ERLEADA™ (apalutamide): For the Treatment of Patients With Non-Metastatic Castration-Resistant Prostate Cancer (CRPC)

CONTRAINDICATIONS

Pregnancy–ERLEADA™ can cause fetal harm and potential loss of pregnancy.

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Program Disclosures

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Program Overview

- Today we will discuss the treatment of patients with non-metastatic castration-resistant prostate cancer (CRPC) with ERLEADA™ (apalutamide)—the first drug approved by the FDA
- Before February 14, 2018, there were no FDA-approved treatments for non-metastatic CRPC[1]
- We will also review a case study of a patient with non-metastatic CRPC

1. US Food and Drug Administration. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm596768.htm. Accessed July 24, 2018.

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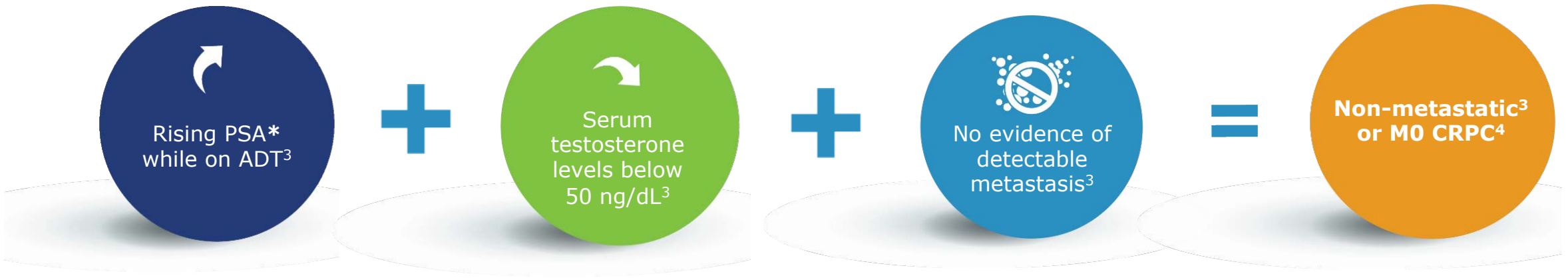
Non-Metastatic CRPC

Certain patients with prostate cancer receiving ADT will eventually develop castration-resistant disease.[1,2] Patients with CRPC who present with the following characteristics are designated non-metastatic (M0) CRPC:



ADT = androgen deprivation therapy; PSA = prostate-specific antigen.
*Despite medical or surgical castration.

1. Pomerantz M, Kantoff P. In: Tindall DJ, James M, eds. *Androgen Action in Prostate Cancer*. Verlag, New York: Springer; 2009. **2.** Kirby M, et al. *Int J Clin Pract*. 2011;65(11):1180-1192. **3.** Cookson MS, et al. https://www.auanet.org/guidelines/castration-resistant-prostate-cancer-(2013-amended-2018). Accessed August 20, 2018. **4.** Tombal B. *Ann Oncol*. 2012;23(suppl 10):x251-x258.

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Patients With Non-Metastatic CRPC: Faster PSADT* Has Been Linked to Shorter Time to Metastasis[1-3]

Median Time to Metastasis by PSADT[2*]

PSADT (months)	Median Time to Metastasis (months)
<3	9
3 to 8.9	19
9 to 14.9	40
≥15	50

Reused from Howard LE, et al. *BJU Int*. 2017;120(5B):E80-E86, with permission from John Wiley & Sons.

Patients with PSADT <10 months had 12 times greater risk of bone metastasis and 4 times greater risk of death than those with PSADT ≥10 months[3†]

PSADT = prostate-specific antigen doubling time.
*PSADT calculated by log(2) divided by the slope of the linear regression of log(PSA) over time in months. Study included data from 441 men with non-metastatic CRPC at 5 Veterans Affairs Medical Centers obtained from the SEARCH database.[1] †Retrospective cohort study of 9547 patients from the Center for Prostate Disease Research database.[3]
1. Moreira DM, et al. *Urology*. 2016;96:171-176. **2.** Howard LE, et al. *BJU Int*. 2017;120(5B):E80-E86. **3.** Metwalli AR, et al. *Urol Oncol*. 2014;32(6):761-768.

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ERLEADA™ (apalutamide) for Non-Metastatic CRPC

FEBRUARY 8, 2018

Phase 3 data on apalutamide published in the *New England Journal of Medicine*[1]

FEBRUARY 14, 2018

US FDA approves ERLEADA™ (apalutamide) for the treatment of patients with non-metastatic, castration-resistant prostate cancer[2,3]

MARCH 8, 2018

Apalutamide was included in the NCCN Guidelines for Prostate Cancer as a **category 1* treatment** recommendation for non-metastatic (M0) CRPC[4†]

MAY 8, 2018

AUA Guideline for CRPC: apalutamide was included as one of the options for patients with asymptomatic non-metastatic CRPC (Index 1), **Standard‡; Evidence Level Grade A[5§]**

***Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

†Especially if PSA doubling time is ≤10 months.

‡**Standard:** Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A or B evidence.

§**Evidence Level Grade A:** The quality of the evidence is high based on AUA nomenclature and methodology.

AUA = American Urological Association; FDA = Food and Drug Administration.

1. Smith MR, et al. *N Engl J Med.* 2018;378(15):1408-1418. **2.** ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **3.** US Food and Drug Administration. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm596768.htm. Accessed July 27, 2018. **4.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.4.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed October 10, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **5.** Cookson MS, et al. https://www.auanet.org/guidelines/castration-resistant-prostate-cancer-(2013-amended-2018). Accessed August 20, 2018.

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ERLEADA™ (apalutamide) Indications and Usage

ERLEADA™ (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic, castration-resistant prostate cancer.

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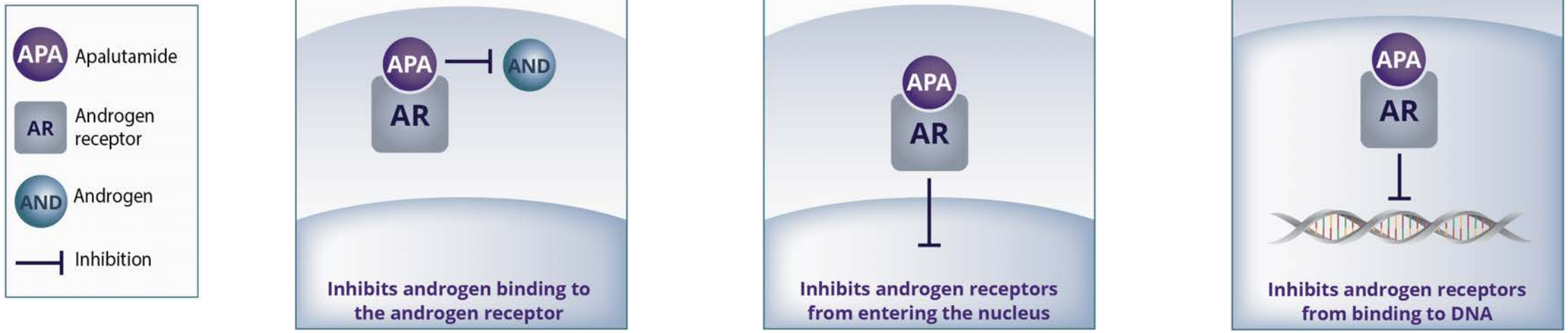
Apalutamide Mechanism of Action

- Apalutamide is an AR inhibitor that binds directly to the ligand-binding domain of the AR
- Apalutamide inhibits AR nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription



AR = androgen receptor.

ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

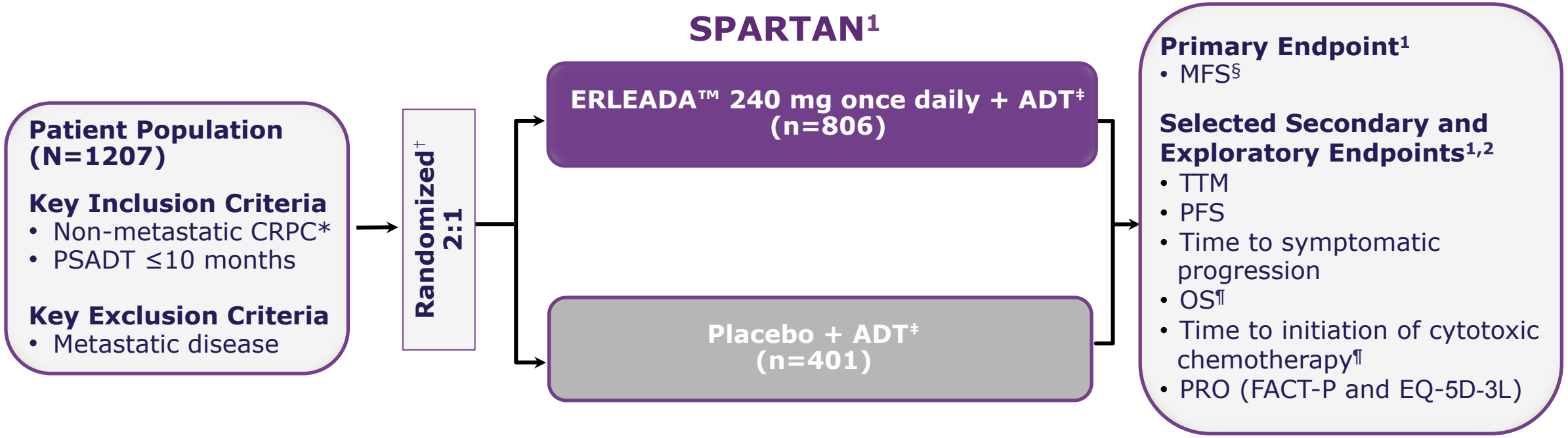
Pharmacokinetics

Summary of PK parameters of apalutamide:

	Apalutamide
Mean absolute oral bioavailability, %	• ~100
Median time to achieve t_{max} (range), h	• 2 (1-5)
Absorption: Effect of food—coadministration with a high-fat meal*	• Administration of apalutamide to healthy subjects under fasting conditions and with a high-fat meal resulted in no clinically relevant changes in C_{max} and AUC • Median time to reach t_{max} delayed by ~2 hours with food
Metabolism and elimination	• Metabolism is the main route of elimination of apalutamide, primarily by CYP2C8 and CYP3A4 to form the active metabolite N-desmethyl apalutamide • Up to 70 days following a single oral administration of radiolabeled apalutamide 65% was eliminated in urine and 24% in feces
Mean effective half-life, d	• ~3
Major circulating compounds	• 45% apalutamide • 44% N-desmethyl apalutamide (active metabolite)

AUC = area under the curve; C_{max} = maximum concentration; CYP2C8 = cytochrome P_{450} 2C8; CYP3A4 = cytochrome P_{450} 3A4; PK = pharmacokinetic; t_{max} = time to achieve peak plasma concentration.
*Approximately 500 to 600 fat calories, 250 carbohydrate calories, and 150 protein calories
ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

ERLEADA™ (apalutamide) Was Evaluated in a Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial in Patients With Non-Metastatic CRPC



- Patients randomized to either arm discontinued treatment for radiographic disease progression‖ confirmed by BICR, locoregional-only progression, initiation of new treatment, unacceptable toxicity, or withdrawal[1]

BICR = blinded independent central review; EQ-5D-3L = EuroQol 5-dimension, 3-level questionnaire; FACT-P = Functional Assessment of Cancer Therapy-Prostate; MFS = metastasis-free survival; PFS = progression-free survival; PRO = patient-reported outcome; OS = overall survival; TTM = time to metastasis.

*Patients with N0 or N1 disease were included in the trial.[2] †Patients were stratified by PSADT, the use of bone-sparing agents, and locoregional disease.[1] ‡All patients in the SPARTAN trial received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy.[1] §MFS is defined as the time from randomization to the time of first evidence of BICR-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.[1] ‖Computed tomography scans and bone scans were used in SPARTAN.[2] ¶Data not mature.[1,2]

1. ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Smith MR, et al. *N Engl J Med*. 2018;378(15):1408-1418.

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SPARTAN: Baseline Patient Characteristics

Selected Baseline Patient Characteristics	Total Patients (N=1207)
Median age[1]	74 years (range: 48 to 97)
Median time from initial diagnosis of prostate cancer to randomization[2]	7.9 years (range: 0.3 to 30.4)
Prior surgery or radiotherapy of the prostate[1]	77%
Prior treatment with an anti-androgen[1]	73%
Bicalutamide	69%
Flutamide	10%
Median PSA[2]	7.8 ng/mL (range: 0.1 to 294.8)
Gleason score ≥7 at initial diagnosis[1]	78%
Local or regional nodal disease (N1)[3]	16%

1. ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Data on file. Janssen Biotech, Inc. **3.** Smith MR, et al. *N Engl J Med*. 2018;378(15):1408-1418.

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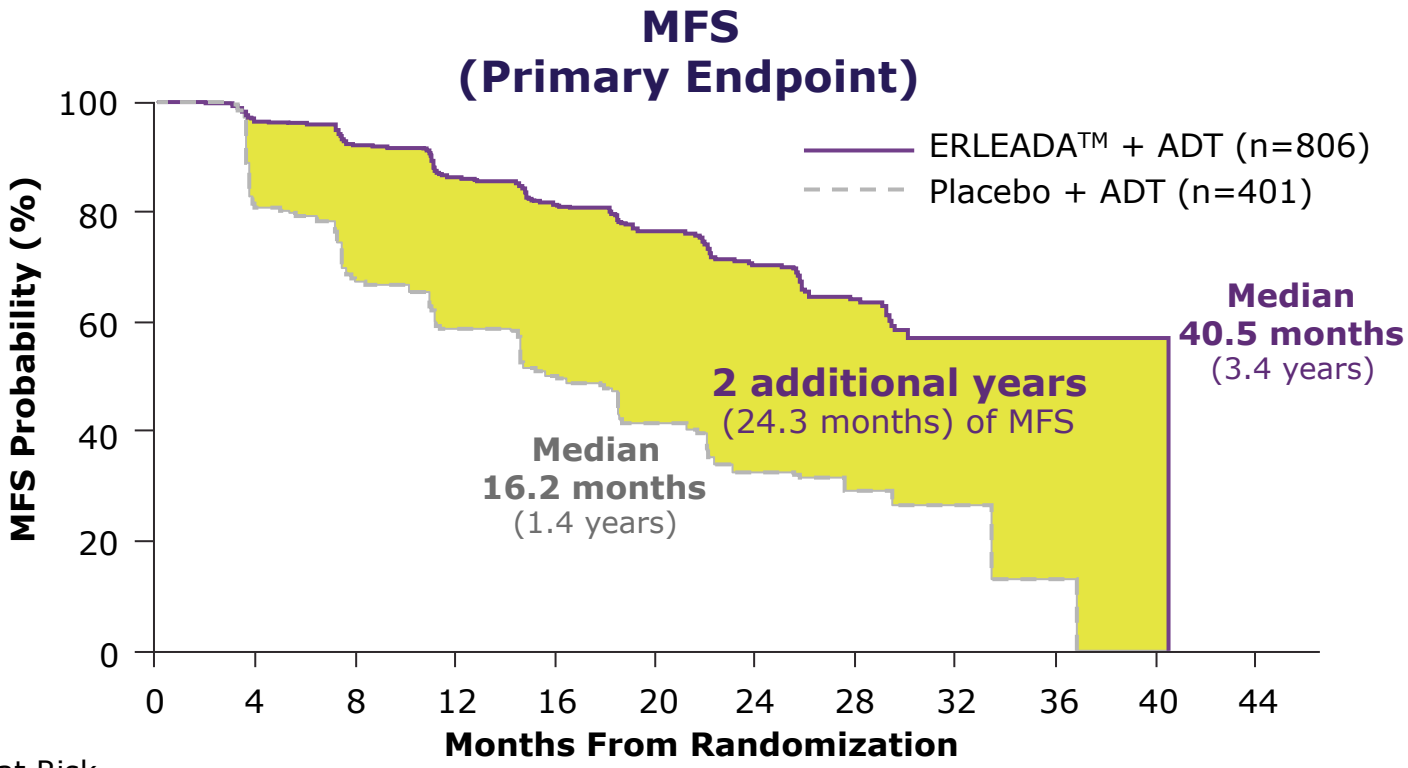
ERLEADA™ (apalutamide) + ADT Significantly Improved Median Metastasis-Free Survival by 2 Years (24.3 Months) vs Placebo + ADT



Patients at Risk

ERLEADA™ + ADT	806	713	652	514	398	282	180	96	36	16	3	0
Placebo + ADT	401	291	220	153	91	58	34	13	5	1	0	0

72%

Reduction in the risk of distant metastasis or death

HR=0.28 (95% CI: 0.23-0.35)
P<0.0001*

**P* value from a log-rank test. All analyses stratified by PSADT, bone-sparing agent use, and locoregional disease.

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ERLEADA™ (apalutamide) + ADT Significantly Improved Median Metastasis-Free Survival by 2 Years (24.3 Months) vs Placebo + ADT[1] *(cont'd)*

Primary Endpoint

ERLEADA™ + ADT improved median MFS by 2 years (24.3 months) compared with placebo + ADT (40.5 months [3.4 years] vs 16.2 months [1.4 years]; HR=0.28; 95% CI: 0.23, 0.35; *P*<0.0001)[1]

- Consistent results in MFS were observed across patient subgroups, including[1]:
  - PSADT (≤6 months or >6 months)
  - Use of a prior bone-sparing agent (yes or no)
  - Locoregional disease (N0 or N1)

- Overall survival (prespecified secondary endpoint) data were not mature at the time of final MFS analysis (24% of the required number of events)[1*]

At the time of the primary analysis for MFS, **60.9%** of patients were still on ERLEADA™ + ADT vs **29.9%** of patients still on placebo + ADT[2]

*Long-term follow-up will continue to assess the overall survival data as they mature. At the time of the first interim analysis of overall survival, a total of 104 deaths had occurred in the SPARTAN study. The final overall survival analysis will be conducted after approximately 427 deaths have been reported.[2,3]

1. ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Smith MR, et al. *N Engl J Med.* 2018;378(15):1408-1418. **3.** Small EJ, et al. Poster presented at: The American Society of Clinical Oncology Genitourinary Cancers Symposium Annual Meeting; February 8-10, 2018; San Francisco, CA.

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Secondary Endpoints: ERLEADA™ (apalutamide) + ADT Delayed Median Time to Metastasis and Improved Median Progression-Free Survival vs Placebo + ADT

The MFS outcome was supported by statistically significant improvements in secondary endpoints, such as time to metastasis and progression-free survival[1]

- The median time to metastasis for ERLEADA™ plus ADT arm was **40.5 months** vs **16.6 months** for the placebo plus ADT arm, representing a longer median time to metastasis with ERLEADA™ plus ADT compared to placebo plus ADT (HR=0.27; 95% CI: 0.22-0.34; *P*<0.0001*)[1†]
- The median progression-free survival for ERLEADA™ plus ADT arm was **40.5 months** vs **14.7 months** for the placebo plus ADT arm, representing a significant decrease in the risk of disease progression or death by 71% (HR=0.29; 95% CI: 0.24-0.36; *P*<0.0001*)[1‡]

**P* value from a log-rank test. All analyses stratified by PSA doubling time, bone-sparing agent use, and locoregional disease. †Time to metastasis was defined as the time from randomization to the time of the scan that showed first evidence of BICR-confirmed radiographically detectable bone or soft tissue distant metastasis.[2] ‡Progression-free survival was defined as the time from randomization to first documentation of BICR-confirmed radiographic progressive disease or death due to any cause, whichever occurred first.[2]

1. ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Smith MR, et al. *N Engl J Med.* 2018;378(15):1408-1418.

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Sites of Metastasis in Patients Participating in the SPARTAN Study

Sites of metastasis[1,2]*

Patients with metastasis (%)	ERLEADA™ + ADT (n=175)	Placebo + ADT (n=191)
Bone	57%	52%
Nodal	30%	40%
Visceral	13%	8%

*As reported in a post hoc analysis of SPARTAN.[2] In the SPARTAN study, 175 patients (22%) in the ERLEADA™ + ADT arm and 191 patients (48%) in the placebo + ADT arm developed metastasis.[1]

1. ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Smith MR, et al. *J Clin Oncol*. 2018;36(15 suppl): Abstract 5033.

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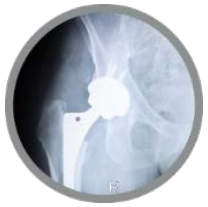
Secondary Endpoint: The MFS Outcome Was Supported by a Statistically Significant Improvement in Time to Symptomatic Progression[1]

Time to symptomatic progression was defined as the time from randomization to documentation of any of the following (whichever occurred earlier)[2,3]:

- Development of a skeletal-related event: pathologic fracture, spinal cord compression, or need for surgical intervention or radiation therapy to the bone
- Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anticancer therapy
- Development of clinically significant symptoms due to locoregional tumor progression requiring surgical intervention or radiation therapy

Examples of symptomatic progression evaluated in the SPARTAN study:

Spinal cord compression



The need for surgical intervention

The need for radiation therapy

1. ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Smith MR, et al. *N Engl J Med.* 2018;378(15):1408-1418.
3. Data on file. Janssen Biotech, Inc.

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The Effect of ERLEADA® (apalutamide) on Health-Related Quality of Life Was Investigated With the Functional Assessment of Cancer Therapy-Prostate (FACT-P) in the SPARTAN Trial

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Patient-Reported Outcomes in SPARTAN

- In a prespecified exploratory analysis, the patient-reported outcomes of HRQoL in men with high-risk non-metastatic CRPC treated with apalutamide + ADT or placebo were compared[1]
- In the SPARTAN study, patient-reported outcomes were measured with the **Functional Assessment of Cancer Therapy – Prostate (FACT-P)** and the EuroQoL 5-dimension, 3-level questionnaire (EQ-5D-3L)[1]
- The **FACT-P** patient-reported outcome questionnaire was used to assess prostate cancer symptoms, pain-related symptoms, and overall HRQoL[1]
- All 5 FACT-P subscales are included in the mean FACT-P total score[1,2]:

Prostate cancer subscale

HRQoL = health-related quality of life.

1. Saad F, et al. [published online September 10, 2018]. *Lancet Oncol*. doi:https://doi.org/10.1016/S1470-2045(18)30456-X. **2.** Appendix to: Saad F, et al. [published online September 10, 2018]. *Lancet Oncol*. doi:10.1016/S1470-2045(18)30456-X.

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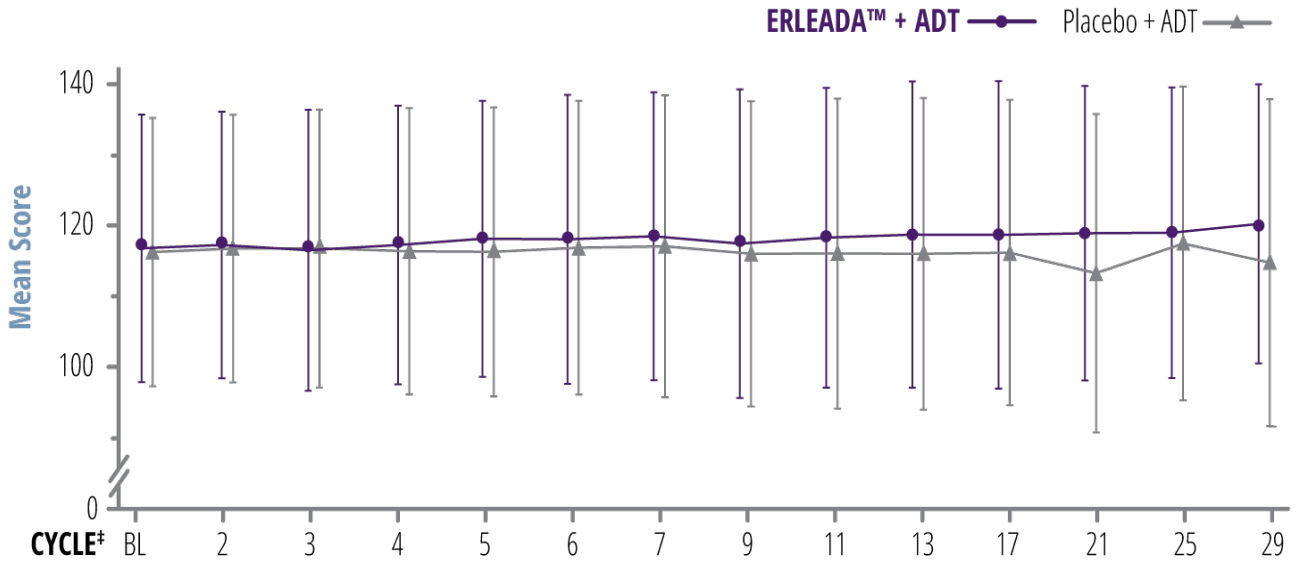
Patients Reported That There Was No Negative Impact to Their HRQoL After Initiation of Treatment With ERLEADA™ (apalutamide) + ADT

Total scores for FACT-P were maintained with ERLEADA™ from baseline until treatment cycle 29

Mean FACT-P Total Score During the Treatment Phase (Exploratory Endpoint)*†



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*Before the development of distant metastasis. †The results were consistent across all FACT-P subscales. ‡Cycle 29 is approximately 25.8 months from the start of treatment.

Saad F, et al. [published online September 10, 2018]. *Lancet Oncol*. doi:https://doi.org/10.1016/S1470-2045(18)30456-X.

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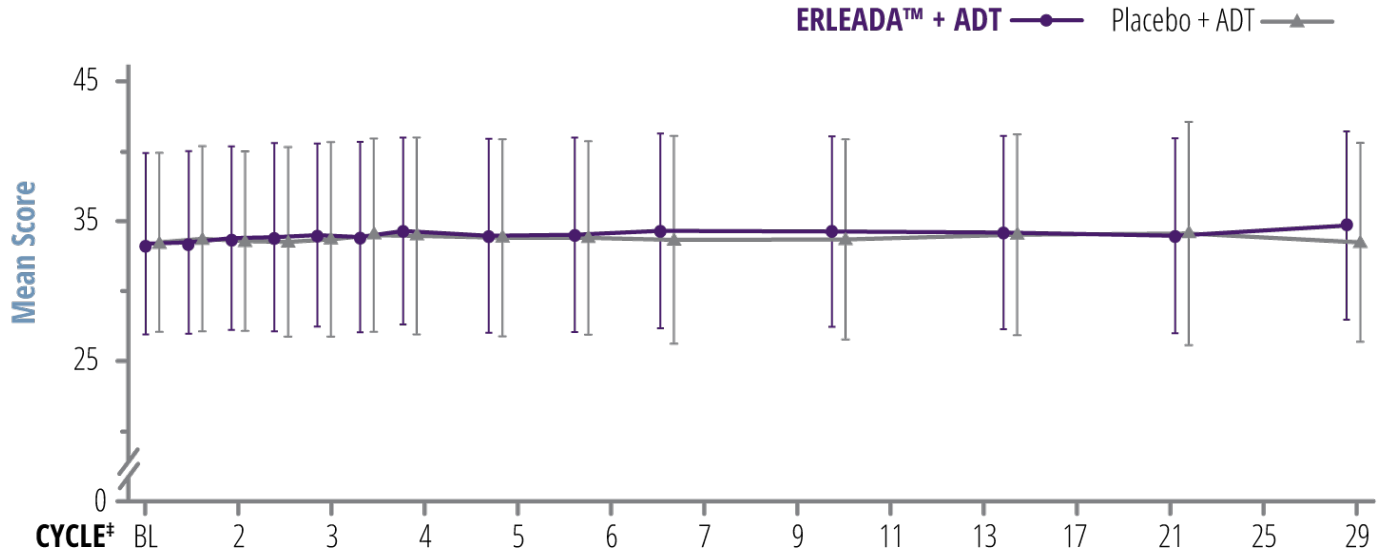
Patients Reported That There Was No Negative Impact to Their HRQoL After Initiation of Treatment With ERLEADA™ (apalutamide) + ADT *(cont'd)*

Mean FACT-P Prostate Cancer Subscale Score During the Treatment Phase (Exploratory Endpoint)*†



NUMBER OF PATIENTS IN EACH CYCLE	BL	2	3	4	5	6	7	9	11	13	17	21	25	29
ERLEADA™ + ADT	792	780	765	742	714	693	675	645	613	589	455	351	257	167
Placebo + ADT	393	389	379	371	350	301	283	265	221	199	135	82	54	35

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*Before the development of distant metastasis. †The results were consistent across all FACT-P subscales. ‡Cycle 29 is approximately 25.8 months from the start of treatment.

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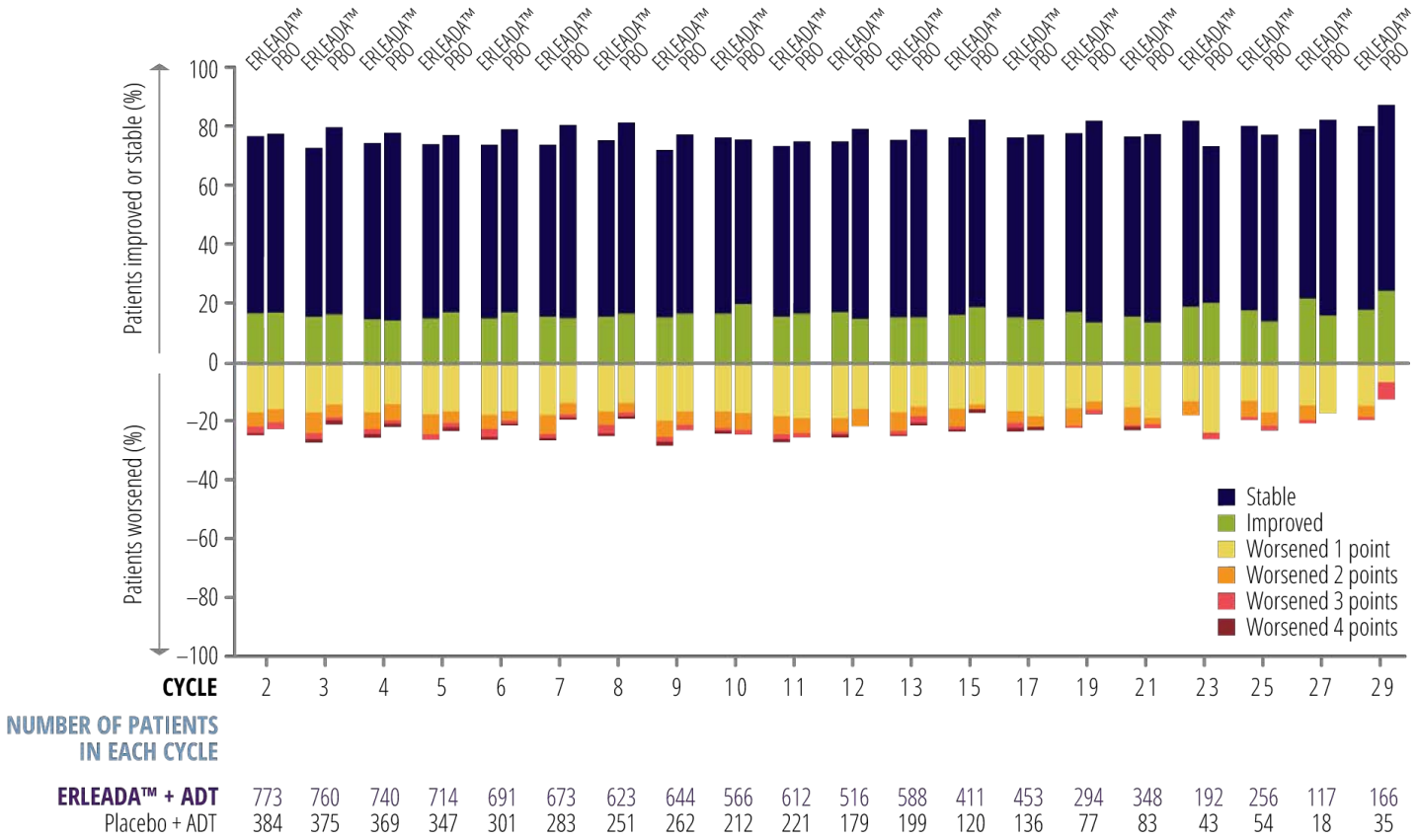
Patients on ERLEADA™ (apalutamide) + ADT Had Similar Responses to Those on Placebo + ADT When Asked About Side Effects

The distribution of responses and distribution of change from baseline (stable, improved, and worsened) were comparable between treatment groups

Post hoc analysis of answers to the question from the FACT-P physical well-being domain

- *"I am bothered by side effects of treatment"**



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PBO = placebo.
*The results were consistent across all FACT-P subscales.
Saad F, et al. [published online September 10, 2018]. *Lancet Oncol*. doi:https://doi.org/10.1016/S1470-2045(18)30456-X.

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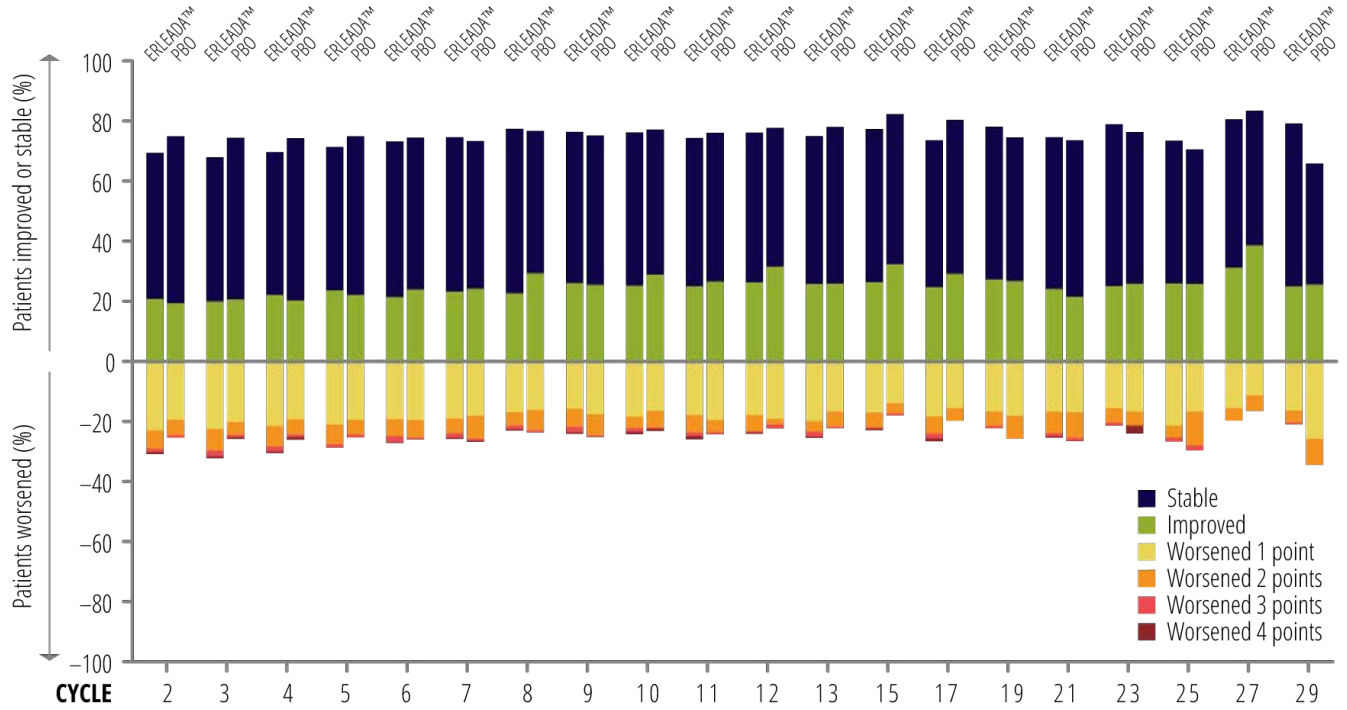
Patients on ERLEADA™ (apalutamide) + ADT Had Similar Responses to Those on Placebo + ADT When Asked About Energy Levels

The distribution of responses and distribution of change from baseline (stable, improved, and worsened) were comparable between treatment groups

Post hoc analysis of answers to the question from the FACT-P physical well-being domain

- *"I have a lack of energy"**



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ERLEADA™ (apalutamide): Safety Profile

WARNINGS AND PRECAUTIONS

Falls and Fractures—In a randomized study (SPARTAN), falls and fractures occurred in 16% and 12% of patients treated with ERLEADA™ compared to 9% and 7% treated with placebo, respectively. Falls were not associated with loss of consciousness or seizure. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone targeted agents.

Seizure—In a randomized study (SPARTAN), 2 patients (0.2%) treated with ERLEADA™ experienced a seizure. Permanently discontinue ERLEADA™ in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA™. Advise patients of the risk of developing a seizure while receiving ERLEADA™ and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

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SPARTAN Safety Profile: Adverse Reactions

Adverse reactions occurring in ≥10% on the ERLEADA™ (apalutamide) arm in SPARTAN that occurred with a 2% absolute increase in frequency compared to placebo:

	ERLEADA™ (n=803)		Placebo (n=398)	
System/Organ Class Adverse reaction	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
General disorders and administration site conditions				
Fatigue	39	1	28	0.3
Musculoskeletal and connective tissue disorders				
Arthralgia	16	0	8	0
Skin and subcutaneous tissue disorders				
Rash	24	5	6	0.3
Metabolism and nutrition disorders				
Decreased appetite	12	0.1	9	0
Peripheral edema	11	0	9	0
Injury, poisoning and procedural complications				
Fall	16	2	9	0.8
Fracture	12	3	7	0.8

- In SPARTAN, rash associated with ERLEADA™ was most commonly described as macular or maculo-papular. The onset of rash occurred at a median of 82 days of ERLEADA™ treatment. Rash resolved in 81% of patients within a median of 60 days (range: 2 to 709 days) from onset of rash

ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

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SPARTAN Safety Profile: Adverse Reactions *(cont'd)*

Adverse reactions occurring in ≥10% on the ERLEADA™ (apalutamide) arm in SPARTAN that occurred with a 2% absolute increase in frequency compared to placebo[1]:

	ERLEADA™ + ADT (n=803)		Placebo + ADT (n=398)	
System/Organ Class Adverse reaction	**All Grades, %**	**Grades 3-4, %**	**All Grades, %**	**Grades 3-4, %**
Investigations				
Weight decreased*	16	1	6	0.3
Vascular disorders				
Hypertension	25	14	20	12
Hot flush	14	0	9	0
Gastrointestinal disorders				
Diarrhea	20	1	15	0.5
Nausea	18	0	16	0

Additional safety information in the SPARTAN study[2,3†]

	ERLEADA™ + ADT (n=803)		Placebo + ADT (n=398)	
Treatment-Emergent Adverse Events	**All Grades, %**	**Grades 3-4, %**	**All Grades, %**	**Grades 3-4, %**
Any mental impairment disorder	3.9	0	3.4	0
Amnesia	1.9	0	1.0	0
Memory impairment	1.6	0	1.5	0
Disturbance in attention	1.2	0	0.3	0
Cognitive disorder	0.7	0	0.8	0

*Grade 4 definitions do not exist for these reactions. †Exposure-adjusted rates. An exposure-adjusted rate is 100 times the number of distinct mental impairment disorder treatment-emergent adverse events divided by total years of exposure.

1. ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Smith MR, et al. *N Engl J Med.* 2018;378(15):1408-1418. **3.** Data on file. Janssen Biotech, Inc.

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Erleada™ (apalutamide) 60 mg tablets

ERLEADA™ (apalutamide): Safety Profile *(cont'd)*

Rash—Rash was most commonly described as macular or maculo-papular. Adverse reactions were 24% with ERLEADA™ versus 6% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA™ treatment (5%) versus placebo (0.3%).

The onset of rash occurred at a median of 82 days. Rash resolved in 81% of patients within a median of 60 days (range: 2 to 709 days) from onset of rash. Four percent of patients treated with ERLEADA™ received systemic corticosteroids. Rash recurred in approximately half of patients who were re-challenged with ERLEADA™.

Hypothyroidism was reported for 8% of patients treated with ERLEADA™ and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA™ and 7% of patients treated with placebo. The median onset was day 113. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

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ERLEADA™ (apalutamide): Safety Profile *(cont'd)*

ADVERSE REACTIONS

Adverse Reactions—The most common adverse reactions (≥10%) were fatigue, hypertension, rash, diarrhea, nausea, weight decreased, arthralgia, fall, hot flush, decreased appetite, fracture, and peripheral edema.

Laboratory Abnormalities—All Grades (Grade 3-4)

- **Hematology**—anemia ERLEADA™ 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA™ 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA™ 41% (2%), placebo 21% (2%)

- **Chemistry**—hypercholesterolemia ERLEADA™ 76% (0.1%), placebo 46% (0%); hyperglycemia ERLEADA™ 70% (2%), placebo 59% (1%); hypertriglyceridemia ERLEADA™ 67% (2%), placebo 49% (0.8%); hyperkalemia ERLEADA™ 32% (2%), placebo 22% (0.5%)

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Erleada™ (apalutamide) 60 mg tablets

ERLEADA™ (apalutamide) Dosage and Administration

Recommended Dosage

The recommended dose of ERLEADA™ is **240 mg** (four 60 mg tablets) administered **orally once daily**

Patients should also receive a GnRH analog concurrently or should have had a bilateral orchiectomy

Can be taken with or without food. Tablets should be swallowed whole

No initial dose adjustments for ERLEADA™ are necessary for renal or hepatic impairment*

No additional laboratory monitoring requirements beyond routine assessments for side effects

Dose Modification

- If a patient experiences a ≥Grade 3 toxicity or an intolerable side effect, hold dosing until symptoms improve to ≤Grade 1 or original grade, and then resume at the same dose or a reduced dose (180 mg or 120 mg), if warranted

*The effect of severe renal impairment or end stage renal disease (estimated glomerular filtration rate [GFR] ≤29 mL/min/1.73m^2, estimated by the modification of diet in renal disease) or severe hepatic impairment (Child-Pugh C) on apalutamide pharmacokinetics is unknown. ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

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ERLEADA™ (apalutamide): Important Safety Information

DRUG INTERACTIONS

Effect of Other Drugs on ERLEADA™—Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA™ dose based on tolerability *[see Dosage and Administration (2.2)].*

Effect of ERLEADA™ on Other Drugs—ERLEADA™ is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA™ with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible, or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA™ with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA™ and evaluate for loss of activity.

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ERLEADA™ (apalutamide): Important Safety Information *(cont'd)*

DRUG INTERACTIONS *(cont'd)*

P-gp, BCRP, or OATP1B1 Substrates—Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA™ with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA™ and evaluate for loss of activity if medication is continued.

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Janssen CarePath

Your One Source for Access, Affordability, and Treatment Support for Patients

Janssen CarePath Savings Program for ERLEADA™ helps verify insurance coverage for your patients, provides reimbursement information, helps find financial assistance options for eligible patients, and provides ongoing support to help them start and stay on ERLEADA™ (apalutamide) as prescribed. For a list of specialty pharmacies that distribute ERLEADA™, call **Janssen CarePath**.

- **Call** a Janssen Care Coordinator at 877-CarePath (877-227-3728), Monday-Friday, 8:00 AM to 8:00 PM ET

- Visit **Erleada.JanssenCarePathSavings.com** for a Benefits Investigation Form, Sample Letter of Medical Necessity, Sample Exception Letter, and other resources to support your patients' access to ERLEADA™

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Erleada™ (apalutamide) 60 mg tablets

Insurance Coverage for ERLEADA™ (apalutamide)

Important Access Information

ERLEADA™ HAS BROAD ACCESS FOR OVER 90% OF MEDICARE PART D AND 80% OF COMMERCIAL PATIENTS*

The information provided represents no statement, promise, or guarantee of Janssen Biotech, Inc., concerning levels of reimbursement, payment, or charge. Please consult your payer organization with regard to local or actual coverage, reimbursement policies, and determination processes. Information is subject to change without notice. Nothing herein may be construed as an endorsement, approval, recommendation, representation, or warranty of any kind by any plan or insurer referenced herein. This communication is solely the responsibility of Janssen Biotech, Inc. Information is valid as of May 25, 2018, and is subject to change.

*Data as of August 9, 2018, includes Letter of Medical Necessity (LMN) and Interim Criteria.

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Discussion Questions and Considerations

SPARTAN Trial

- What are your general impressions of the SPARTAN data?
- What are the clinical implications of the reduction in the risk of metastasis or death in patients on ERLEADA™ (apalutamide)?
- What factors do you consider when deciding if a patient is a candidate for ERLEADA™?

Clinical Practice

- How do you define non-metastatic (M0) CRPC?
  - Does your definition include N1 disease?
  - What type of imaging do you typically use to monitor patients with non-metastatic CRPC?
- For your patients with non-metastatic CRPC, how often is PSA being monitored? How does a fast PSADT affect your treatment approach?
- What is the protocol in your practice for identifying patients who may be at high risk for metastasis?
- What is your current treatment approach for patients with non-metastatic CRPC?

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Summary

In the SPARTAN study:

- ERLEADA™ + ADT improved median metastasis-free survival (MFS) by **2 years** (24.3 months) compared with placebo + ADT (40.5 months [3.4 years] vs 16.2 months [1.4 years]; HR=0.28; 95% CI: 0.23-0.35; *P*<0.0001)[1]
  - ERLEADA™ + ADT demonstrated a statistically significant improvement in time to symptomatic progression compared with placebo + ADT (secondary endpoint)
- Patients reported that there was no new negative impact to their HRQoL after initiation of treatment with ERLEADA™ + ADT[2]
  - Total scores for FACT-P were maintained with ERLEADA™ from baseline until treatment cycle 29

1. ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Saad F, et al. [published online September 10, 2018]. *Lancet Oncol*. doi:https://doi.org/10.1016/S1470-2045(18)30456-X.

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Summary (cont'd)

In the SPARTAN study (cont'd):

- Safety profile
  - ERLEADA™ is contraindicated in pregnant women because ERLEADA™ can cause fetal harm and potential loss of pregnancy
  - Warnings and precautions include falls, fractures, and seizure
- The most common adverse reactions (≥10%) were fatigue, hypertension, rash, diarrhea, nausea, weight decreased, arthralgia, fall, hot flush, decreased appetite, fracture, and peripheral edema
- **Once-daily oral dosing** with no additional laboratory monitoring requirements beyond routine assessments for side effects

ERLEADA™ [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

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Patient Case*

- David is a 75-year old white male with prostate cancer

Diagnosis and Treatment History

Fall 2009

- **Diagnosis:** PSA 8.9 ng/mL; Gleason 8; adenocarcinoma
- EBRT to the prostate and pelvis
- Patient refused neoadjuvant, concurrent or adjuvant ADT

Spring 2012

- PSA recurrence
- Started ADT
- PSA drops to 0.2 ng/mL

Spring-Fall 2017

- PSA started to rise
- Started bicalutamide
- Within 8 months, including 4 laboratory tests:
  - PSA rises from 9.0 to 18.5 ng/mL
  - Serum testosterone remains at ~30 ng/dL

Current visit (Winter 2018)

- Recent scans show no metastatic disease
- No signs of fatigue, weight loss, or pain
- ECOG=0
- PSADT=7.5 months

EBRT = external beam radiation therapy; ECOG = Eastern Cooperative Oncology Group.
*Hypothetical.

Patient Case* *(cont'd)*

Discussion Questions

- For patients on ADT with a rapidly rising PSA, such as David, how do you monitor for signs of progression to metastasis?
- At this point for David, what would be your treatment goals?
- What are the potential implications of delaying further treatment for David?

*Hypothetical.

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Patient Case* *(cont'd)*

For patients like David with non-metastatic CRPC

- ✓ **On ADT**
- ✓ **With rapidly rising PSA†**
- ✓ **And no radiographically detectable metastases**

†PSA doubling time ≤10 months.

Discussion Questions

How are patients with non-metastatic CRPC typically identified in your clinical practice?

Personnel

- Is there a dedicated Nurse Navigator and/or Clinician Champion in your clinical practice?
  - What are his/her responsibilities regarding the identification of patients with non-metastatic CRPC?
  - Does his/her responsibilities include assisting patients' access to treatment?

Operations

- Do you keep a database of information pulled from the EMR?
- Are EMR algorithms or data analytics software used to facilitate the identification of patients with non-metastatic CRPC, such as David? If yes, what are they?

EMR = electronic medical record.
*Hypothetical.

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ERLEADA™ (apalutamide) Post-Program Survey

- **No personal data will be collected**
- **Only 6 multiple choice questions. Should take only 2-3 minutes**
- **Data collected will be used to improve the content of our educational programs**
- **Optional**

1. **Please use your cell phone to text "ERLEADA" to the number 31996.**
2. **You will receive a link, via text, to the survey.**
3. **Click on the link.**
4. **Your representative will supply the program number to type in to respond to question one.**
5. **After you have recorded your responses hit "submit."**

Thank you for your participation!

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Thank You

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