

Astellas and Pfizer Announce Positive Top-Line Results from Phase 3 ARCHES Trial of XTANDI® (enzalutamide) in Men with Metastatic Hormone-Sensitive Prostate Cancer

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TOKYO & NEW YORK--([BUSINESS WIRE](#))--Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., “Astellas”) and Pfizer Inc. (NYSE: PFE) today announced that the Phase 3 ARCHES trial evaluating XTANDI® (enzalutamide) plus androgen deprivation therapy (ADT) in men with metastatic hormone-sensitive prostate cancer (mHSPC) met its primary endpoint, significantly improving radiographic progression-free survival (rPFS) versus ADT alone. The preliminary safety analysis of the ARCHES trial appears consistent with the safety profile of XTANDI in previous clinical trials in castration-resistant prostate cancer (CRPC). Detailed results will be submitted for presentation at an upcoming medical congress.

“While XTANDI is currently approved for both metastatic and non-metastatic CRPC, there still remains a need for more treatment options for men with metastatic hormone-sensitive prostate cancer,” said Mace Rothenberg, M.D., Chief Development Officer, Oncology, Pfizer Global Product Development. “With these top-line results, we believe XTANDI has the potential to help men whose disease has progressed outside the prostate gland, but still responds to treatment to lower testosterone.”

“The results from ARCHES demonstrate a statistically significant improvement in a key marker of disease progression – radiographic progression-free survival,” said Steven Benner, M.D., senior vice president and global therapeutic area head, Oncology Development, Astellas. “Based on the top-line results of ARCHES, we look forward to discussing the data with relevant health authorities to potentially support expanding the indication for XTANDI.”

XTANDI is currently approved in the U.S. and Japan for the treatment of CRPC and in the EU for the treatment of metastatic and high-risk non-metastatic CRPC. Since its initial approval in 2012, XTANDI has been prescribed to more than 330,000 men worldwide.¹

About ARCHES

The Phase 3, randomized, double-blind, placebo-controlled, multi-national trial enrolled 1,150 patients with metastatic hormone-sensitive prostate cancer (mHSPC) at sites in the United States, Canada, Europe, South America and the Asia-Pacific region. Patients in the ARCHES trial were randomized to receive XTANDI 160 mg daily or placebo and continued on a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist or had a history of bilateral orchiectomy. The ARCHES trial included patients with both low- and high- volume disease and both newly diagnosed patients with mHSPC and patients who had prior definitive therapy and subsequently developed metastatic disease. The trial also included some patients who had received recent treatment with docetaxel for mHSPC, but whose disease had not progressed. The primary endpoint of the trial

was radiographic progression-free survival (rPFS), defined as the time from randomization to the first objective evidence of radiographic disease progression as assessed by central review, or death, whichever occurs first. For more information on the ARCHES ([NCT02677896](https://clinicaltrials.gov/ct2/show/study/NCT02677896)) trial go to www.clinicaltrials.gov.

About Metastatic Hormone-Sensitive Prostate Cancer

In men with prostate cancer, the disease is considered metastatic once the cancer has spread outside of the prostate gland to other parts of the body, such as the bones, lymph nodes, bladder and rectum.² Men are considered hormone (or castration) sensitive if their disease still responds to medical or surgical treatment to lower testosterone levels.³ Approximately 38,000 men in the U.S. develop metastatic HSPC every year.^{4,5}

About XTANDI® (enzalutamide) capsules

XTANDI (enzalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with castration-resistant prostate cancer.

As part of Pfizer and Astellas' ongoing commitment to the clinical development of enzalutamide, XTANDI is also being evaluated in the EMBARK trial, in men with high-risk non-metastatic HSPC. Details about EMBARK ([NCT02319837](https://clinicaltrials.gov/ct2/show/study/NCT02319837)) are available on www.clinicaltrials.gov.

Important Safety Information for XTANDI® in CRPC

Warnings and Precautions

Seizure occurred in 0.4% of patients receiving XTANDI in clinical studies. In a study of patients with predisposing factors for seizure, 2.2% of XTANDI-treated patients experienced a seizure. Patients in the study had one or more of the following pre-disposing factors: use of medications that may lower the seizure threshold; history of traumatic brain or head injury, cerebrovascular accident or transient ischemic attack, Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Advise patients of the risk of developing a seizure while taking XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES) In post approval use, there have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with XTANDI in clinical trials. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue XTANDI and promptly seek medical care. Permanently discontinue XTANDI for serious hypersensitivity reactions.

Ischemic Heart Disease In the placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.7% vs 1.2%). Grade 3-4 ischemic events occurred in 1.2% of patients on XTANDI versus 0.5% on placebo. Ischemic events led to death in 0.4% of patients on XTANDI compared to 0.1% on placebo. Monitor for signs and symptoms of ischemic

heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

Falls and Fractures In the placebo-controlled clinical studies, falls occurred in 10% of patients treated with XTANDI compared to 4% of patients treated with placebo. Fractures occurred in 8% of patients treated with XTANDI and in 3% of patients treated with placebo. 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.

Embryo-Fetal Toxicity Safety and efficacy of XTANDI have not been established in females. XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI. XTANDI should not be handled by females who are or may become pregnant.

Adverse Reactions

The most common adverse reactions (? 10%) that occurred more frequently (? 2% over placebo) in the XTANDI patients from the randomized placebo-controlled trials were asthenia/fatigue, decreased appetite, hot flush, arthralgia, dizziness/vertigo, hypertension, headache and weight decreased. In the bicalutamide-controlled study, the most common adverse reactions (? 10%) reported in XTANDI patients were asthenia/fatigue, back pain, musculoskeletal pain, hot flush, hypertension, nausea, constipation, diarrhea, upper respiratory tract infection, and weight loss.

In the placebo-controlled study of metastatic CRPC (mCRPC) patients taking XTANDI who previously received docetaxel, Grade 3 and higher adverse reactions were reported among 47% of XTANDI patients and 53% of placebo patients. Discontinuations due to adverse events were reported for 16% of XTANDI patients and 18% of placebo patients. In the placebo-controlled study of chemotherapy-naïve mCRPC patients, Grade 3-4 adverse reactions were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to adverse events were reported for 6% of both study groups. In the placebo-controlled study of non-metastatic CRPC (nmCRPC) patients, Grade 3 or higher adverse reactions were reported in 31% of XTANDI patients and 23% of placebo patients. Discontinuations with an adverse event as the primary reason were reported for 9% of XTANDI patients and 6% of placebo patients. In the bicalutamide-controlled study of chemotherapy-naïve mCRPC patients, Grade 3-4 adverse reactions were reported in 39% of XTANDI patients and 38% of bicalutamide patients. Discontinuations with an AE as the primary reason were reported for 8% of XTANDI patients and 6% of bicalutamide patients.

Lab Abnormalities: In the two placebo-controlled trials in patients with mCRPC, Grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). In the placebo-controlled trial in patients with nmCRPC, Grade 1-4 neutropenia occurred in 8% of patients receiving XTANDI (0.5% Grade 3-4) and in 5% of patients receiving placebo (0.2% Grade 3-4).

Hypertension: In the two placebo-controlled trials in patients with mCRPC, hypertension was reported in 11% of XTANDI patients and 4% of placebo patients. Hypertension led to study discontinuation in <1% of patients in each arm. In the placebo-controlled trial in patients with nmCRPC, hypertension was reported in 12% of patients receiving XTANDI and 5% of patients receiving placebo.

Drug Interactions

Effect of Other Drugs on XTANDI Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI. Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI.

Effect of XTANDI on Other Drugs Avoid CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

Please see [Full Prescribing Information](#) for additional safety information.

About Pfizer Oncology

At Pfizer Oncology, we are committed to advancing medicines wherever we believe we can make a meaningful difference on the lives of patients. Today, Pfizer Oncology has an industry-leading portfolio of 14 approved cancer medicines across 22 indications, including breast, prostate, kidney, lung and hematology. We also have two oncology biosimilar medicines approved globally and several assets in mid to late-stage development for the treatment of cancer or as supportive care. Pfizer Oncology is striving to change the trajectory of cancer.

About Astellas

Astellas Pharma Inc., based in Tokyo, Japan, is a company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. For more information, please visit our website at <https://www.astellas.com/us/>.

About the Pfizer/Astellas Collaboration

In October 2009, Medivation, Inc., which is now part of Pfizer (NYSE:PFE), and Astellas (TSE: 4503) entered into a global agreement to jointly develop and commercialize enzalutamide. The companies jointly commercialize XTANDI in the United States and Astellas has responsibility for manufacturing and all additional regulatory filings globally, as well as commercializing XTANDI outside the United States.

Astellas Forward-Looking Statement

In this press release, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties.

Information about pharmaceutical products (including products currently in development), which is included in this press release is not intended to constitute an advertisement or medical advice.

Pfizer Disclosure Notice

The information contained in this release is as of December 20, 2018. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about XTANDI® (enzalutamide) and potential new indications being evaluated for the treatment of men with metastatic hormone-sensitive prostate cancer and the treatment of men with high-risk non-metastatic hormone-sensitive prostate cancer, including their potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, uncertainties regarding the commercial success of XTANDI; the uncertainties inherent in research and development, including the ability to meet anticipated clinical trial commencement and completion dates and regulatory submission dates, as well as the possibility of unfavorable clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations, and, even when we view data as sufficient to support the safety and/or effectiveness of a product candidate, regulatory authorities may not share our views and may require additional data or may deny approval altogether; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; the risks associated with interim data; whether and when drug applications for any of the potential new indications for XTANDI or any potential indications for XTANDI may be filed in any jurisdictions; whether and when regulatory authorities in any jurisdictions may approve any such applications, which will depend on the assessment by such regulatory authorities of the benefit-risk profile suggested by the totality of the efficacy and safety information submitted and, if approved, whether XTANDI for any such potential new indications will be commercially successful; decisions by regulatory authorities regarding labeling, safety, and other matters that could affect the availability or commercial potential of XTANDI, including for the potential new indications; risks related to increasing competitive, reimbursement and economic challenges; dependence on the efforts and funding by Astellas Pharma Inc. for the development, manufacturing and commercialization of XTANDI; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2017 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

¹ Data on file. Northbrook, IL: Astellas Inc.

² American Society of Clinical Oncology. ASCO Answers: Prostate Cancer (2018).

https://www.cancer.net/sites/cancer.net/files/asco_answers_guide_prostate.pdf. Accessed 11-13-2018.

³ Cancer.net. Prostate Cancer: Types of Treatment (03-2018). <https://www.cancer.net/cancer-types/prostate-cancer/types-treatment>. Accessed 11-7-2018.

⁴ Scher HI, Solo K, Valant J, Todd MB, Mehra M et al. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS One. 2015; 10(10): 1-2.

⁵ Siegel RL, Miller KD, Jemal A, Cancer statistics, 2018. CA Cancer Journal for Clinicians. 2018;68:7-30.

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