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ERLEADA™ Significantly Reduced Risk of Prostate Specific Antigen (PSA) Progression in Patients with Non-Metastatic Castration-Resistant Prostate Cancer

PSA outcomes data from Phase 3 SPARTAN clinical trial and population-based study of PSA doubling time in patients with non-metastatic castration-resistant prostate cancer were presented at the AUA 2018 Annual Meeting

HORSHAM, PA, May 18, 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson today presented a post-hoc analysis from the Phase 3 SPARTAN study that showed treatment with ERLEADA™ (apalutamide) significantly reduced the risk of prostate specific antigen (PSA) progression in patients with non-metastatic castration-resistant prostate cancer (nmCRPC) who had a rapidly rising PSA while receiving continuous androgen deprivation therapy (ADT) (Abstract [PD10-11](#)). These data were presented during the Prostate Cancer: Advanced (including Drug Therapy) I Oral Podium Session at the 2018 [American Urological Association \(AUA\) Annual Meeting](#).

Additionally, Janssen presented another study that assessed the association between PSA doubling time and both metastasis-free survival (MFS) and overall survival (OS) in patients with nmCRPC (Abstract [PD10-04](#)). Shorter PSA doubling time has been associated with shorter time to metastasis or death.^{1,2}

“Patients with non-metastatic castration-resistant prostate cancer are at risk for metastases and mortality. In these patients, PSA doubling time is an important predictor of outcomes, including time to developing metastases or symptoms from their cancer,” said Eric Small, M.D. FASCO, Professor of Medicine, Chief of the Division of Hematology and Oncology, and Deputy Director of the Helen Diller Comprehensive Cancer Center at the University of California, San Francisco, and co-

principal investigator of the SPARTAN study. “This analysis further underscores the efficacy of apalutamide therapy and helps us understand how PSA changes in these patients are associated with clinical outcomes.”

Key Findings from the SPARTAN Study

According to the data from the SPARTAN study presented at AUA 2018, ERLEADA significantly decreased the risk of PSA progression by 94 percent, compared with the placebo group (median not reached vs. 3.71 months; HR=0.06; 95% CI, 0.05-0.08; $P<0.0001$).³

Additionally, the median time to PSA response was 29 days in the ERLEADA plus ADT group^{1,2} At 12 weeks after randomization, median PSA decreased by 90 percent in the ERLEADA group and increased by 40 percent in the placebo group.²

Among patients treated, baseline median PSA doubling time was 4.4 and 4.5 months, and median baseline PSA was 7.78 and 7.96 ng/mL in the ERLEADA and placebo groups, respectively.³ A ≥ 90 percent maximum decline in PSA from baseline at any time on study was observed in 66 percent of patients in the ERLEADA group and 1 percent of patients in the placebo group.³

The SPARTAN trial was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study that evaluated ERLEADA in combination with ADT in patients with nmCRPC who had a rapidly rising PSA (PSA doubling time ≤ 10 months). The primary endpoint was MFS. ERLEADA plus ADT improved MFS by 2 years (24.3 months) compared to placebo plus ADT (40.5 months vs. 16.2 months; HR=0.28; 95% CI, 0.23-0.35; $P<0.0001$).⁴

Key Findings from the Population-Based Study

Janssen also presented data from a population-based study designed to evaluate the association of PSA doubling time and baseline PSA levels with MFS and OS in patients with nmCRPC. The study was conducted using an integrated electronic health records and claims database.⁵ Specifically, PSA doubling time of ≤ 10 months was associated with shorter MFS and OS and was a marker for high-risk disease.⁵ Of the patients with evaluable PSA doubling time, 38.2 percent were defined as high-risk and 61.8 percent as low-risk, with a median MFS of 15.2 and 30.5 months, ($P<0.0001$) and median OS of 36.0 and 57.6 months ($P=0.0092$), respectively.⁵

“The data presented today demonstrated that a shorter PSA doubling time can result in poor outcomes for patients, supporting the benefit of ERLEADA in reducing the risk of PSA progression in patients with non-metastatic castration-resistant prostate cancer,” said Marco Gottardis, Ph.D., Vice President and Prostate Cancer Disease Area Stronghold Leader for the Oncology Therapeutic Area at Janssen Research & Development, LLC. “Janssen is fully committed to the discovery and development of next-generation treatments and bringing forward data that may help physicians consider treatment options for patients with rapidly rising PSA levels who are at high-risk for metastasis.”

Additionally, Janssen will present a moderated poster titled, “Patient Reported Outcomes (PROs) in SPARTAN, a Phase 3, double-blind, randomized study of apalutamide plus androgen deprivation therapy (ADT) vs. placebo plus ADT in patients with non-metastatic castration-resistant prostate cancer (nmCRPC)” on Sunday, May 20, from 7:00 a.m. to 9:00 a.m. PST (Abstract [MP52-20](#)).⁶

About Non-Metastatic Castration-Resistant Prostate Cancer

Non-metastatic castration-resistant prostate cancer refers to a disease state in which the cancer no longer responds to medical or surgical treatments that lower testosterone, but has not yet been discovered in other parts of the body using a total body bone scan or CT scan.⁷ Features include: lack of detectable metastatic disease;⁷ rapidly rising prostate specific antigen while on androgen deprivation therapy (ADT); and serum testosterone level below 50 ng/dL.^{8,9} Ninety percent of patients with nmCRPC will eventually develop bone metastases, which can lead to pain, fractures and spinal cord compression.¹⁰ The relative 5-year survival rate for patients with distant stage prostate cancer is 30 percent.¹¹ It is critical to delay the onset of metastasis in patients with nmCRPC.

About ERLEADA™

ERLEADA (apalutamide) is an androgen receptor (AR) inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC) and was approved by the FDA on [February 14, 2018](#) as the first approved treatment for this disease state.⁴ Apalutamide is the only therapy with a category 1 recommendation for non-metastatic (M0) CRPC in the NCCN Guidelines® for Prostate Cancer. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer include apalutamide as a treatment option for patients with non-metastatic (M0) CRPC with a category 1 recommendation (especially for those with a PSA doubling time ≤ 10 months)*.¹² Additionally, the AUA Guidelines for Castration-Resistant Prostate Cancer (CRPC) were recently updated to include apalutamide (ERLEADA) with continued androgen

deprivation as a treatment option that clinicians should offer to patients with nmCRPC who are at high-risk for developing metastatic disease (Standard; Evidence Level Grade A)** .¹³

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

***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: A designation indicating the certainty of the results as high, moderate, or low (A, B, or C, respectively) based on AUA nomenclature and methodology.*

INDICATION

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

ERLEADA IMPORTANT SAFETY INFORMATION⁴

CONTRAINDICATIONS

Pregnancy — ERLEADA™ (apalutamide) can cause fetal harm and potential loss of pregnancy.

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.

ADVERSE REACTIONS

Adverse Reactions — The most common adverse reactions ($\geq 10\%$) 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%)

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.

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.

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.

Please see the full [Prescribing Information](#) for ERLEADA™.

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science.

We are Janssen. We collaborate with the world for the health of everyone in it. Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenGlobal and www.twitter.com/JanssenUS. Janssen Research & Development, LLC is part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

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Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding the potential benefits and further benefits of ERLEADA™ (apalutamide). The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC and of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 31, 2017, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the Company's subsequent Quarterly Reports on Form 10-Q and other, filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. Neither the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

¹ Smith MR, Kabbavar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J Clin Oncol* 2005; 23: 2918-2925.

² Smith MR, Saad F, Oudard S, et al. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. *J Clin Oncol* 2013; 31:3800-3806.

³ Small, E. et al. Prostate-Specific Antigen (Psa) Outcomes In Patients (Pts) With Nonmetastatic Castration-Resistant Prostate Cancer (Nmcrpc) Treated With Apalutamide (Apa): Results From Phase 3 Spartan Study. Abstract #PD 10-11.

⁴ ERLEADA Prescribing Information, February 2018.

⁵ Saad F, et al. A Population-Based Study of the Association of Prostate-Specific Antigen Doubling Time (PSADT) with Metastasis-Free Survival (MFS) and Overall Survival (OS) in Nonmetastatic Castration-Resistant Prostate Cancer (nmCRPC) Patients (pts). Abstract #PD10-04.

⁶ Small E., et al. Patient Reported Outcomes (PROS) in Spartan, a Phase 3, Double-Blind, Randomized Study of Apalutamide (Apa) Plus Androgen Deprivation Therapy (ADT) Vs Placebo Plus ADT in Men with Nonmetastatic Castration-Resistant Prostate Cancer (nmCRPC). Abstract MP52-20.

⁷ Scher HI, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol*. 2008;26:1148-1159.

⁸ Scher HI, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol*. 2016;34:1402-1418.

⁹ Virgo K, et al. Second-Line Hormonal Therapy for Men with Chemotherapy-Naïve, Castration-Resistant Prostate Cancer: American Society of Clinical Oncology Provisional Clinical Opinion. *Journal of Clinical Oncology*. 2017; 0732-183X/17/3599-1. Accessed April 2018.

¹⁰ Saad F, et al. The 2015 CUA0CUOG guidelines for the management of castration-resistant prostate cancer (CRPC). *Can Urol Assoc J*. 2015;9(3-4):90-96. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4455631/>. Accessed May 2018.

¹¹ American Cancer Society. Cancer Facts & Figures. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf>. Accessed May 2018.

¹² National Comprehensive Cancer Network. NCCN Clinical Guidelines in Oncology: Prostate Cancer.

https://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf. Accessed May 2018.

¹³ American Urological Association. Castration-Resistant Prostate Cancer Guidelines.

[http://www.auanet.org/guidelines/castration-resistant-prostate-cancer-\(2013-amended-2018\)](http://www.auanet.org/guidelines/castration-resistant-prostate-cancer-(2013-amended-2018)). Accessed May 2018.