Pfizer Logo

XTANDI® Plus Leuprolide Reduced Risk of Death by 40% vs Leuprolide Alone in Men with a Type of Advanced Prostate Cancer

Sunday, October 19, 2025 - 04:15am

- *The probability of survival at 8 years was an unprecedented 78.9% with XTANDI plus leuprolide versus 69.5% with leuprolide, in men with non-metastatic hormone-sensitive prostate cancer with high-risk biochemical recurrence*[1]
- *XTANDI is the first and only androgen receptor inhibitor-based regimen to demonstrate overall survival benefit in this patient population, supporting its earlier use in this setting*
- *Final results from the Phase 3 EMBARK study are being presented in a late-breaking oral session at ESMO 2025 and simultaneously published in The New England Journal of Medicine*

NEW YORK & NORTHBROOK, Ill.--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) and Astellas Pharma U.S. Inc. (Head of Commercial: Mike Petroutsas, "Astellas") today announced final overall survival (OS) results from the Phase 3 EMBARK study evaluating XTANDI® (enzalutamide), in combination with leuprolide and as 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 the key secondary endpoint of OS, XTANDI plus leuprolide reduced the risk of death by 40.3% compared to leuprolide alone (Hazard Ratio [HR]: 0.597; 95% Confidence Interval [CI], 0.444-0.804; p=0.0006), making this the first and only androgen receptor inhibitor-based regimen to demonstrate an OS benefit in nmHSPC with high-risk BCR.[1] The 8-year overall survival was 78.9% (95% CI, 73.9% to 83.1%) among patients receiving XTANDI plus leuprolide and 69.5% (95% CI, 64.0% to 74.3%) among patients taking leuprolide alone.[1] A numerical improvement in OS with XTANDI as monotherapy compared to leuprolide alone (HR: 0.83 [95% CI, 0.63-1.095; p=0.1867) did not reach statistical significance.[1] These data are being presented today in an oral presentation at the European Society for Medical Oncology (ESMO) Congress in Berlin, Germany and have been simultaneously published in *The New England Journal of Medicine*.

“These results highlight the central role of enzalutamide in extending survival for men with conventional imaging negative HSPC with high-risk BCR,” said Stephen J. Freedland, M.D., Director of the Center for Integrated Research in Cancer and Lifestyle at Cedars-Sinai and Associate Director for Training and Education at the Samuel Oschin Comprehensive Cancer Institute. “These data reinforce the benefits of earlier treatment initiation with enzalutamide.”

The median follow up time was 94.2 months for XTANDI in combination with leuprolide, 94 months for leuprolide only, and 93.8 months in the monotherapy XTANDI group.[1]

The safety profile of XTANDI was consistent with that observed at the primary EMBARK analysis, and no new safety signals were identified. The most common adverse events (occurring in ?10% of patients) in the XTANDI

combination group were hot flashes and fatigue. The most common adverse events in the XTANDI monotherapy group were gynecomastia, hot flashes, and fatigue.[1,2]

"With up to 90 percent of men with high-risk BCR developing metastatic disease, early intervention with effective therapy is critical,"[3] said Johanna Bendell, M.D., Chief Development Officer, Oncology, Pfizer. "The final analysis from EMBARK shows that XTANDI plus leuprolide improved outcomes and extended lives for men facing high-risk BCR after local therapy with curative intent."

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.[4] 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]

"This marks the eighth publication of XTANDI data in *The New England Journal of Medicine*, further demonstrating XTANDI's profound impact on clinical outcomes in men with certain types of advanced prostate cancer," said Shontelle Dodson, Executive Vice President, Head of Medical Affairs, Astellas. "These findings reinforce XTANDI's position as a cornerstone therapy in the proactive management of these patients."

The EMBARK trial primary 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 metastasis-free survival (MFS) for patients treated with XTANDI plus leuprolide versus leuprolide alone (HR: 0.42 [95% CI, 0.30-0.61]; p<0.001). Additionally, MFS for XTANDI monotherapy was superior to treatment with leuprolide alone (HR: 0.63 [95% CI, 0.46-0.87]; p=0.005). Of note, the MFS for XTANDI single agent was a secondary endpoint.2

XTANDI is approved for one or more indications in more than 80 countries, including the United States, European Union, and Japan. Earlier approvals were for castration-resistant prostate cancer and metastatic castration-sensitive (hormone-sensitive) prostate cancer. It was then approved for patients with nmCSPC with BCR at high risk for metastasis in 2023 based on improved metastasis-free survival comparing the combination of enzalutamide with leuprolide vs leuprolide alone, as well as enzalutamide monotherapy vs leuprolide alone.

Descriptive updates of multiple secondary and exploratory endpoints (time to new antineoplastic therapy, time to first symptomatic skeletal events, and time to progression on subsequent therapy) were consistent with the primary analyses announced based on the MFS data cutoff in 2023.[1]

About EMBARK[2]

This 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 considered to have high-risk BCR disease 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 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 leuprolide alone.

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 leuprolide alone. MFS is defined as the duration of time 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.[5,6] 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.[4] About nine out of 10 men with high-risk BCR will develop metastatic disease, and one in three will die as a result of the recurrence.[3] 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.[7]

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.[8]

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 is a global life sciences company committed to turning innovative science into VALUE for patients. We provide transformative therapies in disease areas that include oncology, ophthalmology, urology, immunology and women's health. Through our research and development programs, we are pioneering new healthcare solutions for diseases with high unmet medical need. Learn more at www.astellas.com.

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 multispecific 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 Cautionary Notes

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 October 19, 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; 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.

###

References

[1] Shore, D. *et al*. Overall survival with enzalutamide in biochemically recurrent prostate cancer. Presented at the 2025 ESMO Annual Meeting.
[2] Freedland, Stephen J. et al. “Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer.” N Engl J Med 2023;389:1453-1465. DOI: 10.1056/NEJMoa2303974
[3] Antonarakis, Emmanuel S et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. *BJU international* vol. 109,1 (2012): 32-9. doi:10.1111/j.1464-410X.2011.10422
[4] Ward JF, Moul JW. Rising prostate-specific antigen after primary prostate cancer therapy. *Nat Clin Pract Urol*. 2005 Apr;2(4):174-82. doi: 10.1038/ncpuro0145. PMID: 16474760.
[5] Cancer.net. Prostate Cancer: Types of Treatment (11-2023). https://www.cancer.net/cancer-types/prostate-cancer/types-treatment. Accessed September 19, 2025.
[6] American Society of Clinical Oncology. ASCO Answers: Prostate Cancer (2023).
[7] Paller, Channing J et al. Management of patients with biochemical recurrence after local therapy for prostate cancer. *Hematology/oncology clinics of North America* vol. 27,6 (2013): 1205-19, viii. doi:10.1016/j.hoc.2013.08.005
[8] Astellas. Data on file. XTANDI patient. March 2025.

Pfizer Contacts:
PfizerMediaRelations@Pfizer.com

For Investors
IR@pfizer.com

Astellas Contacts:
For Media +1-847-686-1813
Corporate.Communications@us.astellas.com

Corporate Communications
+81-3-3244-3201

Source: Pfizer Inc.