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Astellas' and Pfizer's XTANDI® (enzalutamide) Reduced Risk of Death by 34% in Men with Metastatic Hormone-Sensitive Prostate Cancer in Phase 3 ARCHES Study

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Late-breaking abstract to be presented September 18 during European Society for Medical Oncology Congress 2021

TOKYO and NEW YORK, September 17, 2021 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., "Astellas") and Pfizer Inc. (NYSE: PFE) announced today ahead of the European Society for Medical Oncology (ESMO) Congress 2021 that XTANDI® (enzalutamide) improved overall survival (OS) in the ARCHES study in men with metastatic hormone-sensitive prostate cancer (mHSPC, also known as metastatic castration-sensitive prostate cancer). The Phase 3, randomized, double-blind, placebo-controlled trial compared XTANDI plus androgen deprivation therapy (ADT) versus placebo plus ADT in men with mHSPC and OS was a key secondary endpoint.

In the study, XTANDI plus ADT reduced the risk of death by 34% (n=1,150; hazard ratio [HR]=0.66; [95% confidence interval [CI]: 0.53-0.81]; p<0.0001) compared to placebo plus ADT. Median OS, which represents the time from randomization to death due to any cause, was not reached in either treatment group. The safety profile in both study arms was consistent with findings from the primary analysis.

Results from the final analysis of the ARCHES trial will be presented virtually at ESMO by Andrew Armstrong, M.D., Professor of Medicine, Surgery, Pharmacology and Cancer Biology, and Director of Research in the Duke Cancer Institute's Center for Prostate and Urologic Cancers in Durham, North Carolina, U.S. (Abstract LBA25; September 18, 14:20 CEST).

"Overall survival benefit has been observed in patients treated with enzalutamide in three stages of advanced prostate cancer – metastatic castration-resistant prostate cancer, non-metastatic castration-resistant prostate cancer, and now in metastatic hormone-sensitive prostate cancer," said Dr. Armstrong. "The results from ARCHES provide valuable data on the clinical profile of enzalutamide in this earlier disease setting."

The primary results from the ARCHES trial were published in the Journal of Clinical Oncology in 2019. The study met its primary endpoint of radiographic progression-free survival (rPFS) as assessed by independent central review, finding that treatment with XTANDI plus ADT demonstrated a 61% reduction in the risk of radiographic disease progression or death compared with ADT alone in men with mHSPC (HR=0.39; [95% CI: 0.30-0.50]; p<0.001).[1] The median follow-up time was 14.4 months. Median rPFS was not reached (NR) with XTANDI plus ADT (95% CI: NR to NR) versus 19.0 months (95% CI: 16.6-22.2 months) with placebo plus ADT. At the time of the primary analysis, OS data were not mature.

In the ARCHES primary analysis, Grade 3 or greater adverse events (AEs; defined as severe/disabling or life-threatening) were similar for patients receiving both XTANDI plus ADT and those who received placebo plus ADT (24.3% vs. 25.6%). Common AEs (occurring in at least 5% of patients) that were reported more often in patients treated with XTANDI plus ADT versus those treated with ADT alone included hot flush, fatigue, arthralgia, hypertension, nausea, musculoskeletal pain, diarrhea, asthenia and dizziness.

These data supported global regulatory approvals, including European Commission marketing authorization for mHSPC earlier this year.

About Metastatic Hormone-Sensitive Prostate Cancer
Prostate cancer is considered metastatic once it has spread outside of the prostate gland to other parts of the body, such as the lymph nodes, bones, lungs, and liver.[2] Men are considered hormone- (or castration-) sensitive if their disease still responds to medical or surgical treatment to lower testosterone levels.[3] Metastatic hormone-sensitive prostate cancer (mHSPC) has a median survival of approximately 3-4 years for men starting treatment with ADT.[4]

ARCHES Trial
The company-sponsored, Phase 3, randomized, double-blind, placebo-controlled ARCHES trial (NCT02677896) enrolled 1,150 patients with metastatic hormone-sensitive prostate cancer (mHSPC) at sites in the U.S., Canada, Europe, South America, and the Asia-Pacific region. Patients in the 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 primary endpoint of the trial was radiographic progression-free survival (rPFS) assessed by blinded independent central review. Radiographic progression-free survival was defined as the time from randomization to radiographic disease progression at any time or death within 24 weeks after study drug discontinuation. Radiographic disease progression was defined by identification of two or more new bone lesions on a bone scan with confirmation (Prostate Cancer Working Group 2 criteria) and/or progression in soft tissue disease. Patients were stratified by volume of disease (low vs. high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, 1-5 cycles, or 6 prior cycles).

E.U.: About XTANDI® (enzalutamide) and Important Safety Information
Enzalutamide is an androgen receptor signaling inhibitor indicated in the European Union for the treatment of adult men with:

1. Metastatic hormone-sensitive prostate cancer (mHSPC) in combination with ADT.
2. High-risk non-metastatic castration-resistant prostate cancer (CRPC).
3. Metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. It is also indicated in adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

For Important Safety Information for enzalutamide please see the full Summary of Product Characteristics at: https://www.ema.europa.eu/en/documents/product-information/xtandi-epar-product-information_en.pdf.

U.S.: About XTANDI® (enzalutamide) and Important Safety Information
XTANDI (enzalutamide) is an androgen receptor inhibitor indicated in the U.S. for the treatment of patients with castration-resistant prostate cancer (CRPC) and metastatic castration-sensitive prostate cancer (mCSPC).

Warnings and Precautions

Seizure occurred in 0.5% of patients receiving XTANDI in seven randomized clinical trials. In a study of patients with predisposing factors for seizure, 2.2% of XTANDI-treated patients experienced a seizure. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. 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, history of cerebrovascular accident or transient ischemic attack, and 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. 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) There have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder that 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 seven randomized 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 combined data of four randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.9% vs 1.3%). Grade 3-4 ischemic events occurred in 1.4% of patients on XTANDI versus 0.7% 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 occurred in patients receiving XTANDI. 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. In the combined data of four randomized, placebo-controlled clinical studies, falls occurred in 11% of patients treated with XTANDI compared to 4% of patients treated with placebo. Fractures occurred in 10% of patients treated with XTANDI and in 4% of patients treated with placebo.

Embryo-Fetal Toxicity The 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.

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

In AFFIRM, the placebo-controlled study of metastatic CRPC (mCRPC) patients who previously received docetaxel, Grade 3 and higher ARs were reported among 47% of XTANDI-treated patients. Discontinuations due to adverse events (AEs) were reported for 16% of XTANDI-treated patients. In PREVAIL, the placebo-controlled study of chemotherapy-naive mCRPC patients, Grade 3-4 ARs were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to AEs were reported for 6% of XTANDI-treated patients. In TERRAIN, the bicalutamide-controlled study of chemotherapy-naive mCRPC patients, Grade 3-4 ARs 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.

In PROSPER, the placebo-controlled study of non-metastatic CRPC (nmCRPC) patients, Grade 3 or higher ARs were reported in 31% of XTANDI patients and 23% of placebo patients. Discontinuations with an AE as the primary reason were reported for 9% of XTANDI patients and 6% of placebo patients.

In ARCHES, the placebo-controlled study of metastatic CSPC (mCSPC) patients, Grade 3 or higher AEs were reported in 24% of XTANDI-treated patients. Permanent discontinuation due to AEs as the primary reason was reported in 5% of XTANDI patients and 4% of placebo patients.

Lab Abnormalities: Lab abnormalities that occurred in ? 5% of patients, and more frequently (> 2%) in the XTANDI arm compared to placebo in the pooled, randomized, placebo-controlled studies are neutrophil count decreased, white blood cell decreased, hyperglycemia, hypermagnesemia, hyponatremia, and hypercalcemia.

Hypertension: In the combined data from four randomized placebo-controlled clinical trials, hypertension was reported in 12% of XTANDI patients and 5% of placebo patients. Hypertension led to study discontinuation in < 1% of patients in each arm.

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 in the lives of people living with cancer. Today, we have an industry-leading portfolio of 24 approved innovative cancer medicines and biosimilars across more than 30 indications, including breast, genitourinary, colorectal, blood and lung cancers, as well as melanoma.

About Astellas
Astellas Pharma Inc. is a pharmaceutical company conducting business in more than 70 countries around the world. We are promoting the Focus Area Approach that is designed to identify opportunities for the continuous creation of new drugs to address diseases with high unmet medical needs by focusing on Biology and Modality. Furthermore, we are also looking beyond our foundational Rx focus to create Rx+® healthcare solutions that combine our expertise and knowledge with cutting-edge technology in different fields of external partners.

Through these efforts, Astellas stands on the forefront of healthcare change to turn innovative science into value for patients. For more information, please visit our website at https://www.astellas.com/en.

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.

Pfizer Disclosure Notice
The information contained in this release is as of September 17, 2021. 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), including its 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, the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when applications for XTANDI may be filed in any jurisdictions for any other potential indications; whether and when any applications for XTANDI that may be pending or filed may be approved by regulatory authorities, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether XTANDI will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of XTANDI; uncertainties regarding the impact of COVID-19 on Pfizer's business, operations and financial results; 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, 2020 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.

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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[1] Armstrong A, et al. Phase 3 study of androgen deprivation therapy (ADT) with enzalutamide (ENZA) or placebo
(PBO) in metastatic hormone-sensitive prostate cancer (mHSPC): the ARCHES trial. J Clin Oncol. 2019;7:687.
[2] American Society of Clinical Oncology. ASCO Answers: Prostate Cancer (2021). http://www.cancer.net/sites/cancer.net/files/asco_answers_guide_prostate.pdf. Accessed September 17, 2021.
[3] Cancer.net. Prostate Cancer: Types of Treatment (09-2020). https://www.cancer.net/cancer-types/prostate-cancer/types-treatment. Accessed September 17, 2021.
[4] Mottet N, et al. Updated Guidelines for Metastatic Hormone-sensitive Prostate Cancer: Abiraterone Acetate Combined with Castration Is Another Standard. Eur Urol. 2018;3:316-321.

Pfizer Contacts:
For Media
Eamonn Nolan
212-733-4626
Eamonn.Nolan@pfizer.com

For Investors
Bryan Dunn
212-733-8917
Bryan.Dunn@pfizer.com

Astellas Contacts:
For Media
Chris Goldrick
847-224-3014
chris.goldrick@astellas.com

For Investors
Astellas Pharma Inc. Corporate Advocacy & Relations
+81-3-3244-3202