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XTANDI® Plus Leuprolide Significantly Improves Survival Outcomes in Men with Non-Metastatic Hormone-Sensitive Prostate Cancer with High-Risk Biochemical Recurrence

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- *XTANDI: the first and only androgen receptor inhibitor-based regimen to demonstrate overall survival benefit in non-metastatic hormone-sensitive prostate cancer (nmHSPC) with high-risk biochemical recurrence (BCR)*

NEW YORK & NORTHBROOK, ILL.--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) and Astellas Pharma U.S. Inc. today announced positive topline results from the overall survival (OS) analysis from the Phase 3 EMBARK study evaluating XTANDI® (enzalutamide), in combination with leuprolide and as a monotherapy, in men with non-metastatic hormone-sensitive prostate cancer (nmHSPC; also known as nonmetastatic castration-sensitive prostate cancer or nmCSPC) with biochemical recurrence (BCR) at high risk for metastasis.

For patients treated with XTANDI plus leuprolide versus placebo plus leuprolide, EMBARK met the key secondary endpoint with a statistically significant and clinically meaningful improvement in OS. Results also showed a favorable trend towards improved OS for patients treated with XTANDI monotherapy versus placebo plus leuprolide, however the difference did not reach statistical significance. No new safety signals were observed in the analysis, and the safety results were consistent with the demonstrated safety profile of XTANDI.[1]

“These data demonstrate that treatment with XTANDI can extend life for men with nmHSPC and high-risk BCR who have relapsed after initial curative-intent therapy with prostatectomy, radiation therapy or both, further validating EMBARK’s metastasis-free survival (MFS) data,” said Neal Shore, M.D., F.A.C.S, START Carolinas/Carolina Urologic Research Center. “While men with nmHSPC with high-risk BCR now have expanded treatment choices, these results demonstrate a clear clinical benefit, including both MFS and OS, supporting the clinical practice of initiating XTANDI for these patients.”

Among men who have undergone definitive prostate cancer treatment, including radical prostatectomy, radiotherapy, or both, an estimated 20-40% will experience BCR within 10 years.[2] About nine out of 10 men with high-risk BCR will develop metastatic disease, and one in three will die as a result of their metastatic prostate cancer.[3]

“XTANDI is the only androgen receptor inhibitor-based regimen to demonstrate a survival benefit in metastatic HSPC and nmHSPC with high-risk BCR, as well as castration-resistant prostate cancer, highlighting its significant patient impact in advanced prostate cancer,” said Johanna Bendell, M.D., Oncology Chief Development Officer, Pfizer. “These positive results add to the robust clinical support for the use of XTANDI and broaden clinical confidence, offering men with high-risk BCR evidence that they might live longer when

they start XTANDI early."

In the EMBARK study, patients were randomized to one of three study arms: XTANDI plus leuprolide, placebo plus leuprolide, or XTANDI monotherapy. An initial analysis was previously reported in *The New England Journal of Medicine* in 2023, demonstrating that the study met its primary endpoint with a statistically significant and clinically meaningful improvement in MFS for patients treated with XTANDI plus leuprolide versus placebo plus leuprolide.[4]

The most common adverse events (occurring in ?10% of patients) in the combination group and the leuprolide-alone group were hot flashes and fatigue. The most common adverse events in the monotherapy group were gynecomastia, hot flashes, and fatigue.[4]

XTANDI is currently approved in more than 80 countries, including in the United States, European Union, and Japan.

"Over 1.5 million men with advanced prostate cancer around the world have benefited from treatment with XTANDI since its initial approval in 2012,"[5] said Shontelle Dodson, Executive Vice President, Head of Medical Affairs, Astellas. "The scope and rigor of the EMBARK trial exemplify Astellas' and Pfizer's longstanding commitment to the prostate cancer community, and we look forward to sharing detailed findings in a future scientific forum."

Detailed OS results from EMBARK will be presented at a future medical meeting.

About EMBARK[4]
The Phase 3, randomized, double-blind, placebo-controlled, multi-national trial enrolled 1,068 patients with non-metastatic hormone-sensitive prostate cancer (nmHSPC; also known as non-metastatic castration-sensitive prostate cancer or nmCSPC) with high-risk biochemical recurrence (BCR) at sites in the United States, Canada, Europe, South America, and the Asia-Pacific region. Patients who were considered high-risk BCR had a prostate-specific antigen (PSA) doubling time ? 9 months, serum testosterone ? 150 ng/dL (5.2 nmol/L), and screening PSA by the central laboratory ? 1 ng/mL if they had a radical prostatectomy (with or without radiotherapy) as primary treatment for prostate cancer or at least 2 ng/mL above the nadir if they had radiotherapy only as primary treatment for prostate cancer. Patients in the EMBARK trial were randomized to receive enzalutamide 160 mg daily plus leuprolide, enzalutamide 160 mg as monotherapy, or placebo plus leuprolide.

The primary results from the EMBARK trial were published in *The New England Journal of Medicine* in 2023. The primary endpoint of the trial was metastasis-free survival (MFS) for enzalutamide plus leuprolide versus placebo plus leuprolide. MFS is defined as the duration of time in months between randomization and the earliest objective evidence of radiographic progression by central imaging or death.

For more information on the EMBARK (NCT02319837) trial go to www.clinicaltrials.gov.

About Non-Metastatic Hormone-Sensitive Prostate Cancer with High-Risk Biochemical Recurrence
Non-metastatic hormone- (or castration-) sensitive prostate cancer (nmHSPC or nmCSPC) means there is no detectable evidence of the cancer spreading to distant parts of the body (metastases) with conventional radiological methods (CT/MRI) and the cancer still responds to medical or surgical treatment to lower testosterone levels.[6,7] Of men who have undergone definitive prostate cancer treatment, including radical prostatectomy, radiotherapy, or both, an estimated 20-40% will experience a biochemical recurrence (BCR) within 10 years.[8] About 9 out of 10 men with high-risk BCR will develop metastatic disease, and 1 in 3 will die as a result of the recurrence.[8] The EMBARK trial focused on men with high-risk BCR. Per the EMBARK

protocol, patients with nmHSPC with high-risk BCR are those initially treated by radical prostatectomy or radiotherapy, or both, with a PSA doubling time ? 9 months. Patients with nmCSPC who experience BCR after local therapy may be at a higher risk of metastases and death if their PSA doubling time is ? 9 months.[9]

About XTANDI® (enzalutamide)
XTANDI (enzalutamide) is an androgen receptor signaling inhibitor. XTANDI is a standard of care and has received regulatory approvals in one or more countries around the world for use in men with metastatic hormone-sensitive prostate cancer (mHSPC), metastatic castration-resistant prostate cancer (mCRPC), non-metastatic castration-resistant prostate cancer (nmCRPC) and non-metastatic hormone-sensitive prostate cancer (nmHSPC) with high-risk biochemical recurrence (BCR). XTANDI is currently approved for one or more of these indications in more than 80 countries, including in the United States, European Union and Japan. Over 1.5 million patients have been treated with XTANDI globally.[5]

About XTANDI (enzalutamide) and U.S. Important Safety Information
XTANDI (enzalutamide) is indicated for the treatment of patients with:

- castration-resistant prostate cancer (CRPC)
- metastatic castration-sensitive prostate cancer (mCSPC)
- nonmetastatic castration sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR)

Important Safety Information

Warnings and Precautions

Seizure occurred in 0.6% of patients receiving XTANDI in eight 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 eight 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 five randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm

(3.5% vs 2%). Grade 3-4 ischemic events occurred in 1.8% of patients on XTANDI versus 1.1% 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 five randomized, placebo-controlled clinical studies, falls occurred in 12% of patients treated with XTANDI compared to 6% of patients treated with placebo. Fractures occurred in 13% of patients treated with XTANDI and in 6% 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.

Dysphagia or Choking Severe dysphagia or choking, including events that could be life-threatening requiring medical intervention or fatal, can occur due to XTANDI product size. Advise patients to take each capsule or tablet whole with a sufficient amount of water to ensure that all medication is successfully swallowed. Consider use of a smaller tablet size of XTANDI in patients who have difficulty swallowing. Discontinue XTANDI for patients who cannot swallow capsules or tablets.

Adverse Reactions (ARs)
In the data from the five randomized placebo-controlled trials, the most common ARs (? 10%) that occurred more frequently (? 2% over placebo) in XTANDI-treated patients were musculoskeletal pain, fatigue, hot flush, constipation, decreased appetite, diarrhea, hypertension, hemorrhage, fall, fracture, and headache. 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 EMBARK, the placebo-controlled study of nonmetastatic CSPC (nmCSPC) with high-risk biochemical recurrence (BCR) patients, Grade 3 or higher adverse reactions during the total duration of treatment were reported in 46% of patients treated with XTANDI plus leuprolide, 50% of patients receiving XTANDI as a single agent, and 43% of patients receiving placebo plus leuprolide. Permanent treatment discontinuation due to adverse reactions during the total duration of treatment as the primary reason was reported in 21% of patients treated with XTANDI plus leuprolide, 18% of patients receiving XTANDI as a single agent, and 10% of patients receiving placebo plus leuprolide.

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 hemoglobin decrease, neutrophil count decreased, white blood cell decreased, hyperglycemia, hypermagnesemia, hyponatremia, hypophosphatemia, and hypercalcemia.

Hypertension: In the combined data from five randomized placebo-controlled clinical trials, hypertension was reported in 14.2% of XTANDI patients and 7.4% of placebo patients. Hypertension led to study discontinuation in < 1% of patients in each arm.

Drug Interactions

Effect of Other Drugs on XTANDI Avoid coadministration with strong CYP2C8 inhibitors. If coadministration cannot be avoided, reduce the dosage of XTANDI.
Avoid coadministration with strong CYP3A4 inducers. If coadministration cannot be avoided, increase the dosage of XTANDI.

Effect of XTANDI on Other Drugs Avoid coadministration with certain CYP3A4, CYP2C9, and CYP2C19 substrates for which minimal decrease in concentration may lead to therapeutic failure of the substrate. If coadministration cannot be avoided, increase the dosage of these substrates in accordance with their Prescribing Information. In cases where active metabolites are formed, there may be increased exposure to the active metabolites.

Please see Full Prescribing Information for additional safety information.

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 at 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 Pfizer Oncology
At Pfizer Oncology, we are at the forefront of a new era in cancer care. Our industry-leading portfolio and extensive pipeline includes three core mechanisms of action to attack cancer from multiple angles, including small molecules, antibody-drug conjugates (ADCs), and bispecific antibodies, including other immune-oncology biologics. We are focused on delivering transformative therapies in some of the world's most common cancers, including breast cancer, genitourinary cancer, hematology-oncology, and thoracic cancers, which includes lung cancer. Driven by science, we are committed to accelerating breakthroughs to help people with cancer live better and longer lives.

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 XTANDI (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 10, 2025. 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 Pfizer Oncology, XTANDI (enzalutamide) and an overall survival analysis from the Phase 3 EMBARK study evaluating XTANDI in combination with leuprolide and as a monotherapy, in men with non-metastatic hormone-sensitive prostate cancer with biochemical recurrence at high risk for metastasis, 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 endpoints, commencement and/or completion dates for 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 the clinical studies; whether and when drug applications for XTANDI may be filed in particular jurisdictions for any potential indications; whether and when regulatory authorities in any jurisdictions may approve any such applications that may be pending or filed for XTANDI, which will depend on a myriad of 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 for any potential indication 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; dependence on the efforts and funding by Astellas Pharma Inc. for the development, manufacturing and commercialization of XTANDI; risks and uncertainties related to issued or future executive orders or other new, or changes in, laws or regulations; 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, 2024, 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.

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