ERLEADA® (apalutamide)
Use of ERLEADA in Patients with Cerebrovascular or Cardiovascular Disease

SUMMARY

- Ischemic cardiovascular events and ischemic cerebrovascular events, including events leading to death, occurred in patients treated with ERLEADA. Monitor for signs and symptoms of ischemic heart disease and ischemic cerebrovascular disorders. Optimize management of risk factors, such as hypertension, diabetes, or dyslipidemia.[1] Please refer to local labeling for additional considerations.
- Patients with a history of severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (eg, pulmonary embolism), clinically significant ventricular arrhythmias within 6 months prior to randomization, or a history of seizure or condition that may predispose to seizure (eg, cerebrovascular accident) within 1 year prior to randomization were excluded from the SPARTAN and TITAN studies.[2,3]
- In SPARTAN, the phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of ERLEADA plus androgen deprivation therapy (ADT) compared to placebo in patients with high-risk nonmetastatic castration-resistant prostate cancer (nmCRPC; N=1207)[4]:
    - Cardiac disorder treatment-emergent adverse events (TEAEs) by presence of cardiac risk factors prior to enrollment in SPARTAN are summarized in Table: Cardiac Disorder TEAEs by Presence of Cardiac Risk Factors Prior to Enrollment in SPARTAN. Cardiac disorder TEAEs occurred in 15.4% and 9.0% of patients in the ERLEADA and placebo groups, respectively, in patients with a history of cardiac disorders, diabetes, hypertension, hypercholesteremia, stroke, pulmonary embolism, or transient ischemic attack (TIA).[5]
    - A post hoc analysis of the impact of patient baseline comorbidities, including diabetes/hyperglycemia, cardiac disorder, and hypertension on efficacy outcomes, demonstrated a significant treatment benefit in the ERLEADA group for metastasis-free survival (MFS), time to symptomatic progression, and second progression-free survival (PFS2) regardless of baseline comorbidities, except for PFS2 in patients with diabetes/hyperglycemia. TEAE incidence was similar between patients with and without baseline comorbidities. TEAEs in the ERLEADA group were not affected by comorbidities.[6,7]
- In TITAN, the phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of ERLEADA plus ADT compared to placebo in patients with metastatic castration-sensitive prostate cancer (mCSPC; N=1052)[8]:
    - Cardiac disorder TEAEs were reported in 8.8% of patients in the ERLEADA group and 5.9% of patients in the placebo group, and ischemic heart disease TEAEs were reported in 4.4% of patients in the ERLEADA group and 1.5% of patients in the placebo group.[9]
    - Cardiac disorder TEAEs by presence of cardiac risk factors prior to enrollment in TITAN are summarized in Table: Cardiac Disorder TEAEs by Presence of Cardiac Risk Factors Prior to Enrollment in TITAN.
    - A post hoc analysis of the impact of baseline cardiovascular or metabolic risk factor comorbidities on efficacy outcomes revealed a significant treatment benefit in the ERLEADA group for prostate-specific antigen (PSA) response, radiographic progression-free survival (rPFS), and overall survival (OS), regardless of the baseline comorbidities or use of associated concomitant medications. TEAE incidences were similar between patients with and without baseline comorbidities regardless of associated concomitant medication use.[10]
- In post hoc pooled analyses of the SPARTAN and TITAN studies, statin exposure was associated with longer OS in patients treated with ERLEADA and there was a higher risk of grade ≥3 cardiac adverse events irrespective of treatment regimen.[11,12]

CLINICAL DATA

Phase 3 SPARTAN Study in Patients with nmCRPC

The phase 3 SPARTAN study evaluated the efficacy and safety of ERLEADA compared to placebo in patients with high-risk nmCRPC (defined as PSA doubling time ≤10 months) on continuous ADT (N=1207).[4] Patients were excluded if they had a history or evidence of any of the following conditions:

- Uncontrolled hypertension (≥160 mm Hg systolic blood pressure and/or diastolic blood pressure ≥100 mm Hg)[2]
- Severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (eg, pulmonary embolism, cerebrovascular accident including TIAs), or clinically significant ventricular arrhythmias within 6 months prior to randomization[2]
- History of seizure or condition that may predispose to seizure (eg, stroke within 1 year prior to randomization)[2]

Patients enrolled in the study had risk factors for cardiac disorders including age (median of 74 years) as well as a history of cardiac disorders, diabetes, hypertension, hypercholesterolemia/lipidemia, stroke, pulmonary embolism, or TIA, (combined incidence: 87.8% in the ERLEADA group and 86.9% in the placebo group). Five of the 32 patients who experienced a cerebrovascular event in the ERLEADA group had a history of an ischemic cerebrovascular event (stroke or TIA) and 13 of 32 had a history of ischemic heart disease or carotid artery stenosis.[5]

Cardiac disorder TEAEs occurred in 15.4% and 9.0% of patients in the ERLEADA and placebo groups, respectively, in patients with a history of cardiac disorders, diabetes, hypertension, hypercholesteremia, stroke, pulmonary embolism, or TIA. In patients with no prior history of cardiac disorders, diabetes, hypertension, hypercholesteremia, stroke, pulmonary embolism, or TIA, cardiac disorder TEAEs occurred in 1.2% and 0.5% of patients in the ERLEADA and placebo groups, respectively.[5] Cardiac disorder TEAEs by presence of cardiac risk factors prior to enrollment in SPARTAN are summarized in Table: Cardiac Disorder TEAEs by Presence of Cardiac Risk Factors Prior to Enrollment in SPARTAN.

Cardiac Disorder TEAEs by Presence of Cardiac Risk Factors Prior to Enrollment in SPARTAN[5]

TEAEs, n (%)	ERLEADA Group (n=803)	Placebo Group (n=398)
Cardiac arrhythmia TEAEs		
History of cardiac risk factor[a]	80 (10.0)	24 (6.0)
No history of cardiac risk factor	7 (0.9)	2 (0.5)
Ischemic heart disease TEAEs		
History of cardiac risk factor[a]	42 (5.2)	11 (2.8)
No history of cardiac risk factor	2 (0.2)	0
Cardiac failure TEAEs		
History of cardiac risk factor[a]	23 (2.9)	4 (1.0)
No history of cardiac risk factor	1 (0.1)	0

Abbreviation: TEAE, treatment-emergent adverse event.
[a]Patients had a history of cardiac disorders, diabetes, hypertension, hypercholesterolemia/lipidemia, stroke, pulmonary embolism, or transient ischemic attack.
Median treatment duration was 32.9 months in the ERLEADA group and 11.5 months in the placebo group.[13]

Post Hoc Analysis in Patients with Baseline Comorbidities

A post hoc analysis of the impact of patient baseline comorbidities, including diabetes/hyperglycemia, cardiac disorder, and hypertension on MFS (primary endpoint), time to symptomatic progression (secondary endpoint), and PFS2 (exploratory endpoint) was performed.[6,7]

Patients with baseline comorbidities were older than patients without baseline comorbidities (median age in the ERLEADA and placebo groups: 75 years vs 69 years and 74 years vs 69 years, respectively) and had a higher Eastern Cooperative Oncology Group performance status (ECOG-PS) score (percentage of patients with ECOG-PS score of 1 in the ERLEADA and placebo groups: 25% vs 9% and 23% vs 12%, respectively).[7] A statistically significant treatment benefit was observed in the ERLEADA group for MFS, time to symptomatic progression, and PFS2 regardless of patient baseline comorbidities except for PFS2 in patients with diabetes/hyperglycemia (see Tables: Impact of Patient Baseline Comorbidities on MFS in SPARTAN, Impact of Patient Baseline Comorbidities on Time to Symptomatic Progression in SPARTAN, and Impact of Patient Baseline Comorbidities on PFS2 in SPARTAN).

Impact of Patient Baseline Comorbidities on MFS in SPARTAN[7]

	Median, Months		HR (95% CI)	Events/N	
	ERLEADA Group	Placebo Group		ERLEADA Group	Placebo Group
All patients	40.5	16.2	0.28 (0.23-0.35)	184/806	194/401
Diabetes/hyperglycemia					
Yes	29.5	18.4	0.26 (0.16-0.43)	34/159	32/67
No	40.5	15.7	0.30 (0.24-0.38)	150/647	162/334
Hypertension					
Yes	NE	18.4	0.33 (0.26-0.43)	123/541	115/257
No	40.5	14.5	0.41 (0.24-0.71)	61/265	79/144
Cardiac disorder					
Yes	30.0	11.2	0.31 (0.22-0.43)	67/260	73/138
No	NE	18.3	0.29 (0.22-0.38)	117/546	121/263

Abbreviations: CI, confidence interval; HR, hazard ratio; MFS, metastasis-free survival; NE, not estimable.

Impact of Patient Baseline Comorbidities on Time to Symptomatic Progression in SPARTAN[7]

	Median, Months		HR (95% CI)	Events/N	
	ERLEADA Group	Placebo Group		ERLEADA Group	Placebo Group
All patients	NE	NE	0.45 (0.32-0.64)	64/806	63/401
Diabetes/hyperglycemia					
Yes	NE	36.8	0.34 (0.14-0.87)	9/159	9/67
No	NE	NE	0.47 (0.33-0.69)	55/647	54/334
Hypertension					
Yes	NE	NE	0.60 (0.38-0.95)	44/541	32/257
No	NE	30.0	0.28 (0.16-0.50)	20/265	31/144
Cardiac disorder					
Yes	NE	NE	0.51 (0.27-0.96)	20/260	19/138
No	NE	36.8	0.42 (0.28-0.64)	44/546	44/263

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable.

Impact of Patient Baseline Comorbidities on PFS2 in SPARTAN[7]

	Median, Months		HR (95% CI)	Events/N	
	ERLEADA Group	Placebo Group		ERLEADA Group	Placebo Group
All patients	NE	39.0	0.49 (0.36-0.66)	91/806	78/401
Diabetes/hyperglycemia					
Yes	NE	39.0	0.53 (0.23-1.23)	14/159	9/67

	Median, Months		HR (95% CI)	Events/N	
	ERLEADA Group	Placebo Group		ERLEADA Group	Placebo Group
No	NE	NE	0.50 (0.36-0.69)	77/647	69/334
Hypertension					
Yes	NE	39.0	0.52 (0.36-0.76)	65/541	51/257
No	NE	NE	0.41 (0.24-0.71)	26/265	27/144
Cardiac disorder					
Yes	NE	NE	0.58 (0.37-0.90)	43/260	34/138
No	NE	39.0	0.44 (0.30-0.67)	48/546	44/263

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS2, second progression-free survival.

Adverse events in the ERLEADA group were not affected by comorbidities (see Table: Summary of TEAEs by Presence of Comorbidities in SPARTAN).

Summary of TEAEs by Presence of Comorbidities in SPARTAN[7]

TEAEs, n (%)	ERLEADA Group			Placebo Group		
	Any CM (n=700)	No CM (n=103)	Overall (n=803)	Any CM (n=356)	No CM (n=42)	Overall (n=398)
Grade 3/4 TEAE	323 (46)	39 (38)	362 (45)	120 (34)	16 (38)	136 (34)
Serious TEAE	174 (25)	25 (24)	199 (25)	82 (23)	10 (24)	92 (23)
Drug-related SAE	30 (4)	1 (1)	31 (4)	6 (2)	0	6 (2)
TEAE leading to treatment discontinuation	79 (11)	6 (6)	85 (11)	26 (7)	2 (5)	26 (7)

Abbreviations: CM, comorbidity; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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).

Phase 3 TITAN Study in Patients with mCSPC

The phase 3 TITAN study evaluated the efficacy and safety of ERLEADA compared to placebo in patients with mCSPC on continuous ADT (N=1052).[8] Patients were excluded if they had a history of any of the following conditions:

- Uncontrolled hypertension, severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, clinically significant arterial or venous thromboembolic events (eg, pulmonary embolism), or clinically significant ventricular arrhythmias within 6 months prior to randomization[3]
- History of seizure or condition that may predispose to seizure (including, but not limited to prior cerebrovascular accident, TIA, or loss of consciousness within 1 year prior to randomization)[3]

Patients enrolled in the study had risk factors for cardiac disorders including age (median of 68 years; range: 43-94 years) and a history of cardiac disorders, diabetes, or hypertension (combined incidence: 66% in the ERLEADA group and 61% in the placebo group).[9] Cardiac disorder TEAEs by presence of cardiac risk factors prior to enrollment in TITAN are summarized in Table: Cardiac Disorder TEAEs by Presence of Cardiac Risk Factors Prior to Enrollment in TITAN.

Cardiac Disorder TEAEs by Presence of Cardiac Risk Factors Prior to Enrollment in TITAN[9]

TEAEs, n (%)	ERLEADA Group (n=524)	Placebo Group (n=527)
All cardiac disorder TEAEs	46 (8.8)	31 (5.9)
History of cardiac risk factor[a]	32/524 (6.1)	26/527 (4.9)
No history of cardiac risk factor	14/524 (2.7)	5/527 (0.9)
Ischemic heart disease TEAEs	23 (4.4)	8 (1.5)
History of cardiac risk factor[a]	17/23 (73.9)	6/8 (75.0)
No history of cardiac risk factor	6/23 (26.1)	2/8 (25.0)

Abbreviation: TEAE, treatment-emergent adverse event.
[a]Patients had a history of cardiac disorders, diabetes, or hypertension.
The median treatment duration was 20.5 months in the ERLEADA group and 18.3 months in the placebo group.[8]

Post Hoc Analysis in Patients with Baseline Comorbidities

A post hoc analysis was performed to assess the impact of patient baseline comorbidities, including cardiovascular and metabolic risk factors, on PSA, rPFS, OS, and safety. Patients receiving associated concomitant medications for these risk factors were additionally analyzed.[10] Common concomitant medications included: antihypertensives (~60%), statins (~30%), beta blockers (~30%), calcium channel blockers (~25%), and anti-thrombotic agents (~20%), including direct factor Xa inhibitors (~5%).[14]

In the ERLEADA and placebo groups, respectively, 72% and 69% of patients had a baseline history of cardiovascular or metabolic risk factors (eg, cardiovascular ischemia, cardiovascular failure, cardiovascular arrhythmia, diabetes, hyperlipidemia, hypertension, and obesity), 68% and 66% of patients had cardiovascular or metabolic risk factors and concomitant medication usage, and 28% and 31% of patients did not have cardiovascular or metabolic risk factors.[10]

The percentage of patients achieving PSA90 or PSA <0.2 ng/mL was similar across all 3 subgroups. Treatment with ERLEADA vs placebo significantly improved rPFS and OS regardless of baseline comorbidities or use of associated concomitant medications.[10] Results are summarized in Tables: PSA Effect per Baseline Cardiovascular or Metabolic Risk Factors ± Concomitant Medications and rPFS and OS per Baseline Cardiovascular or Metabolic Risk Factors ± Concomitant Medications.

PSA Effect per Baseline Cardiovascular or Metabolic Risk Factors ± Concomitant Medications[a][10]

	With CV/ Metabolic Risk Factors		With CV/ Metabolic Risk Factors and Con Meds		Without CV/ Metabolic Risk Factors	
	ERLEADA Group (n=378)	Placebo Group (n=364)	ERLEADA Group (n=358)	Placebo Group (n=347)	ERLEADA Group (n=146)	Placebo Group (n=163)
PSA90 or PSA <0.2 ng/mL achieved, %	86.2	43.1	85.8	42.1	82.3	43.6

Abbreviations: Con Meds, concomitant medications; CV, cardiovascular; PSA, prostate-specific antigen.
[a]PSA was assessed at the final analysis cutoff (median follow-up: 44 months) that analyzed crossover patients as a part of the intention-to-treat population in the placebo group.

rPFS and OS per Baseline Cardiovascular or Metabolic Risk Factors ± Concomitant Medications[10]

	With CV/ Metabolic Risk Factors		With CV/ Metabolic Risk Factors and Con Meds		Without CV/ Metabolic Risk Factors	
	ERLEADA Group (n=378)	Placebo Group (n=364)	ERLEADA Group (n=358)	Placebo Group (n=347)	ERLEADA Group (n=146)	Placebo Group (n=163)
rPFS[a]						
HR, *P*-value	0.49, <0.0001		0.47, <0.0001		0.48, <0.0001	
OS[b]						
HR, *P*-value	0.63, 0.001		0.61, <0.0001		0.71, <0.0604	

Abbreviations: Con Meds, concomitant medications; CV, cardiovascular; HR, hazard ratio; OS, overall survival; rPFS, radiographic progression-free survival, .
[a]Point estimates shown based on the first interim analysis cut off (median follow-up: 22.7 months), which was prespecified to be final.
[b]OS was assessed at the final analysis cutoff (median follow-up: 44 months) that analyzed crossover patients as a part of the intention-to-treat population in the placebo group.

TEAE incidences were similar between patients with and without baseline comorbidities regardless of associated concomitant medication use (Table: TEAEs per Baseline Cardiovascular or Metabolic Risk Factors ± Concomitant Medications).

TEAEs per Baseline Cardiovascular or Metabolic Risk Factors ± Concomitant Medications[10]

TEAEs, n (%)	With CV/ Metabolic Risk Factors		With CV/ Metabolic Risk Factors and Con Meds		Without CV/ Metabolic Risk Factors	
	ERLEADA Group (n=378)	Placebo Group (n=364)	ERLEADA Group (n=358)	Placebo Group (n=347)	ERLEADA Group (n=146)	Placebo Group (n=163)
TEAEs	368 (97.4)	353 (97.0)	350 (97.8)	337 (97.1)	142 (97.3)	157 (96.3)
Grade 3/4 TEAEs	183 (48.4)	165 (45.3)	177 (49.4)	161 (46.4)	76 (52.1)	55 (33.7)
SAEs	117 (31.0)	81 (22.3)	115 (32.1)	80 (23.1)	36 (24.7)	34 (20.9)
TEAEs leading to treatment discontinuation	48 (12.7)	21 (5.8)	48 (13.4)	20 (5.8)	14 (9.6)	9 (5.5)
TEAEs leading to death	15 (4.0)	11 (3.0)	15 (4.2)	11 (3.2)	5 (3.4)	6 (3.7)
TEAEs of special interest						
Skin rash						
All grades	113 (29.9)	37 (10.2)	104 (29.1)	37 (10.7)	40 (27.4)	12 (7.4)
≥Grade 3	22 (5.8)	5 (1.4)	22 (6.1)	5 (1.4)	11 (7.5)	0
Fall						
All grades	38 (10.1)	30 (8.2)	37 (10.2)	29 (8.4)	11 (7.5)	7 (4.3)
≥Grade 3	6 (1.6)	3 (0.8)	6 (1.7)	3 (0.9)	1 (0.7)	2 (1.2)
Fracture						
All grades	38 (10.1)	17 (4.7)	38 (10.6)	16 (4.6)	16 (11)	9 (5.5)
≥Grade 3	10 (2.6)	4 (1.1)	10 (2.8)	4 (1.2)	8 (5.5)	0
Ischemic heart disease						
All grades	26 (6.9)	10 (2.7)	25 (7.0)	5 (1.4)	5 (3.4)	1 (0.6)
≥Grade 3	14 (3.7)	4 (1.0)	14 (4.1)	4 (1.0)	2 (1.4)	0
Ischemic cerebrovascular disorders						
All grades	13 (3.4)	5 (1.4)	13 (3.6)	5 (1.4)	0	3 (1.8)
≥Grade 3	8 (2.1)	1 (0.3)	8 (2.2)	1 (0.3)	0	0
Seizure						
All grades	1 (0.3)	2 (0.5)	1 (0.3)	2 (0.5)	2 (1.4)	0
≥Grade 3	0	0	0	0	1 (0.7)	0
TEAEs associated with long-term ADT use						
Diabetes						
All grades	32 (8.5)	19 (5.2)	31 (8.7)	19 (5.5)	4 (2.7)	0

TEAEs, n (%)	With CV/ Metabolic Risk Factors		With CV/ Metabolic Risk Factors and Con Meds		Without CV/ Metabolic Risk Factors	
	ERLEADA Group (n=378)	Placebo Group (n=364)	ERLEADA Group (n=358)	Placebo Group (n=347)	ERLEADA Group (n=146)	Placebo Group (n=163)
≥Grade 3	9 (2.4)	6 (1.6)	9 (2.5)	6 (1.7)	0	0
Arrhythmia and cardiac disorders						
All grades	23 (6.1)	15 (4.1)	22 (6.1)	15 (4.3)	7 (4.8)	2 (1.2)
≥Grade 3	9 (2.4)	6 (1.6)	8 (2.2)	6 (1.8)	4 (2.8)	0
Cardiac failure						
All grades	14 (3.7)	9 (2.5)	14 (3.9)	9 (2.6)	1 (0.7)	1 (0.6)
≥Grade 3	8 (2.1)	3 (0.8)	8 (2.2)	3 (0.9)	0	0
Cognitive deficits						
All grades	13 (3.4)	6 (1.6)	13 (3.6)	6 (1.7)	3 (2.1)	4 (2.5)
≥Grade 3	1 (0.3)	0	1 (0.3)	0	1 (0.7)	0

Abbreviations: ADT, androgen deprivation therapy; Con Meds, concomitant medications; CV, cardiovascular; SAE, serious adverse events; TEAE, treatment-emergent adverse events.

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 26 December 2025. 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.

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