ERLEADA® (apalutamide) SPARTAN Study

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SPARTAN

SPARTAN (NCT01946204) was a phase 3, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of apalutamide compared to placebo in 1207 patients with high-risk nmCRPC. Continuous ADT with a GnRH analog or surgical castration was required.[1]

Key Efficacy Outcomes

- At the final analysis (following 378 events) for MFS, significant improvement in median MFS was observed in the apalutamide vs placebo group (40.5 vs 16.2 months; HR, 0.28; 95% CI, 0.23-0.35; *P*<0.001).[1]
  - Apalutamide was associated with improvements in all secondary endpoints, including significant improvement observed in:[1,2]

    - TTM: HR, 0.27; 95% CI, 0.22-0.34; P<0.001
    - PFS: HR, 0.29; 95% CI, 0.24-0.36; P<0.001

- At the final analysis (following 428 events) for OS, after a median follow up of 52 months, a statistically significant improvement in median OS was observed in the apalutamide vs placebo group (73.9 vs 59.9 months; HR, 0.78; 95% CI, 0.64-0.96, *P*=0.016).[3]
  - A statistically significant delay in median time to initiation of cytotoxic chemotherapy was observed in the apalutamide vs placebo group (median NR in both groups; HR, 0.63; 95% CI, 0.49-0.81), *P*=0.0002).
  - Additionally, an improvement in median time to symptomatic progression was observed in the apalutamide vs placebo group (median NR in both groups; HR, 0.57; 95% CI, 0.44-0.73), nominal *P*<0.0001). This endpoint was not adjusted for multiple comparisons. Therefore, the P-value displayed is nominal, and statistical significance has not been established.

Key Safety Outcomes

- AEs that occurred in ≥15% of patients in the apalutamide group included: fatigue, hypertension, diarrhea, fall, arthralgia, nausea, weight decreased, back pain, and hot flush.[3]

On the basis of the efficacy and safety data, the independent data and safety monitoring committee unanimously recommended unblinding the study and offering patients assigned to the placebo group the option to receive apalutamide.[1]

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- This study evaluated the efficacy and safety of apalutamide compared to placebo in 1207 patients with high-risk (defined as PSADT ≤10 months during continuous ADT) nmCRPC.[1]
- Phase 3, randomized, double-blind, placebo-controlled, multicenter (332 sites in 26 countries in North America, Europe, and Asia-Pacific) study.[1]

SPARTAN Study Design[1,4]

Patients (N=1207)

Eligibility:
- nmCRPC
  - Negative ^{99m}Tc bone scan
  - Negative CT of pelvis, abdomen, chest, and brain
  - No local or regional nodal disease (N0); however, pelvic nodes <2 cm below iliac bifurcation (N1) were allowed[5]
- PSADT ≤10 months

On-Study Requirement:
- Continuous ADT[a]

Stratification Factors:
- PSADT >6 months or ≤6 months
- Bone-sparing agents (yes vs no)
- Locoregional disease (N0 vs N1)

Randomization 2:1

Apalutamide 240 mg daily + **ADT** (n=806)

Placebo + **ADT** (n=401)

Primary Endpoint MFS

Secondary Treatment Option

Patients eligible to receive secondary therapy open-label at physician's discretion for mCRPC[b]

Progression

[a]Continuous ADT with a GnRH analog or surgical castration was required for patients in both treatment arms in order to maintain castrate levels of testosterone (<50 ng/dL); choice of medical castration was at the discretion of the investigator.[4]

[b]After the first detection of distant metastasis, patients were eligible to receive sponsor-provided abiraterone acetate plus prednisone as a treatment option. All post study treatment for mCRPC was at the treating physician's discretion.[1]

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Select Inclusion Criteria[1,4]	**Select Exclusion Criteria**[1,4]
• ≥18 years of age • Histologically or cytologically confirmed adenocarcinoma of the prostate • Castration-resistant, with high risk for development of metastases (defined as PSADT ≤10 months) during continuous ADT (surgical or medical castration) • Maintenance of castrate testosterone levels within 4 weeks prior to randomization and throughout the study • ECOG PS of 0 or 1 • Adequate organ function	• Presence of detectable distant metastases • Prior treatment with second-generation antiandrogens, CYP17 inhibitors, radiopharmaceutical agents, immunotherapy, or any other investigational agent(s) for nmCRPC • Prior chemotherapy for prostate cancer, except if administered in the adjuvant/ neoadjuvant setting • History of seizure or condition that may predispose to seizure

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Primary Endpoint[4,5]

- MFS

Secondary Endpoints[1,4]

- TTM
- PFS
- Time to symptomatic progression
- OS
- Time to initiation of cytotoxic chemotherapy
- Safety and tolerability

Exploratory Endpoints[1,4]

- Time to PSA progression
- PSA response rate
- PROs, assessed by the FACT-P questionnaire and the EQ-5D-3L questionnaire
- PFS2

Endpoint Definitions

Endpoint Definitions[1,4,5]

- ***MFS,*** defined as the time from randomization to the time of first evidence of blinded independent central review-confirmed distant metastasis, defined as new bone or soft-tissue lesions or enlarged lymph nodes above the iliac bifurcation, or death due to any cause, whichever occurred first
- ***TTM,*** defined as time from randomization to first detection of distant metastasis involving bone or soft tissue on imaging, as assessed by blinded independent central review
- ***PFS***, defined as time from randomization to first detection of local or distant metastatic disease on imaging, assessed by blinded independent central review, or death from any cause, whichever occurred first
- ***Time to symptomatic progression,*** defined as time from randomization to skeletal-related event, pain progression, or worsening of disease-related symptoms leading to initiation of a new systemic anticancer therapy, or the time to development of clinically significant symptoms due to local or regional tumor progression requiring surgery or radiation therapy
- ***Time to PSA progression***, defined as time from randomization to PSA progression per PCWG2 criteria
- ***PSA response rate***, defined as the percentage of patients who had a decline from baseline in the PSA level of at least 50% per PCWG2 criteria
- ***PFS2***, defined as 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

mCRPC, metastatic castration-resistant prostate cancer; MFS, metastasis-free survival; PCWG2, Prostate Cancer Working Group 2; PFS, progression-free survival; PFS2, second PFS; PSA, prostate-specific antigen; TTM, time to metastasis.

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- Patient demographic and disease characteristics were well balanced between the 2 groups, and there were no significant differences.[1]

Parameters[1,6]	**Apalutamide Group (n=806)**	**Placebo Group (n=401)**
Median age, years (range)	74 (48-94)	74 (52-97)
Race, n (%)		
White	524 (65.0)	276 (68.8)
Asian	93 (11.5)	47 (11.7)
Black or African American	48 (6.0)	20 (5.0)
Not reported	135 (16.7)	57 (14.2)
Median time from initial diagnosis to randomization, years	7.95	7.85
Median PSADT, months	4.40	4.50
Median PSA level at study entry, ng/mL	7.78	7.96
Median testosterone level at study entry, nmol/L (range)	0.80 (0.3-3.1)	0.80 (0.3-2.8)
Gleason score at initial diagnosis, n (%)[a]		
<7	152 (19.4)	72 (18.6)
7	291 (37.1)	146 (37.7)
>7	341 (43.5)	169 (43.7)
ECOG PS score, n (%)		
0	623 (77.3)	311 (77.8)
1	183 (22.7)	89 (22.3)
PSADT, n (%)		
≤6 months	576 (71.5)	284 (70.8)
>6 months	230 (28.5)	117 (29.2)
Use of bone-sparing agent, n (%)		
Yes	82 (10.2)	39 (9.7)
No	724 (89.8)	362 (90.3)
Classification of local or regional nodal disease, n (%)		
N0	673 (83.5)	336 (83.8)
N1	133 (16.5)	65 (16.2)
Previous prostate cancer treatment, n (%)		
Prostatectomy or radiation therapy	617 (76.6)	307 (76.6)
GnRH analog agonist	780 (96.8)	387 (96.5)
First-generation antiandrogen agent[b]	592 (73.4)	290 (72.3)

[a]Apalutamide, n=784; placebo, n=387.
[b]First-generation antiandrogen agents included flutamide, bicalutamide, and nilutamide.

Additional Baseline Characteristics Data

Additional Baseline Characteristics Data

Primary Analysis

- Six patients (3 per group) were randomized, but never received study treatment.[1]
- At the clinical cutoff date for this analysis, driven by metastasis events or death, the median follow-up was 20.3 months, with 60.9% of patients still on treatment in the apalutamide group vs 29.9% in the placebo group.[1]

Final Analysis

- After unblinding of the study, 19% (76) of patients in the placebo group received therapy with apalutamide plus ADT (crossover group).[3]
- Thirty percent (237/803) of patients randomized to the apalutamide group and 61% (46/76) of patients in the crossover group continued treatment with apalutamide plus ADT.[3]

ADT, androgen deprivation therapy.

Gleason score at initial diagnosis, n (%)[a]		
<7	152 (19.4)	72 (18.6)
7	291 (37.1)	146 (37.7)
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Additional Baseline Characteristics Data

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- Significant improvement in median **MFS** was observed at the final analysis for MFS performed after 378 events of distant metastasis or death (184 [22.8%] patients in the apalutamide group and 194 [48.4%] patients in the placebo group).[1]

Endpoint, Months[1]	**Apalutamide Group (n=806)**	**Placebo Group (n=401)**	**HR (95% CI)**	***P*-Value**
Median MFS	40.5	16.2	0.28 (0.23-0.35)	<0.001

- The treatment effect of apalutamide on MFS was consistently favorable across prespecified subgroups, including patients with PSADT ≤6 months vs >6 months, use of bone-sparing agents, and local-regional disease.[1]

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- This analysis was the final analysis for the secondary endpoints of **TTM** and **PFS** and was the first interim analysis for **OS** and **time to initiation of cytotoxic chemotherapy**.[1]
  - At the time of this analysis, 104/427 (24%) OS events had occurred.[2]
- Apalutamide was associated with improvements in all secondary endpoints, with significant improvement observed in TTM, PFS, and **time to symptomatic progression**.[1]

Endpoint, Months[1]	**Apalutamide Group (n=806)**	**Placebo Group (n=401)**	**HR (95% CI)**	***P*-Value**[a]
Median TTM	40.5	16.6	0.27 (0.22-0.34)	<0.001
Median PFS	40.5	14.7	0.29 (0.24-0.36)	<0.001
Median time to symptomatic progression	NR	NR	0.45 (0.32-0.63)	<0.001
Median OS (interim)	NR	39.0	0.70 (0.47-1.04)	0.07
Median time to initiation of cytotoxic chemotherapy (interim)	NR	NR	0.44 (0.29-0.66)	-

[a]The *P*-value for time to symptomatic progression crossed the O'Brien-Fleming efficacy boundary of 0.00008; the *P*-value for OS did not. The *P*-value for time to initiation of cytotoxic chemotherapy was not calculated because the *P*-value for OS did not cross the O'Brien-Fleming efficacy boundary.

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- The final analysis for **OS** was performed after 428 events (274 vs 154 patients in the apalutamide vs placebo group) and a median follow-up of 52 months.[3]
- This analysis was additionally the final analysis for **time to initiation of cytotoxic chemotherapy** and an updated analysis for t**ime to symptomatic progression**.[3]

Endpoint, Months	Apalutamide Group (n=806)	Placebo Group (n=401)	HR (95% CI)	*P*-Value
Median OS	73.9	59.9	0.78 (0.64-0.96)	0.016[a]
Median time to initiation of cytotoxic chemotherapy[b]	NR	NR	0.63 (0.49-0.81)	0.0002[c]
Median time to symptomatic progression[d]	NR	NR	0.57 (0.44-0.73)	Nominal *P*<0.0001[e]

[a]*P*-value confirmed statistically significant improvement of OS, crossing the prespecified O'Brien-Fleming boundary of 0.046.
[b]258 patients initiated cytotoxic chemotherapy (155 vs 103 patients in the apalutamide vs placebo group).
[c]*P*-value was below the prespecified boundary for statistical significance.
[d]264 patients experienced symptomatic progression (156 vs 108 patients in the apalutamide vs placebo group).
[e]These endpoints were not adjusted for multiple comparisons. Therefore, the *P*-values displayed are nominal, and statistical significance has not been established.

- Based on 2 exploratory sensitivity analyses of OS (naïve censoring and IPCW analysis) that accounted for patients in the crossover group, a median 21.1-month increase in OS was observed for apalutamide vs placebo. With naïve censoring and IPCW analysis, median OS was 73.9 vs 52.8 months in the apalutamide vs placebo groups, respectively (HR, 0.69; 95% CI, 0.56-0.84; nominal *P*=0.0002 for naïve censoring and nominal *P*=0.0003 for IPCW analysis). This endpoint was not adjusted for multiple comparisons. Therefore, the *P*-values displayed are nominal, and statistical significance has not been established.[3]
  - In the naïve-censoring approach, patients were censored at the date of crossover.
  - In the IPCW analysis, treatment effect of apalutamide on OS was estimated by reweighting the patients that received placebo based on the following stratification factors: PSADT, bone-sparing agent use, and locoregional disease.

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Endpoint[1,4]	**Apalutamide Group (n=806)**	**Placebo Group (n=401)**	**HR/RR (95% CI)**
Median PFS2, months	NR	39.0	HR: 0.49 (0.36-0.66)
Median time to PSA progression, months	NR	3.7	HR: 0.06 (0.05-0.08)
Patients with a PSA response, %	89.7	2.2	RR: 40 (21-77)
Change in total FACT-P score from baseline to 29 months[a,b]	–0.99±0.98	–3.29±1.97	-
Change in total EQ VAS score from baseline to 29 months[a,c]	1.44±0.87	0.26±1.75	-

[a]± values are means±SE.
[b]Scores on the FACT-P questionnaire range from 0 to 156, with higher scores indicating more favorable HRQoL.
[c]Scores on the EQ VAS range from 0 to 100, with 0 indicating the worst health imaginable and 100 the best health imaginable.

Subpopulation[1]	**Apalutamide Group (n=806)**	**Placebo Group (n=401)**
Among patients who developed metastasis		
Bone metastasis, %	60.5	54.4
Among patients who discontinued treatment		
Patients receiving subsequent approved treatment for mCRPC, %	52.5	77.8

Additional Data on PSA, PROs, and Subsequent Treatments

PSA Level, PROs, and Subsequent Treatments

PSA Level

- At 12 weeks after randomization, the median PSA level had decreased by 89.7% in the apalutamide group vs an increase of 40.2% in the placebo group.1 In an exploratory analysis of patients treated in the SPARTAN study:[7]
  - Apalutamide decreased the risk of PSA progression by 94% vs the placebo group (not reached vs 3.71 months; HR, 0.064; 95% CI, 0.052-0.080; *P*<0.0001).
  - Confirmed PSA response was reported in 90% of patients in the apalutamide group and 2% of patients in the placebo group (RR, 40.09; 95% CI, 20.99-76.58; *P*<0.0001).
  - The median time to PSA response was 29 days (range, 8-310 days) in the apalutamide group.
  - A ≥90% maximum decline in PSA from baseline at any time during the study was reported in 66% of patients in the apalutamide group and 1% of patients in the placebo group.

PROs (FACT-P and EQ-5D-3L Results)

- PROs (FACT-P and EQ-5D-3L) indicated maintenance of stable overall HRQoL over time in patients from both treatment arms.[1,8]
- During the treatment phase, mean PRO scores demonstrated that HRQoL was maintained from baseline through treatment with apalutamide plus ADT and was similar over time between the apalutamide and placebo groups.[9]
  - HRQoL deterioration from baseline was more apparent in the placebo group.
- During the postprogression phase, mean PRO scores were similar between treatment groups up to 12 months after metastases and following symptomatic PD.[9]

Subsequent Treatments

- The most common subsequent treatment was abiraterone acetate plus prednisone (75.8% in the apalutamide group and 74.2% in the placebo group), which was offered as a sponsor-provided treatment option for patients after the first detection of distant metastasis.[1]
- Median time from detection of distant metastasis to initiation of subsequent therapy was 56 vs 44 days in the apalutamide vs placebo group.[1]

ADT, androgen deprivation therapy; CI, confidence interval; EQ-5D-3L, European Quality of Life-5 Dimensions-3-level; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HR, hazard ratio; HRQoL, health-related quality of life; NR, not reached; PD, progressive disease; PRO, patient-reported outcome; PSA, prostate-specific antigen; RR, relative risk.

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- This analysis was an updated analysis for **PFS2** and **time to PSA progression**.[3]

Endpoint, Months	Apalutamide Group (n=806)	Placebo Group (n=401)	HR (95% CI)	*P*-Value
Median PFS2[a]	55.6	41.2	0.55 (0.46-0.66)	Nominal *P*<0.0001[b]
Median time to PSA progression[c]	40.5	3.7	0.07 (0.06-0.09)	Nominal *P*<0.0001[b]

[a]509 patients experienced progression on or after first subsequent therapy or death (319 vs 190 patients in the apalutamide vs placebo group).
[b]These endpoints were not adjusted for multiple comparisons. Therefore, the *P*-values displayed are nominal, and statistical significance has not been established.
[c]572 patients in the study experienced PSA progression (235 vs 337 patients in the apalutamide vs placebo group).

- A total of 48% vs 71% of apalutamide- vs placebo-treated patients received first subsequent systemic therapy for prostate cancer, with abiraterone acetate plus prednisone as the most common first subsequent therapy (73% vs 72%), respectively.[10]
  - Of the 401 patients randomized to the placebo group, 338 (84%) patients received either life-prolonging active therapy as the first subsequent therapy upon disease progression or apalutamide as a crossover treatment option without progression after study unblinding.[3]
- The relative **PSA response rate** based on confirmed response was 40.2 with apalutamide vs placebo, (95% CI, 21-77; nominal *P*<0.001), with 38% of patients in the apalutamide group attaining a confirmed PSA level ≤0.2 ng/mL compared to 0 patients in the placebo group. This endpoint was not adjusted for multiple comparisons. Therefore, the *P*-values displayed are nominal, and statistical significance has not been established.[3]
- **HRQoL** results indicated that overall, patients in the apalutamide group generally maintained favorable scores for all FACT-P subscales and EQ-5D-3L VAS while scores in the placebo group tended to decline over time.[11]
  - Among patients who remained on treatment, the LSM-MMRM indicated that change in FACT-P total score from baseline to cycles 21 and 25 significantly favored the apalutamide group vs the placebo group (*P*=0.0138 and *P*=0.0009, respectively).

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- The safety population included all patients who received at least 1 dose of study drug.[1]

Safety Parameters[1,6]	**Apalutamide Group (n=803)**	**Placebo Group (n=398)**
Treatment discontinuation due to, n (%)		
PD	155 (19.3)	210 (52.8)
AE	85 (10.6)	28 (7.0)
Rash was the most common AE that led to, %		
Treatment discontinuation	2.4	0
Dose reduction	2.7	0.3
Dose interruption	6.8	1.3

- AEs were associated with death in 10 patients in the apalutamide group:[1]
  - Prostate cancer (n=2)
  - Sepsis (n=2)
  - Acute myocardial infarction (n=1)
  - Cardiorespiratory arrest (n=1)
  - Cerebral hemorrhage (n=1)
  - Myocardial infarction (n=1)
  - Multiple organ dysfunction (n=1)
  - Pneumonia (n=1)
- Incidence of AEs in the primary analysis is presented in the following pop-up:

AEs – Primary Analysis

AEs – Primary Analysis[1]

AE,[a] n (%)	Apalutamide Group (n=803)		Placebo Group (n=398)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any AE	775 (96.5)	362 (45.1)	371 (93.2)	136 (34.2)
Serious AEs	199 (24.8)	-	92 (23.1)	-
AEs leading to discontinuation of the trial regimen	85 (10.6)	-	28 (7.0)	-
AEs associated with death	10 (1.2)	-	1 (0.3)	-
AEs that occurred in ≥15% of patients in either group[b]				
Fatigue[c]	244 (30.4)	7 (0.9)	84 (21.1)	1 (0.3)
Hypertension	199 (24.8)	115 (14.3)	79 (19.8)	47 (11.8)
Rash[c]	191 (23.8)	42 (5.2)	22 (5.5)	1 (0.3)
Diarrhea	163 (20.3)	8 (1.0)	60 (15.1)	2 (0.5)
Nausea	145 (18.1)	0	63 (15.8)	0
Weight loss	129 (16.1)	9 (1.1)	25 (6.3)	1 (0.3)
Arthralgia	128 (15.9)	0	30 (7.5)	0
Falls[c]	125 (15.6)	14 (1.7)	36 (9.0)	3 (0.8)
Other AEs of interest				
Fracture[c]	94 (11.7)	22 (2.7)	26 (6.5)	3 (0.8)
Dizziness	75 (9.3)	5 (0.6)	25 (6.3)	0
Hypothyroidism[c]	65 (8.1)	0	8 (2.0)	0
Mental impairment disorder[d]	41 (5.1)	0	12 (3.0)	0
Seizure[c]	2 (0.2)	0	0	0

[a]The incidences of the following AEs were adjusted for exposure (events per 100 patient-years) in the apalutamide and placebo groups, respectively: fatigue (incidence 32.3 vs 27.2), hypertension (36.3 vs 38.7), rash (29.6 vs 8.3), diarrhea (21.6 vs 22.6), nausea (15.8 vs 20.4), weight loss (18.3 vs 10.5), arthralgia (14.7 vs 8.0), falls (13.6 vs 10.0), fracture (10.5 vs 7.8), dizziness (7.7 vs 6.6), hypothyroidism (7.6 vs 2.2), mental impairment disorder (3.9 vs 3.4), and seizure (0.2 vs 0).
[b]This category includes AEs that occurred up to 28 days after the last dose of the trial regimen was administered.
[c]These AEs were considered by the investigators to be related to the trial regimen.
[d]Mental impairment disorders included the following AEs: disturbance in attention, memory impairment, cognitive disorder, or amnesia.

AE, adverse event.

AEs – Primary Analysis

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- The safety population included all patients who received at least 1 dose of study drug.[3]

Safety Parameter[3,10]	**Apalutamide Group (n=803)**	**Placebo Group (n=398)**	**Crossover Group (n=76)**
Median treatment duration, months	32.9	11.5	26.1
Total patient-years of exposure	2117.9	446.0	134.5
Exposure-adjusted grade 3-4 events, %	51	68	-
Skin rash	5.2	0.3	-
Fractures	4.9	1.0	-
Falls	2.7	0.8	-
Ischemic heart disease	2.6	1.8	-
Ischemic cerebrovascular disorders	1.6	0.8	-
Treatment discontinuation due to, n (%)			
PD	343 (43)	238 (74)	11 (14)
AE[a]	122 (15)	27 (8.4)	8 (11)

[a]The most common AEs, by preferred term, leading to discontinuation in the apalutamide group were fatigue (1.1%), maculo-papular rash (0.7%), and sepsis (0.7%) and in the placebo group were dizziness (0.5%) and hydronephrosis (0.5%).

- One AE leading to death (myocardial infarction) was considered potentially related to apalutamide.[3]
- Incidence of AEs in the final analysis is presented in the following pop-up:

AEs – Final Analysis

AEs – Final Analysis[3,10]

AE	Apalutamide Group (n=803)		Placebo Group (n=398)		Crossover Group (n=76)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any AE, n (%)	781 (97)	449 (56)	373 (94)	145 (36)	68 (89)	29 (38)
Any serious AE, n (%)	290 (36)	-	99 (25)	-	19 (25)	-
Any AE leading to treatment discontinuation,[a] n (%)	120 (15)	-	29 (7.3)	-	8 (11)	-
AE leading to death, n (%)	24 (3.0)	-	2 (0.5)	-	2 (2.6)	-
TEAEs that occurred in ≥15% of patients in the apalutamide group, %						
Fatigue	33	0.9	21	0.3	16	1.3
Hypertension	28	16	21	12	11	5.3
Diarrhea	23	1.5	15	0.5	13	1.3
Fall	22	2.7	9.5	0.8	11	2.6
Arthralgia	20	0.4	8.3	0	12	1.3
Nausea	20	0	16	0	6.6	0
Weight decreased	20	1.5	6.5	0.3	11	1.3
Back pain	18	1.4	15	1.5	11	0
Hot flush	15	0	8.5	0	9.2	0
AEs of special interest, by group term, n (%)[b]						
Skin rash	212 (26)	42 (5.2)	25 (6.3)	1 (0.3)	19 (25)	2 (2.6)
Fall	177 (22)	22 (2.7)	38 (9.5)	3 (0.8)	8 (11)	2 (2.6)
Fracture	145 (18)	39 (4.9)	30 (7.5)	4 (1.0)	7 (9.2)	4 (5.3)
Hypothyroidism	79 (9.8)	0	8 (2.0)	0	3 (3.9)	0
Seizure	5 (0.6)	0	0	0	0	0

[a]All AEs leading to discontinuation are reported. However, reported AEs may not be the primary reason for discontinuation. Patients were counted only once for any given event, regardless of the number of times they experienced the event. The event experienced by the patient with the worst toxicity grade was used. If a patient had all AEs with missing toxicity grades, the patient was only counted in the total column.

[b]The incidences of the following AEs (any grade) were adjusted for exposure (event rate per 100 patient-year of exposure) in the apalutamide, placebo, and crossover groups, respectively: skin rash (394 [19%] vs 39 [8.7%] vs 28 [21%]), fall (262 [12%] vs 43 [9.6%] vs 10 [7.4%]), fracture (202 [9.5%] vs 37 [8.3%] vs 14 [10%]), hypothyroidism (107 [5.1%] vs 10 [2.2%] vs 3 [2.2%]), and seizure (5 [0.2%] vs 0 vs 0).

AE, adverse event; TEAE, treatment-emergent AE.

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ADT	androgen deprivation therapy	**nmCRPC**	nonmetastatic castration-resistant prostate cancer
AE	adverse event	**NR**	not reached
CI	confidence interval	**OS**	overall survival
CT	computed tomography	**PCWG2**	Prostate Cancer Working Group 2
CYP17	cytochrome P450 17	**PD**	progressive disease
ECOG PS	Eastern Cooperative Oncology Group performance status	**PFS**	progression-free survival
EQ VAS	European Quality of Life visual analogue scale	**PFS2**	second PFS
EQ-5D-3L	European Quality of Life-5 Dimensions-3-level	**PRO**	patient-reported outcome
FACT-P	Functional Assessment of Cancer Therapy-Prostate	**PSA**	prostate-specific antigen
GnRH	gonadotropin-releasing hormone	**PSADT**	PSA doubling time
HR	hazard ratio	**RR**	relative risk
HRQoL	health-related quality of life	**SE**	standard error
LSM-MMRM	least squares mean changes from baseline using mixed model for repeated measures	**TEAE**	treatment-emergent AE
IPCW	inverse probability of censoring weighted	**TTM**	time to metastasis
mCRPC	metastatic castration-resistant prostate cancer	**VAS**	visual analogue scale
MFS	metastasis-free survival		

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ADDITIONAL INFORMATION

Additional information regarding the SPARTAN study, including the clinical study report, protocol, and statistical analysis plan, can be found at 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).

Additional analyses, including the second interim analysis for OS, post-hoc analyses, and multivariate analyses, have been conducted.[9,12-25]

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 08 October 2020. Summarized in this response are relevant data from the pivotal phase 3, randomized study.

Thank you for your interest in ERLEADA® (apalutamide). This information is presented in response to your inquiry. This information is taken from the references cited but is not intended to serve as a substitute for review of these references. This information is not intended to advocate the use of our product in any manner other than as described in the product monograph. Please refer to the ERLEADA® (apalutamide) Product Monograph for full prescribing information available at https://www.janssenmedicalinformation.ca/product-monographs or contact Janssen Medical Information at 1-800-567-3331 or http://www.janssenmedicalinformation.ca

1. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418.

2. Small EJ, Saad F, Chowdhury S, et al. SPARTAN, a phase 3 double-blind, randomized study of apalutamide vs placebo in patients with nonmetastatic castration-resistant prostate cancer. Oral presentation presented at: the American Society of Clinical Oncology Genitourinary (ASCO-GU) Cancers Symposium; February 8-10, 2018; San Francisco, CA.

3. Smith MR, Saad F, Chowdhury S, et al. Apalutamide and overall survival in prostate cancer. *Eur Urol*. 2020;In press.

4. Smith MR, Saad F, Chowdhury S, et al. Protocol for: Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418.

5. Center for Drug Evaluation and Research. NDA/BLA Multi-Disciplinary Review and Evaluation (Summary Review, Offi Director, Cross Discipline Team Leader Review, Clinical Review, Non-Clinical Review, Statistical Review and Clinical Pharmacology Review) NDA 210951 - ERLEADA (apalutamide) - Reference ID: 4221387. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210951Orig1s000MultidisciplineR.pdf. Published March 19, 2018. Accessed May 21, 2020.

6. Smith MR, Saad F, Chowdhury S, et al. Supplement for: Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418.

7. Small EJ, Lee JY, Lopez-Gitlitz A, et al. Prostate-specific antigen (P A) outcomes in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC) treated with apalutamide (APA): results from phase 3 SPARTAN study [abstract]. J Urol. 2018;199(Suppl 4). Abstract PD10-11.

8. Saad F, Cella D, Basch E, et al. Effect of apalutamide on health-related quali y of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the SPARTAN randomised, placebo-controlled phase 3 trial. *Lancet Oncol.* 2018;19(10):1404-1416.

9. Graff JN, Saad , Hadaschik BA, et al. Metastasis-free survival in nonmetastatic castration-resistant prostate cancer patients with prostate-specific antigen decline to < 0.2 ng/mL following apalutamide treatment: post hoc results from th phase 3 SPARTAN study. Poster presented at: American Urological Association Annual Meeting; May 3-6, 2019; Chicago, IL.

10. Smith MR, Saad F, Chowdhury S, et al. Supplement for: Apalutamide and overall survival in prostate cancer. *Eur Urol*. 2020;In press.

11. Oudard S, Hadaschik B, Saad F, et al. Health-related quality of life at final analysis of the S ARTAN study of apalutamide vs placebo in patients with nonmetastatic castration-resistant prostate cancer receiving androgen deprivation therapy. Poster presented at the: European Society for Medical Oncology (ESMO) Virtual Congress 2020; September 18-22, 2020.

12. Small EJ, Saad F, Chowdhury M, et al. Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. *Ann Oncol*. 2019;30(11):1813-1820.

13. Small EJ, Saad F, Chowdhury S, et al. Updated analysis of progression-free survival with first subsequent the apy and safety in the SPARTAN study of apalutamide in patients with high-risk nonmetastatic castration-resistant prostate cancer. Poster presented at: 2019 Genitourinary Cancers Symposium; February 14-16, 2019; San Francisco, CA.

14. Smith MR, Saad F, Rathkopf D, et al. Relationship of time to metastasis and site of metastases in patients with nonmetastatic castration-resistant prostate cancer: results from the phase 3 SPARTAN trial. Poster presented at: The American Society of Clinical Oncology Annual Meeting; June 1-5, 2018; Chicago, IL.

15. Hadaschik BA, Saad F, Graff JN, et al. Efficacy and sa y of apalutamide plus ongoing androgen deprivation therapy in nonmetastatic castration-resistant prostate cancer patients with or without prior radical prostatectomy and/or external radiotherapy: post hoc analysis of SPARTAN. Poster presented at: the American Urological Association Annual Meeting; May 3-6, 2019; Chicago, IL.

16. Graff JN, Smith MR, Saad , et al. Age-related efficacy and saf y of apalutamide (APA) plus ongoing androgen deprivation therapy (ADT) in subgroups of patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC): Post hoc analysis of SPARTAN. Poster presented at: 2019 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4, 2019; Chicago, IL.

17. Small EJ, Saad F, Chowdhury S, et al. Efficacy of apalutamide plus ongoing androgen depr ation therapy in patients with nonmetastatic castration-resistant prostate cancer and baseline comorbidities. Poster presented at: 2019 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31 - June 4, 2019; Chicago, IL.

18. Small EJ, Saad F, Rathkopf D, et al. Predicting disease progression in patients with nonmetastatic castration-resistant prostate cancer: an analysis from the phase 3 SPARTAN trial. Poster presented at: The American Society of Clinical Oncology Annual Meeting; June 1-5, 2018; Chicago, IL.

19. Pollock YY, Smith MR, Saad F, et al. Predictors of falls and fractures in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC) treated with apalutamide (APA) plus ongoing androgen deprivation therapy (ADT). Poster presented at: 2019 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31 - June 4, 2019; Chicago, IL.

20. Chi KN, Saad F, Chowdhury S, et al. Prostate-specific antigen kinetics in patients with ad anced prostate cancer treated with apalutamide: results from the TITAN and SPARTAN studies. Poster presented at: American Society of Clinical Oncology (ASCO) 20 Virtual Scientific Prog am; May 29-31, 2020.

21. Saad F, Graff JN, Hadaschik , et al. Molecular determinants of prostate-specific antigen kinetics and clinical respons to apalutamide in patients with nonmetastatic castration-resistant prostate cancer in SPARTAN. Poster presented at: American Society of Clinical Oncology (ASCO) 20 Virtual Scientific Prog am; May 29-31, 2020.

22. Feng FY, Thomas S, Gormley M, et al. Identifying molecular determinants of response to apalutamide in patients with nonmetastatic castration-resistant prostate cancer in the SPARTAN study. Poster presented at: 2019 Genitourinary Cancers Symposium; February 14-16, 2019; San Francisco, CA.

23. Smith MR, Mehra M, Nair S, et al. Relationship between metastasis-free survival and overall survival in patients with nonmetastatic castration-resistant prostate cancer. *Clin Genitourin Cancer.* 2020;18(2):e180-189.

24. Aguilar C, Gormley M, Thomas S, et al. Novel molecular subtypes identified in prostate cancer: results from the S ARTAN study. Poster presented at: American Association for Cancer Research (AACR) 2020 Virtual Meeting II; June 22-24, 2020.

25. Perez-Ruixo C, Ackaert O, Ouellet D, et al. Efficacy and saf y exposure-response relationships of apalutamide in patients with nonmetastatic castration-resistant prostate cancer. *Clin Cancer Res*. 2020;26(17):4460-4467.