (VHR), node negative (N0) prostate cancer (PCa) [abstract]. *J Clin Oncol*. 2021;39(Suppl. 15):Abstract 5012.

24. Aggarwal R, Heller G, Hillman DW, et al. PRESTO: a phase III, open-label study of intensification of androgen blockade in patients with high-risk biochemically relapsed castration-sensitive prostate cancer (AFT-19). *J Clin Oncol*. 2024;42(10):1114-1123.

25. Aggarwal R, Eggener S, Heller G, et al. Updated progression-free survival from PRESTO: a phase 3 randomized study of androgen annihilation for high-risk biochemically relapsed prostate cancer (AFT-19) [abstract]. *J Urol*. 2023;209(Suppl. 4). Abstract LBA02-11.

26. Maluf FC, Soares A, Bastos DA, et al. Survival analysis of the randomized phase II trial to investigate androgen signaling inhibitors with or without androgen deprivation therapy (ADT) for castration-sensitive prostate cancer: LACOG 0415 [abstract]. *J Clin Oncol*. 2022;40(Suppl. 16):Abstract 5076.

27. Chen RC, Mazza GL, Fruth B, et al. Health-related quality of life (HRQOL) results from PRESTO (AFT-19), a phase 3 randomized trial of intensification of androgen blockade in patients with high-risk biochemically relapsed castration sensitive prostate cancer [abstract]. *J Clin Oncol*. 2024;42(Suppl. 16):Abstract 5006.

28. Saad F, Efstathiou E, Attard G, et al. Supplement to: Apalutamide plus abiraterone acetate and prednisone versus placebo plus abiraterone and prednisone in metastatic, castration-resistant prostate cancer (ACIS): a randomised, placebo-controlled, double-blind, multinational, phase 3 study. *Lancet Oncol*. 2021;22(11):1541-1559.

29. Janssen Research & Development, LLC. Apalutamide and abiraterone acetate in African American and Caucasian men with metastatic castrate resistant prostate cancer (PANTHER). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2024 May 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT03098836. NLM Identifier: NCT03098836.

30. Posadas EM, Chi KN, Wit R de, et al. Pharmacokinetics and safety of ARN-509 with abiraterone acetate and prednisone in patients with metastatic castration-resistant prostate cancer. Poster presented at: American Association for Cancer Research (AACR) Annual Meeting; April 18-22, 2015; Philadelphia, PA.

31. Weill Medical College of Cornell University. A phase 1 trial of apalutamide plus abiraterone acetate, docetaxel, and prednisone in patients with metastatic castrate resistant prostate cancer (mCRPC). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2024 May 21]. Available from: https://clinicaltrials.gov/show/NCT02913196. NLM Identifier: NCT02913196.

32. Nauseef JT, Christos PJ, Thomas C, et al. Phase I trial of apalutamide (Apa) with abiraterone acetate (AA) plus prednisone (P) and docetaxel (Doce) in patients with metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol*. 2021;39(Suppl. 6):140-140.

33. Molina A, Christos P, Hackett A, et al. Phase 1 trial of apalutamide plus abiraterone acetate, docetaxel, and prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) [abstract]. *Cancer Res*. 2019;79:Abstract CT097.