Press Release

Astellas Receives Positive CHMP Opinion for XTANDI™ (enzalutamide) for Adult Men with High-Risk Non-Metastatic Castration-Resistant Prostate Cancer

Results from the PROSPER trial show a median metastasis-free survival (MFS) of 36.6 months for enzalutamide plus androgen deprivation therapy (ADT) vs 14.7 months for men who received placebo plus ADT[1]

TOKYO and CHERTSEY, September 24, 2018 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., "Astellas") announced today that The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion to expand the indication for Xtandi (enzalutamide) to include adult men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC).[2] If approved by the European Commission (EC), enzalutamide will be one of the first treatments approved for this critical stage of disease, currently associated with a significant unmet medical need. Enzalutamide was first approved by the EC in June 2013 and is currently indicated in the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated or whose disease has progressed on or after docetaxel therapy.[3]

"In nmCRPC, the high risk patient is at a stage where his cancer is growing even though it's not visible yet despite hormone therapy and will manifest itself given time. The objective of early access to enzalutamide in these patients is to delay the emergence of metastasis with the hope of improving quantity and quality of life" said Maha Hussain, MD, FACP, FASCO, Genevieve Teuton Professor of Medicine, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, United States, and lead study investigator. "The potential of an effective treatment option for this stage of disease signifies an important therapeutic advancement."

The CHMP opinion is based on the results from the pivotal phase 3 PROSPER trial which evaluated enzalutamide plus ADT vs placebo plus ADT in patients with nmCRPC and rapidly rising prostate-specific antigen (PSA) levels.[1] The trial met its primary endpoint of metastasis-free survival (MFS). The median MFS was 36.6 months for men who received enzalutamide plus ADT, compared to 14.7 months with placebo plus ADT (n=1401; HR=0.29 [95% CI: 0.24–0.35]; p<0.001).[1]

The PROSPER trial results indicated a 71% reduction in the risk of radiographic progression or death in men with nmCRPC and rapidly rising PSA levels, compared to placebo plus ADT (HR=0.29 [95% CI: 0.24–0.35]; p<0.001).[1] The most common adverse events of any grade for patients ≥10% and higher for enzalutamide plus ADT vs placebo plus ADT were: fatigue (33% vs 14%), hot flush (13% vs 8%), hypertension (12% vs 5%), nausea (11% vs 9%), fall (11% vs 4%), dizziness (10% vs 4%) and decreased appetite (10% vs 4%).[1] These results were published in the June 2018 edition of the *New England Journal of Medicine*.[1]

"This positive CHMP opinion represents an important step towards providing specialist health

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care professionals with a new treatment option for patients with nmCRPC and rapidly rising levels of prostate specific antigen. These patients are at higher risk of developing metastasis and death. Subject to EMA approval, we have the potential to expand the use of enzalutamide in a patient population where there is a clear unmet medical need" said Steven Benner, M.D, Senior Vice President and Global Therapeutic Area Head, Oncology Development, Astellas.

The positive opinion from the CHMP will now be reviewed by the EC, which has the authority to approve medicines for the 28 European Union member countries plus Iceland, Norway and Liechtenstein. The EC, which generally follows the recommendation of the CHMP, is expected to make its final decision in the final quarter of 2018.

PROSPER Trial Results
PROSPER is a double-blind, placebo-controlled, pivotal phase 3 trial conducted at 300 sites in 32 countries that randomised 1,401 patients with non-metastatic castration-resistant prostate cancer (nmCRPC) and a prostate-specific antigen (PSA) doubling time of 10 months or less, 2:1 to either receive once-daily enzalutamide plus androgen deprivation hormone therapy (ADT) (n=933) or placebo plus ADT (ADT alone [n=468]), respectively.[1]

Secondary outcomes included a statistically significant delay in the median time to first use of new antineoplastic therapy (TTA) of 39.6 vs 17.7 months; HR=0.21 [95% CI: 0.17–0.26]; p<0.001 for patients who received enzalutamide plus ADT compared to those who received placebo plus ADT.[1]

About Prostate Cancer
Prostate cancer is the most common cancer diagnosis for men in the European Union (EU).[4] There are 375,842 men in the EU currently diagnosed with prostate cancer, accounting for an estimated 23.2% of all cancers in men in 2018.[4] Some studies estimate that, within five years of diagnosis,10–20% of men with prostate cancer will develop CRPC.[5]

CRPC refers to the subset of men whose prostate cancer progresses despite castrate levels of testosterone (i.e., less than 50 ng/dL).[6] 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 PSA level.[6] Many men with non-metastatic CRPC and a rapidly rising PSA level go on to develop metastatic CRPC.[7,8]

About Enzalutamide
Enzalutamide is an oral, once-daily androgen receptor signaling inhibitor. Enzalutamide directly targets the androgen receptors (AR) and exerts its effects on three steps of the AR signaling pathway:[3]

- Inhibits androgen binding: Androgen binding induces a conformational change that triggers activation of the receptor[3]
- Prevents nuclear translocation: Translocation of the AR to the nucleus is an essential step in AR-mediated gene regulation[3]
- Impairs DNA binding: Binding of the AR to the DNA is essential for modulation of gene expression[3]

Enzalutamide is currently approved in Japan for castration-resistant prostate cancer[9] and in July 2018 the United States Food and Drug Administration (FDA) broadened the approved indication for enzalutamide to include men with nmCRPC.[10]

Important Safety Information for Enzalutamide in the EU
For important Safety Information for enzalutamide please see the full Summary of Product Characteristics at: https://www.medicines.org.uk/emc/product/3203

About XTANDI® (enzalutamide) capsules in the U.S.

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

Important Safety Information for XTANDI® in the U.S.

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 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 Astellas Pharma Europe Ltd.
Astellas Pharma Europe Ltd. operates in 40 countries across Europe, the Middle East and Africa, and is the regional business of Tokyo-based Astellas Pharma Inc. Astellas is a pharmaceutical company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceuticals. The organization's focus is to deliver outstanding R&D and marketing to continue growing in the world pharmaceutical market.

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 commercialise enzalutamide. The companies jointly commercialise enzalutamide in the United States and Astellas has responsibility for manufacturing and all additional regulatory filings globally, as well as commercialising enzalutamide 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.

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