Pfizer Logo

European Commission Approves Pfizer’s TALZENNA® in Combination with XTANDI® for Adult Patients with Metastatic Castration-Resistant Prostate Cancer

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TALZENNA is the first and only PARP inhibitor approved in combination with standard of care XTANDI for mCRPC patients in the European Union

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) today announced that the European Commission (EC) has approved TALZENNA® (talazoparib), an oral poly ADP-ribose polymerase (PARP) inhibitor, in combination with XTANDI® (enzalutamide), for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated. With this approval, TALZENNA is now the first and only PARP inhibitor licensed in the European Union for use with XTANDI for patients with mCRPC, with or without gene mutations.

“New treatment options are needed to increase the proportion of patients with metastatic castration-resistant prostate cancer who can benefit from current anticancer medicines that keep the disease under control for longer,” said Robert Jones, MBChB, PhD, Professor of Clinical Cancer Research, University of Glasgow. “The European Commission’s approval of talazoparib in combination with enzalutamide offers a meaningful advancement for the treatment of patients with metastatic castration-resistant prostate cancer, the most advanced and aggressive stage of the disease.”

“After years of fighting prostate cancer, it can be devastating for a patient to learn that their cancer has stopped responding to testosterone-lowering treatments. At this stage of the disease, the prognosis is generally poor,” said Erik Briers, MS, PhD, Vice Chairman, Europa UOMO, a European advocacy movement for people with prostate cancer. “Patients urgently need new treatment options and TALZENNA in combination with XTANDI can bring new hope to these patients.”

This approval by the European Commission of TALZENNA in combination with XTANDI for the mCRPC indication is valid in all 27 EU member states plus Iceland, Liechtenstein, and Norway.

The approval is based on data from the Phase 3 TALAPRO-2 trial, a multicenter, randomized, double-blind, placebo-controlled study, evaluating two mCRPC patient cohorts: Cohort 1 (all-comers [n=805]) and Cohort 2 (those with HRR gene mutations [HRRm; n=399]). The results from TALAPRO-2 Cohort 1, which were published in *The Lancet*, showed that treatment with TALZENNA plus XTANDI reduced the risk of disease progression or death by 37% versus placebo plus XTANDI (Hazard Ratio [HR]: 0.63; 95% Confidence Interval [CI], 0.51–0.78; P< 0.0001), meeting the study’s primary endpoint of improving radiographic progression-free survival (rPFS). At the time of the analysis, the median rPFS for those treated with TALZENNA plus XTANDI had not yet been reached versus 21.9 months for those treated with placebo plus XTANDI. Median rPFS is

defined as the timepoint in which 50% of patients in each treatment arms have progressed. A trend in overall survival (OS), a key secondary endpoint, favoring TALZENNA plus XTANDI was also observed, though these data are immature. The safety of TALZENNA plus XTANDI in the TALAPRO-2 trial was generally consistent with the known safety profile of each medicine.

“Today’s approval of TALZENNA in combination with XTANDI represents an important advancement for men living with prostate cancer in Europe,” said Chris Boshoff, M.D., Ph.D., Chief Oncology Officer, Executive Vice President, Pfizer. “The results from the pivotal TALAPRO-2 trial showed that this combination offers an effective treatment that addresses disease progression in patients with or without any specific gene mutation.”

TALZENNA in combination with XTANDI was approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult patients with HRR gene-mutated mCRPC in June 2023. Pfizer has also shared the TALAPRO-2 data with other regulatory agencies to support regulatory filings.

About Metastatic Castration-Resistant Prostate Cancer

Metastatic castration-resistant prostate cancer (mCRPC) is a cancer that has spread beyond the prostate gland and has progressed despite medical or surgical treatment to lower testosterone. There were ~1.4 million new cases of prostate cancer reported worldwide in 2020, of which ~470,000 new cases were in Europe.[1] Approximately 10%–20% of prostate cancer patients develop mCRPC within 5?7 years of diagnosis.[2] Between 1.2%–2.1% of all prostate cancer cases globally are mCRPC.[3]

About TALAPRO-2

The Phase 3 TALAPRO-2 trial is a two-part, two-cohort, multicenter, randomized, double-blind, placebo-controlled study that enrolled 1,106 patients with mCRPC (with no systemic treatments initiated after documentation of mCRPC) at sites in the U.S., Canada, Europe, South America, and the Asia-Pacific region. The study included two patient cohorts: all-comers (n=805) and those with and without gene mutations (HRRm; n=399). Patients on androgen deprivation therapy (ADT) or who had bilateral orchiectomy in the trial were randomized to receive TALZENNA 0.5 mg/day plus XTANDI 160mg/day, or placebo plus XTANDI 160 mg/day.

The primary endpoint of the trial is radiographic progression-free survival (rPFS), defined as the time from the date of randomization to first objective evidence of radiographic progression by blinded independent review, or death, whichever occurs first, in both Cohort 1 (all-comers) and Cohort 2 (those with HRRm). Secondary endpoints include overall survival (OS), objective response rate, duration of response, and PSA response.

For more information on the TALAPRO-2 trial (NCT03395197), go to www.clinicaltrials.gov.

About TALZENNA® (talazoparib)

TALZENNA (talazoparib) is an oral inhibitor of poly ADP-ribose polymerase (PARP), which plays a role in DNA damage repair. Preclinical studies have demonstrated that TALZENNA blocks PARP enzyme activity and traps PARP at the site of DNA damage, leading to decreased cancer cell growth and cancer cell death.

TALZENNA is approved in over 70 countries, including the U.S and the EU, as a once-daily monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer. In the U.S., TALZENNA is approved in combination with XTANDI® (enzalutamide) for the treatment of adult patients with homologous recombination repair (HRR) gene-mutated

metastatic castration-resistant prostate cancer (mCRPC). In the EU, TALZENNA is now approved in combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.

TALZENNA ® (talazoparib) Indication in the U.S.

TALZENNA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for:

Breast Cancer:

- As a single agent, for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA.

HRR Gene-mutated mCRPC:

- In combination with enzalutamide for the treatment of adult patients with homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC).

TALZENNA ® (talazoparib) Important Safety Information

WARNINGS and PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including cases with a fatal outcome, has been reported in patients who received TALZENNA. Overall, MDS/AML has been reported in 0.4% (3 out of 788) of solid tumor patients treated with TALZENNA as a single agent in clinical studies. In TALAPRO-2, MDS/AML occurred in 2 out of 511 (0.4%) patients treated with TALZENNA and enzalutamide and in 0 out of 517 (0%) patients treated with placebo and enzalutamide. The durations of TALZENNA treatment in these five patients prior to developing MDS/AML were 0.3, 1, 2, 3, and 5 years, respectively. Most of these patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.

Do not start TALZENNA until patients have adequately recovered from hematological toxicity caused by previous chemotherapy. Monitor blood counts monthly during treatment with TALZENNA. For prolonged hematological toxicities, interrupt TALZENNA and monitor blood counts weekly until recovery. If counts do not recover within 4 weeks, refer the patient to a hematologist for further investigations including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue TALZENNA.

Myelosuppression consisting of anemia, neutropenia, and/or thrombocytopenia have been reported in patients treated with TALZENNA. In TALAPRO-2, Grade ?3 anemia, neutropenia, and thrombocytopenia were reported, respectively, in 45%, 18%, and 8% of patients receiving TALZENNA and enzalutamide. Overall, 39% of patients (199/511) required a red blood cell transfusion, including 22% (111/511) who required multiple transfusions. Discontinuation due to anemia, neutropenia, and thrombocytopenia occurred, respectively, in 7%, 3%, and 0.4% of patients.

Withhold TALZENNA until patients have adequately recovered from hematological toxicity caused by previous therapy. Monitor blood counts monthly during treatment with TALZENNA. If hematological toxicities do not resolve within 28 days, discontinue TALZENNA and refer the patient to a hematologist for further investigations including bone marrow analysis and blood sample for cytogenetics.

Embryo-Fetal Toxicity TALZENNA can cause fetal harm when administered to pregnant women. Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment with TALZENNA and for 4 months after receiving the last dose.

ADVERSE REACTIONS

Serious adverse reactions reported in >2% of patients included anemia (9%) and fracture (3%). Fatal adverse reactions occurred in 1.5% of patients, including pneumonia, COVID infection, and sepsis (1 patient each).

The most common adverse reactions (? 10%, all Grades), including laboratory abnormalities, for patients in the TALAPRO-2 study who received TALZENNA in combination with enzalutamide vs patients receiving placebo with enzalutamide were hemoglobin decreased (79% vs 34%), neutrophils decreased (60% vs 18%), lymphocytes decreased (58% vs 36%), fatigue (49% vs 40%), platelets decreased (45% vs 8%), calcium decreased (25% vs 11%), nausea (21% vs 17%), decreased appetite (20% vs 14%), sodium decreased (22% vs 20%), phosphate decreased (17% vs 13%), fractures (14% vs 10%), magnesium decreased (14% vs 12%), dizziness (13% vs 9%), bilirubin increased (11% vs 7%), potassium decreased (11% vs 7%), and dysgeusia (10% vs 4.5%).

Clinically relevant adverse reactions in <10% of patients who received TALZENNA with enzalutamide included abdominal pain (9%), vomiting (9%), alopecia (7%), dyspepsia (4%), venous thromboembolism (3%) and stomatitis (2%).

Based on animal studies, TALZENNA may impair fertility in males of reproductive potential.

DRUG INTERACTIONS

Coadministration with P-gp inhibitors The effect of coadministration of P-gp inhibitors on talazoparib exposure when TALZENNA is taken in combination with enzalutamide has not been studied. Monitor patients for increased adverse reactions and modify the dosage as recommended for adverse reactions when TALZENNA is coadministered with a P-gp inhibitor.

Coadministration with BCRP inhibitors Monitor patients for increased adverse reactions and modify the dosage as recommended for adverse reactions when TALZENNA is coadministered with a BCRP inhibitor. Coadministration of TALZENNA with BCRP inhibitors may increase talazoparib exposure, which may increase the risk of adverse reactions.

USE IN SPECIFIC POPULATIONS

Renal Impairment The recommended dosage of TALZENNA for patients with moderate renal impairment (CLcr 30 - 59 mL/min) is 0.35 mg taken orally once daily in combination with enzalutamide. The recommended dosage of TALZENNA for patients with severe renal impairment (CLcr 15 - 29 mL/min) is 0.25 mg taken orally once daily in combination with enzalutamide. No dose adjustment is required for patients with mild renal impairment. TALZENNA has not been studied in patients requiring hemodialysis.

Please see full U.S. Prescribing Information and Patient Information for TALZENNA® (talazoparib) at www.TALZENNA.com.

About XTANDI® (enzalutamide) and Important Safety Information

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

castration-sensitive prostate cancer (mCSPC; also known as metastatic hormone-sensitive prostate cancer or mHSPC), metastatic castration-resistant prostate cancer (mCRPC), non-metastatic castration-resistant prostate cancer (nmCRPC) and nonmetastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR). XTANDI is currently approved for one or more of these indications in more than 90 countries, including in the U.S., EU, and Japan. Over one million patients have been treated with XTANDI globally.[4]

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.

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 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 ARs 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 ARs 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 AR as the primary reason were reported for 8% of XTANDI patients and 6% of bicalutamide patients.

In PROSPER, the placebo-controlled study of nonmetastatic CRPC (nmCRPC) patients, Grade 3 or higher ARs were reported in 31% of XTANDI patients and 23% of placebo patients. Discontinuations with an AR 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 ARs were reported in 24% of XTANDI-treated patients. Permanent discontinuation due to ARs as the primary reason was reported in 5% of XTANDI patients and 4% of placebo patients.

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, hyperphosphatemia, 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 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 game-changing mechanisms of action to attack cancer from multiple angles, including antibody-drug conjugates (ADCs), small molecules, bispecifics and other immunotherapies. We are focused on delivering transformative therapies in some of the world's most common cancers, including breast cancer, genitourinary cancer and hematologic malignancies, as well as melanoma, gastrointestinal, gynecological and thoracic cancers, which includes lung cancer. Driven by science, we are committed to accelerating breakthroughs to extend and improve patients' 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.

Disclosure Notice

The information contained in this release is as of January 8, 2024. 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, TALZENNA and XTANDI, including their potential benefits, and an approval by the European Commission for TALZENNA in combination with XTANDI for the treatment of adult patients with metastatic castration-resistant prostate cancer in whom chemotherapy is not clinically indicated, 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 TALZENNA in combination with XTANDI;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; whether TALAPRO-2 trial will meet the secondary endpoint for overall survival; 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 TALZENNA, XTANDI or a combination may be filed in any jurisdictions for any potential indications; whether and when any such applications for TALZENNA, XTANDI or a combination 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 TALZENNA, XTANDI or a combination 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 TALZENNA,

XTANDI or a combination; 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, 2022 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.

Category: Prescription Medicines

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[1] World Health Organization Global Cancer Observatory. 27-Prostate-fact-sheet.pdf (iarc.fr)
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[3] Shore N, Oliver L, Shui I, Gayle A, Wong OY, Kim J, Payne S, Amin S, Ghate S. Systematic Literature Review of the Epidemiology of Advanced Prostate Cancer and Associated Homologous Recombination Repair Gene Alterations. J Urol. 2021 Apr;205(4):977-986. doi: 10.1097/JU.0000000000001570. Epub 2020 Dec 17. PMID: 33332152.
[4] Data on file. Northbrook, IL: Astellas Inc.

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