



U.S. FDA Approves XTANDI® (enzalutamide) for the Treatment of Men with Non-Metastatic Castration-Resistant Prostate Cancer (CRPC)

Friday, July 13, 2018 - 10:30am

First and Only Oral Treatment FDA-Approved for Both Non-Metastatic and Metastatic CRPC

TOKYO & Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., “Astellas”) and Pfizer Inc. (NYSE: PFE) today announced the U.S. Food and Drug Administration (FDA) approved a supplemental New Drug Application (sNDA) for XTANDI® (enzalutamide), following FDA Priority Review designation, based on results from the Phase 3 PROSPER trial. The FDA action broadens the indication for XTANDI to men with castration-resistant prostate cancer (CRPC), now including men with non-metastatic CRPC. This approval makes XTANDI the first and only oral medication FDA-approved for both non-metastatic and metastatic CRPC. XTANDI was first approved by the FDA in 2012 for the treatment of patients with metastatic CRPC who had previously received docetaxel, and was granted approval in 2014 for chemotherapy-naïve men with metastatic CRPC.

“With today’s approval, there is now a new option for men with non-metastatic CRPC, who are in between the failure of androgen deprivation therapy resulting in CRPC and the onset of metastatic disease,” said Jonathan Simons, M.D., Prostate Cancer Foundation President and CEO. “As a foundation that drives research aimed at improving patient outcomes, it is exciting to see approvals like this, which are vital to help address unmet patient needs.”

The updated label is based on results from the Phase 3 PROSPER trial, which demonstrated that the use of XTANDI plus androgen deprivation therapy (ADT) significantly reduced the risk of developing metastasis or death compared to ADT alone in men with non-metastatic CRPC. The median for the primary endpoint, metastasis-free survival (MFS), was 36.6 months for men who received XTANDI plus ADT compared to 14.7 months with ADT alone (N=1401; HR=0.29 [95% CI: 0.24-0.35]; p<0.0001). The most common adverse reactions (greater than or equal to 10%) that occurred more frequently (greater than or equal to 2% over placebo) in XTANDI plus ADT-treated patients were: asthenic conditions (40% vs 20%), hot flush (13% vs 7.7%), hypertension (12% vs 5.2%), dizziness (12% vs 5.2%), nausea (11% vs 8.6%) and fall (11% vs 4.1%). Grade 3 or higher adverse reactions were reported in 31 percent of men treated with XTANDI plus ADT and in 23 percent of men treated with ADT alone. Data from the PROSPER study were presented at the 2018 Genitourinary Cancers Symposium (ASCO GU) in February and published in the New England Journal of Medicine in June.

“Reducing the risk of disease progression is an important treatment goal in castration-resistant prostate cancer, since the disease becomes harder to treat as it advances,” said Andy Schmeltz, global president, Oncology, Pfizer. “With XTANDI, men with CRPC now have a clinically proven treatment option that reduces the risk of metastasis. This approval delivers on the potential for XTANDI to help men at an earlier stage of the disease, and we are continuing to evaluate the medicine in an extensive development program across additional prostate cancer populations.”

“This approval is important progress for men with CRPC, who now have XTANDI as a treatment option regardless of whether or not they have detectable metastatic disease,” said Steven Benner, M.D., senior vice president and global therapeutic area head, Oncology Development, Astellas. “XTANDI is a standard of care in the treatment of men with metastatic CRPC and has been prescribed to more than 250,000 men worldwide since its initial approval in 2012. The expanded indication based on the PROSPER data builds on the body of evidence for XTANDI.”

Pfizer and Astellas are committed to helping patients access XTANDI by providing them with access and reimbursement support resources regardless of their situation. Patients can visit www.XTANDI.com or call 1-855-898-2634 to learn more.

PROSPER Trial Results

The Phase 3 PROSPER trial enrolled 1,401 patients with non-metastatic CRPC. Patients were randomized 2:1 and received either XTANDI plus ADT or placebo plus ADT (ADT

alone). Data in the updated XTANDI label demonstrates that the use of XTANDI plus ADT significantly reduced the risk of developing metastases or death compared to ADT alone. The median for the primary endpoint, MFS, was 36.6 months for men who received XTANDI compared to 14.7 months with ADT alone (HR=0.29 [95% CI: 0.24-0.35]; $p < 0.0001$).

The primary efficacy outcome was supported by a statistically significant delay in the time to first use of new antineoplastic therapy (TTA) for patients who received XTANDI plus ADT compared to those who received ADT alone (median 39.6 months vs 17.7 months; HR=0.21 [95% CI: 0.17-0.26]; $p < 0.0001$). Overall survival (OS) data were not mature at the time of final MFS analysis.

The most common adverse reactions (greater than or equal to 10%) that occurred more frequently (greater than or equal to 2% over placebo) in XTANDI plus ADT-treated patients compared to the ADT alone patients were: asthenic conditions (40% vs 20%), hot flush (13% vs 7.7%), hypertension (12% vs 5.2%), dizziness (12% vs 5.2%), nausea (11% vs 8.6%) and fall (11% vs 4.1%). Grade 3 or higher adverse reactions were reported in 31 percent of men treated with XTANDI plus ADT and in 23 percent of men treated with ADT alone. In the study, 3.4 percent of patients in the XTANDI plus ADT arm and 0.6 percent in the ADT alone arm died from adverse events. Discontinuations with an adverse event as the primary reason were reported for 9.4 percent of patients treated with XTANDI plus ADT vs 6 percent treated with ADT alone.

About Prostate Cancer

Prostate cancer is the second most common cancer in men worldwide.¹ More than 164,000 men in the United States are estimated to be newly diagnosed with prostate cancer in 2018.² In the European Union, the estimated number of new prostate cancer cases in 2015 was 365,000.³

Castration-resistant prostate cancer (CRPC) refers to the subset of men whose prostate cancer progresses despite castrate levels of testosterone (i.e., less than 50 ng/dL).⁴ Non-metastatic CRPC means there is no clinically detectable evidence of the cancer spreading to other parts of the body (metastases), and there is a rising prostate-specific antigen (PSA) level.⁵ Many men with non-metastatic CRPC and a rapidly rising PSA level go on to develop metastatic CRPC.⁶

About XTANDI® (enzalutamide) capsules

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

Important Safety Information for XTANDI ®

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 predisposing 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 ($\geq 10\%$) that occurred more frequently ($\geq 2\%$ 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 ($\geq 10\%$) 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 the Enzalutamide Development Program

Pfizer and Astellas are collaborating on a comprehensive development program that includes studies of enzalutamide across the full spectrum of advanced prostate cancer. Ongoing studies of enzalutamide in prostate cancer include the ARCHES trial in metastatic hormone-sensitive prostate cancer and the EMBARK trial in non-metastatic hormone-sensitive prostate 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/en>.

About Pfizer Oncology

Pfizer Oncology is committed to pursuing innovative treatments that have a meaningful impact on people living with cancer. Our growing pipeline of biologics, small molecules, and immunotherapies is focused on identifying and translating the best scientific breakthroughs into clinical application for patients across a diverse array of solid tumors and hematologic cancers. Today, we have 10 approved oncology medicines and 14 assets currently in clinical development. By maximizing our internal scientific resources and collaborating with other companies, government and academic institutions, as well as patients and non-profit and professional organizations, we are bringing together the brightest and most enterprising minds to take on the toughest cancers. Together we can accelerate breakthrough treatments to patients around the world and work to redefine life with cancer.

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 July 13, 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 an expanded indication in the U.S. to include men with non-metastatic castration-resistant 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 in the expanded indication; 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 other potential indications for XTANDI will be filed in any jurisdictions; whether and when regulatory authorities in any jurisdictions may approve any such other 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 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; 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 American Cancer Society. Global Cancer Facts and Figures (2015). <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-cancer-facts-and-figures-3rd-edition.pdf>. Accessed 01-11-2018. 2 American Cancer Society. Key Statistics for Prostate Cancer. <https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html>. Accessed 01-08-2018. 3 European Commission. Epidemiology of prostate cancer in Europe (03-17-2017). <https://ec.europa.eu/jrc/en/publication/epidemiology-prostate-cancer-europe>. Accessed 01-19-2018. 4 Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract* 2011;65(11):1180-92. 5 Luo J, Beer T, Graff J. Treatment of nonmetastatic castration-resistant prostate cancer. *Oncology* 2016;30(4):336-44. 6 Smith MR, Kabbinavar 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(13):2918-25.

Pfizer: For Media Jessica Smith, 212-733-6213 jessica.m.smith@pfizer.com or For Investors Ryan Crowe, 212-733-8160 ryan.crowe@pfizer.com or Astellas: For Media Colin McBean, 847-420-3421 colin.mcbean@astellas.com or For Investors Shin Okubo, 81-3-3244-3202 shin.ohkubo@astellas.com