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Pfizer Announces Positive Topline Results from Phase 3 TALAPRO-2 Trial

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- *TALZENNA® first PARP inhibitor to demonstrate clinical benefit in combination with XTANDI ® in metastatic castration-resistant prostate cancer (mCRPC)*
- *Study achieves primary endpoint of radiographic progression-free survival*
- *Robust, highly consistent efficacy demonstrated in mCRPC both with or without homologous recombination repair gene mutations*

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) today announced positive topline results from the Phase 3 TALAPRO-2 study of TALZENNA® (talazoparib), an oral poly ADP-ribose polymerase (PARP) inhibitor, in combination with XTANDI® (enzalutamide) compared to placebo plus XTANDI in men with metastatic castration-resistant prostate cancer (mCRPC), with or without homologous recombination repair (HRR) gene mutations. The study met its primary endpoint with a statistically significant and clinically meaningful improvement in radiographic progression-free survival (rPFS) compared with placebo plus XTANDI. The results of the primary endpoint exceeded the pre-specified hazard ratio of 0.696.

Results showed a trend toward improved overall survival, a key secondary endpoint, at the time of the analysis, but these data are not yet mature. Benefits were also observed in other secondary endpoints, including investigator assessed rPFS, prostate specific antigen (PSA) response, time to PSA progression, and overall response rate. Other secondary endpoints are being analyzed. At the time of topline analysis, the safety of TALZENNA plus XTANDI were generally consistent with the known safety profile of each medicine.

“XTANDI is a global standard of care, with overall survival demonstrated in mCRPC, non-metastatic CRPC, and metastatic castration-sensitive prostate cancer (mCSPC),” said Chris Boshoff, M.D., Ph.D., Chief Development Officer, Oncology and Rare Disease, Pfizer Global Product Development. “We are very pleased with the strong findings from TALAPRO-2, and although no definitive conclusions can be made across trials, the rPFS appears to be the longest observed in a randomized trial in this setting. These data highlight the potential for TALZENNA in combination with XTANDI, if approved, to become a new standard of care for mCRPC, irrespective of HRR gene mutation status. We look forward to discussing these data with global health authorities.”

“These exciting results from TALAPRO-2 underscore our long-standing commitment to men living with prostate cancer and delivering the next scientific breakthroughs,” said Suneet Varma, Global Oncology and U.S. President, Pfizer. “Based on these compelling combination data with XTANDI, we believe TALZENNA in prostate cancer may become the next potential blockbuster opportunity in our leading Pfizer Oncology portfolio, subject to regulatory approval.”

Detailed results from TALAPRO-2 will be submitted for presentation at a near-term medical congress. These data will also be shared with global regulatory authorities to potentially support a regulatory filing.

TALZENNA or the combination of TALZENNA plus XTANDI have not been approved by any regulatory agency for the treatment of mCRPC. In addition to the TALAPRO-2 trial, the combination of TALZENNA plus XTANDI is being investigated in the TALAPRO-3 trial (NCT04821622), a global, randomized, double-blind, placebo-controlled Phase 3 study in men with HRR-deficient mCSPC.

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. Approximately 10%–20% of prostate cancer patients develop mCRPC within 5?7 years of diagnosis,[1] and in the U.S., in 2020, approximately 60-90 thousand cases of the three million prostate cancer cases were mCRPC.[2]

About TALAPRO-2

The Phase 3 TALAPRO-2 trial is a two-part, two-cohort, multicenter, randomized, double-blind, placebo-controlled study that enrolled 1,095 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=750) and those with HRR mutations (HRRm; n=380). 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). The trial is still ongoing for cohort 2. Secondary endpoints include overall survival, 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 inhibitor of PARP enzymes, which play a role in the DNA damage repair response. 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 being evaluated in several ongoing clinical trials in prostate cancer, as well as other novel combinations with targeted therapies in various solid tumors. TALZENNA was approved by the U.S. Food and Drug Administration in 2018 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.

Indication in the U.S.

TALZENNA (talazoparib) is indicated 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. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA.

TALZENNA® (talazoparib) Important Safety Information

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) have been reported in patients who received TALZENNA. Overall, MDS/AML has been reported in <1% (3 out of 787, 0.4%) of solid tumor patients treated with TALZENNA in clinical studies. The duration of TALZENNA treatment in these three patients prior to developing MDS/AML was 4 months, 24 months, and 60 months respectively. These patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.

Myelosuppression consisting of anemia, leukopenia/neutropenia, and/or thrombocytopenia have been reported in patients treated with TALZENNA. Grade ?3 anemia, neutropenia, and thrombocytopenia were reported, respectively, in 39%, 21%, and 15% of patients receiving TALZENNA. Discontinuation due to anemia, neutropenia, and thrombocytopenia occurred, respectively, in 0.7%, 0.3%, and 0.3% of patients.

Monitor complete blood counts for cytopenia at baseline and monthly thereafter. Do not start TALZENNA until patients have adequately recovered from hematological toxicity caused by previous therapy. If hematological toxicity occurs, dose modifications (dosing interruption with or without dose reduction) are recommended. With respect to MDS/AML, for prolonged hematological toxicities, interrupt TALZENNA and monitor blood counts weekly until recovery. If the levels have not recovered after 4 weeks, refer the patient to a hematologist for further investigations. If MDS/AML is confirmed, discontinue TALZENNA.

TALZENNA can cause **fetal harm** when administered to pregnant women. Advise women of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose. A pregnancy test is recommended for females of reproductive potential prior to initiating TALZENNA treatment. Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment with TALZENNA and for at least 4 months after receiving the last dose. Based on animal studies, TALZENNA may impair fertility in males of reproductive potential. Advise women not to breastfeed while taking TALZENNA and for at least 1 month after receiving the last dose because of the potential for serious adverse reactions in nursing infants.

The **most common adverse reactions (?20%)** of any grade for TALZENNA vs chemotherapy were fatigue (62% vs 50%), anemia (53% vs 18%), nausea (49% vs 47%), neutropenia (35% vs 43%), headache (33% vs 22%), thrombocytopenia (27% vs 7%), vomiting (25% vs 23%), alopecia (25% vs 28%), diarrhea (22% vs 26%), and decreased appetite (21% vs 22%).

The **mostfrequently reported Grade ?3 adverse reactions (?10%)** for TALZENNA vs chemotherapy were anemia (39% vs 5%), neutropenia (21% vs 35%), and thrombocytopenia (15% vs 2%).

The **most common lab abnormalities (?25%)** for TALZENNA vs chemotherapy were decreases in hemoglobin (90% vs 77%), leukocytes (84% vs 73%), lymphocytes (76% vs 53%), neutrophils (68% vs 70%), platelets (55% vs 29%), and calcium (28% vs 16%) and increases in glucose (54% vs 51%), aspartate aminotransferase (37% vs 48%), alkaline phosphatase (36% vs 34%), and alanine aminotransferase (33% vs 37%).

Coadministration with P-gp inhibitors or **BCRP inhibitors** may increase TALZENNA exposure. If coadministering with the P-gp inhibitors amiodarone, carvedilol, clarithromycin, itraconazole, or verapamil is unavoidable, reduce the TALZENNA dose to 0.75 mg once daily. When the P-gp inhibitor is discontinued, increase the TALZENNA dose (after 3–5 half-lives of the P-gp inhibitor) to the dose used prior to the initiation of the P-gp inhibitor. When coadministering TALZENNA with other known P-gp inhibitors or BCRP inhibitors, monitor patients for potential increased adverse reactions.

For patients with moderate **renal impairment**, the recommended dose of TALZENNA is 0.75 mg once daily. For patients with severe renal impairment, the recommended dose of TALZENNA is 0.5 mg once daily. 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 inhibitor indicated in the U.S. for the treatment of patients with castration-resistant prostate cancer (CRPC) and metastatic castration-sensitive prostate cancer (mCSPC).

Overall survival benefit has been observed in patients treated with XTANDI in mCRPC, nmCRPC, and 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 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.

Disclosure Notice

The information contained in this release is as of October 4, 2022. 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, a potential indication in men with metastatic castration-resistant prostate cancer, physician and patient uptake and potential blockbuster opportunity 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; whether TALAPRO-2 trial will meet the primary endpoint for cohort 2 or 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 the potential indication or for any other indications; whether and when any such applications for TALZENNA, XTANDI or a combination 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 our 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, 2021 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.

[1] Kirby M, et al. Int J Clin Pract. 2011;11:1180-1192.
[2] ScherHI, et al. PLoSOne. 2015;10:e0139440.

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