



# Phase 3 PROSPER Trial Shows XTANDI® (enzalutamide) Significantly Reduced the Risk of Metastasis or Death by 71 Percent in Men with Non-Metastatic Castration-Resistant Prostate Cancer

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TOKYO and NEW YORK, February 5, 2018 - Astellas Pharma Inc. (TSE: 4503, President and CEO: Yoshihiko Hatanaka, "Astellas") and Pfizer Inc. (NYSE: PFE) announced today results from the Phase 3 PROSPER trial in patients with non-metastatic (M0) Castration-Resistant Prostate Cancer (CRPC). The results show that the use of XTANDI® (enzalutamide) plus androgen deprivation therapy (ADT) significantly reduced the risk of developing metastases or death by 71 percent compared to ADT alone. The median for the primary endpoint, metastasis-free survival (MFS), was 36.6 months for men who received XTANDI compared to 14.7 months with ADT alone (n=1401; HR=0.29 [95% CI: 0.24-0.35];  $p < 0.0001$ ). These data will be presented at the 2018 Genitourinary Cancers Symposium in San Francisco.

Marketing applications based on the results of the PROSPER study have been submitted to the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The FDA and EMA each have a filing review period during which they evaluate whether an application is complete and acceptable for filing. The data are also being submitted to additional regulatory authorities around the world.

“In patients with non-metastatic CRPC, there is a high unmet need to delay development of metastases and the progression to advanced prostate cancer. There are currently no approved systemic therapies for patients with non-metastatic CRPC in the U.S.,” said Maha Hussain, M.D., Robert H. Lurie Comprehensive Cancer Center of Northwestern University, who will present the data. “In the PROSPER trial, treatment with enzalutamide plus ADT delayed the development of metastases compared to standard of care ADT alone and, if approved, may provide men with non-metastatic CRPC an important new treatment option.”

PROSPER also investigated time to prostate-specific antigen (PSA) progression, time to first use of new antineoplastic therapy and overall survival (OS) as key secondary endpoints. The analysis demonstrated that patients who received XTANDI plus ADT had a 93 percent reduction in relative risk of PSA progression compared to patients who received ADT alone (HR=0.07 [95% CI: 0.05-0.08]; P<0.0001). XTANDI plus ADT delayed the median time to PSA progression by 33.3 months (37.2 months [95% CI: 33.1-NR] versus 3.9 months with ADT alone [95% CI: 3.8-4.0]).

XTANDI plus ADT prolonged the median time to first use of new antineoplastic therapy by 21.9 months versus ADT alone (39.6 months [95% CI: 37.7-NR] vs. 17.7 months [95% CI: 16.2-19.7]), a 79 percent relative risk reduction (HR=0.21 [95% CI: 0.17-0.26]; p<0.0001). At the time of the first interim analysis, median OS had not yet been reached in either treatment arm. However, these interim results demonstrated a trend in favor of XTANDI that was not statistically significant (HR=0.80 [95% CI: 0.58-1.09]; p=0.1519).

Adverse events in the PROSPER trial were generally consistent with those reported in prior enzalutamide clinical trials in patients with metastatic CRPC. Grade 3 or higher adverse events were reported in 31 percent of men treated with XTANDI plus ADT and in 23 percent of men treated with ADT alone. The most common ( $\geq 2\%$ ) Grade 3 or higher adverse events that were reported more often in XTANDI plus ADT-treated patients included hypertension (5% vs. 2%) and fatigue (3% vs. 1%). Major adverse cardiovascular events were reported in 5 percent of patients who received XTANDI plus ADT and 3 percent with ADT alone. Three seizures (<1%) were reported with XTANDI plus ADT patients and none were reported for those who received ADT alone. The percentage of patients in whom adverse events were the primary reason leading to treatment discontinuation was low in both study arms (9% with XTANDI plus ADT versus 6% with ADT alone).

## **About PROSPER**

The Phase 3 randomized, double-blind, placebo-controlled, multi-national trial enrolled approximately 1,400 patients with non-metastatic castration-resistant prostate cancer (CRPC) at sites in the United States, Canada, Europe, South America and the Asia-Pacific region. PROSPER enrolled patients with prostate cancer that had progressed, based on a rising prostate-specific antigen (PSA) level despite androgen deprivation therapy (ADT), but who had no symptoms and no prior or present evidence of metastatic disease. The trial evaluated enzalutamide at a dose of 160 mg taken orally once daily plus ADT, versus placebo plus ADT.

The primary endpoint of the PROSPER trial, metastasis-free survival (MFS), is a measure of the amount of time that passes until a cancer can be radiographically detected as having metastasized, or until death, within 112 days of treatment discontinuation. Secondary endpoints included time to PSA progression, time to first use of antineoplastic therapy and overall survival.

For more information on the PROSPER trial, go to [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### **About Castration-Resistant Prostate Cancer**

Prostate cancer is the second most common cancer in men worldwide.<sup>1</sup> More than 164,000 men in the United States are estimated to be newly diagnosed with prostate cancer in 2018.<sup>2</sup> In the European Union, the estimated number of new prostate cancer cases in 2015 was 365,000.<sup>3</sup>

Castration-resistant prostate cancer (CRPC) refers to the subset of men whose prostate cancer progresses despite castration levels of testosterone.<sup>4</sup> Non-metastatic CRPC means there is no clinically detectable evidence of the cancer spreading to other parts of the body (metastases), and there is a rising prostate-specific antigen (PSA) level.<sup>5</sup> Many men with non-metastatic CRPC and a rapidly rising PSA level go on to develop metastatic CRPC.<sup>6</sup>

### **About XTANDI® (enzalutamide) capsules**

XTANDI (enzalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with metastatic castration-resistant prostate cancer.

### **Important Safety Information**

#### **Contraindications**

XTANDI is not indicated for women. XTANDI can cause fetal harm and potential loss of pregnancy.

### **Warnings and Precautions**

**Seizure** occurred in 0.5% of patients receiving XTANDI in clinical studies. In a study of patients with predisposing factors, seizures were reported in 2.2% of patients. See section 5.1 of the Prescribing Information for the list of predisposing factors. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

**Posterior Reversible Encephalopathy Syndrome (PRES)** In post approval use, there have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder which 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.

### **Adverse Reactions**

The most common adverse reactions ( $\geq 10\%$ ) that occurred more commonly ( $\geq 2\%$  over placebo) in the XTANDI patients from the two placebo-controlled clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo. In the bicalutamide-controlled study of chemotherapy-naïve patients, the most common adverse reactions ( $\geq 10\%$ ) reported in XTANDI patients were asthenia/fatigue, back pain, musculoskeletal pain, hot flush, hypertension, nausea, constipation, upper respiratory tract infection, diarrhea, and weight loss.

In the placebo-controlled study of patients taking XTANDI who previously received docetaxel, Grade 3 and higher adverse reactions were reported among 47% of XTANDI patients and 53% of placebo patients. Discontinuations due to adverse events were reported for 16% of XTANDI patients and 18% of placebo patients. In the placebo-controlled study of chemotherapy-naïve patients, Grade 3-4 adverse reactions were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to adverse events were reported for 6% of both study groups. In the bicalutamide-controlled study of chemotherapy-naïve patients, Grade 3-4 adverse reactions were reported in 38.8% of XTANDI patients and 37.6% of bicalutamide patients. Discontinuations due to adverse events were reported for 7.6% of XTANDI patients and 6.3% of bicalutamide

patients.

**Lab Abnormalities:** In the two placebo-controlled trials, Grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). Grade 1-4 thrombocytopenia occurred in 6% of XTANDI patients (0.3% Grade 3-4) and 5% of placebo patients (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of XTANDI patients (0.2% Grade 3-4) and 16% of placebo patients (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of XTANDI patients (0.1% Grade 3-4) and 2% of placebo patients (no Grade 3-4).

**Infections:** In the study of patients taking XTANDI who previously received docetaxel, 1% of XTANDI patients compared to 0.3% of placebo patients died from infections or sepsis. In the study of chemotherapy-naïve patients, 1 patient in each treatment group (0.1%) had an infection resulting in death.

**Falls (including fall-related injuries)** occurred in 9% of XTANDI patients and 4% of placebo patients in the two placebo-controlled trials. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in XTANDI patients, and included non-pathologic fractures, joint injuries, and hematomas.

**Hypertension** occurred in 11% of XTANDI patients and 4% of placebo patients in the two placebo-controlled trials. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. 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 Astellas**

Astellas Pharma Inc., based in Tokyo, Japan, is a company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. We focus on Urology, Oncology, Immunology, Nephrology and Neuroscience as prioritized therapeutic areas while advancing new therapeutic areas and discovery research leveraging new technologies/modalities. We are also creating new value by combining internal capabilities and external expertise in the medical/healthcare business. Astellas is on the forefront of healthcare change to turn innovative science into value for patients. For more information, please visit our website at [www.astellas.com/en](http://www.astellas.com/en).

### **About Pfizer Oncology**

Pfizer Oncology is committed to pursuing innovative treatments that have a meaningful impact on those living with cancer. As a leader in oncology speeding cures and accessible breakthrough medicines to patients, Pfizer Oncology is helping to redefine life with cancer. Our strong pipeline of biologics, small molecules and immunotherapies, one of the most robust in the industry, is studied with precise focus on identifying and translating the best scientific breakthroughs into clinical application for patients across a wide range of cancers. By working collaboratively with academic institutions, individual researchers, cooperative research groups, governments and licensing partners, Pfizer Oncology strives to cure or control cancer with its breakthrough medicines. Because Pfizer Oncology knows that success in oncology is not measured solely by the medicines you manufacture, but rather by the meaningful partnerships you make to have a more positive impact on people's lives. Learn more about how Pfizer Oncology is applying innovative approaches to improve the outlook for people living with cancer at [http://www.pfizer.com/research/therapeutic\\_areas/oncology](http://www.pfizer.com/research/therapeutic_areas/oncology).

### **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 are collaborating on a comprehensive development program that includes studies to develop enzalutamide across the full spectrum of advanced prostate cancer as well as other cancers. Ongoing studies of enzalutamide in prostate cancer include the ARCHES trial in metastatic hormone-sensitive prostate cancer and the EMBARK trial in non-metastatic hormone-sensitive prostate cancer. 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 February 5, 2018. 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) and a potential indication in patients with non-metastatic castration-resistant prostate cancer, 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, the uncertainties inherent in research and development, including the ability to meet anticipated clinical trial completion dates and regulatory submission dates, as well as the possibility of unfavorable clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations, and, even when we view data as sufficient to support the safety and/or effectiveness of a product candidate, regulatory authorities may not share our views and may require additional data or may deny approval altogether; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; the risks associated with interim data; whether and when the FDA will accept the sNDA submitted and whether and when the European Medicines Agency will validate the filing for the potential indication; whether and when any supplemental drug applications may be filed for XTANDI for the potential indication in any other jurisdictions; whether and when regulatory authorities may approve any such applications, which will depend on the assessment by such regulatory authority of the benefit-risk profile suggested by the totality of the efficacy and safety information submitted and, if approved, whether XTANDI for the potential indication will be commercially successful; decisions by regulatory authorities regarding labeling, safety, and other matters that could affect the availability or commercial potential of XTANDI; risks related to increasing competitive, reimbursement and economic challenges; dependence on the efforts and funding by Astellas Pharma Inc. for the development, manufacturing and commercialization of XTANDI; 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, 2016 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](http://www.sec.gov) and [www.pfizer.com](http://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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<https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-cancer-facts-and-figures-3rd-edition.pdf>. Accessed January 10, 2018.

2 American Cancer Society. Cancer Facts & Figures 2018.

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3 European Commission. Epidemiology of Prostate Cancer in Europe.

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[www.urologyhealth.org/educational-materials](http://www.urologyhealth.org/educational-materials). Accessed February 16, 2017.

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6 Smith MR, Kabbinavar F, Saad F, Hussain A et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J Clin Oncol* 2005; 23: 2918-2925.

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