Press Release

Astellas Announces Acceptance by the European Medicines Agency of a Variation Application for Regulatory Review for Use of XTANDI™ (enzalutamide) in metastatic Hormone-Sensitive Prostate Cancer

TOKYO AND CHERTSEY, July 24 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., "Astellas") announced the acceptance by the European Medicines Agency (EMA) of a Type II Variation Application for regulatory review for the use of XTANDI™ (enzalutamide) in metastatic hormone-sensitive prostate cancer (mHSPC) patients.

Assessment by the EMA means the Committee for Medicinal Products for Human Use (CHMP) will evaluate the Type II Variation Application for enzalutamide and provide a Scientific Opinion on whether the medicine may be authorised for this new indication, following 90 days of assessment.[1]

"When prostate cancer begins to spread to other parts of the body, it can be an acutely distressing time for patients. As well as the emotional burden this places on them, daily life can be impacted by debilitating symptoms of progressing cancer, such as pain," said Andrew Krivoshik, M.D., Ph.D., Senior Vice President and Oncology Therapeutic Area Head, Astellas. "We look forward to the CHMP's opinion as we continue to address the unmet medical need for men with advanced prostate cancer by providing additional treatment options across the disease continuum."

The Type II Variation Application is based on data from both the pivotal Phase 3 ARCHES trial, and the Phase 3 ENZAMET trial, investigating enzalutamide in men with mHSPC.[2,3]

The data from the ARCHES trial were presented in an oral session at the 2019 Genitourinary Cancers Symposium in San Francisco (Abstract #687), and demonstrated that enzalutamide plus androgen deprivation therapy (ADT) significantly reduced the risk of radiographic progression by 61% versus placebo plus ADT in men with mHSPC (n=1,150; HR=0.39 [95% CI: 0.30-0.50]; P<0.0001). In the ARCHES trial, enzalutamide demonstrated a safety profile which was consistent with previous trials in castration-resistant prostate cancer (CRPC). Grade 3–4 adverse events (AEs) (defined as severe/disabling or life-threatening) were similar for patients receiving both enzalutamide plus ADT and those who received placebo plus ADT (23.6% vs. 24.7%).[2]

Data from the ENZAMET trial, organised by the international research group Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) Ltd, demonstrated a 33% decrease in the risk of death in men with mHSPC receiving enzalutamide plus ADT compared to those who took a conventional non-steroidal antiandrogen (NSAA) plus ADT (n=1,125; HR=0.67 [95% CI: 0.52-0.86]; P=0.002). Overall survival (OS) at 3 years was 80% for patients receiving enzalutamide plus ADT versus 72% receiving NSAA plus ADT. AEs during the follow-

up period were consistent with the stage of disease, the age of the patients, and known safety profiles of the trial regimen. The incidence of seizure and fatigue were higher with enzalutamide plus ADT and treatment discontinuation due to AEs was more frequent among patients taking enzalutamide than with NSAA plus ADT.[3] Astellas provided funding and support for the ENZAMET trial.

Enzalutamide is currently approved in Europe for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC) and adult men with metastatic castration-resistant prostate cancer (mCPRC) in whom chemotherapy is not yet clinically indicated, or following disease progression on or after docetaxel therapy.[4] In the U.S. and Japan enzalutamide is indicated for the treatment of CRPC.[5,6]

About ARCHES
The Phase 3, randomised, double-blind, placebo-controlled, multi-national trial enrolled 1,150 patients with metastatic hormone-sensitive prostate cancer (mHSPC) at sites in the United States, Canada, Europe, South America and the Asia-Pacific region. Patients in the ARCHES trial were randomised to receive enzalutamide 160 mg daily or placebo and continued on a luteinising hormone-releasing hormone (LHRH) agonist or antagonist, or had a history of bilateral orchiectomy. The ARCHES trial included patients with both low and high-volume disease, and both newly diagnosed patients with mHSPC and patients who had prior definitive therapy and subsequently developed metastatic disease. The trial also included some patients who had received recent treatment with docetaxel for mHSPC, but whose disease had not progressed. The primary endpoint of the trial was radiographic progression-free survival (rPFS), defined as the time from randomisation to the first objective evidence of radiographic disease progression as assessed by central review, or death within 24 weeks of treatment discontinuation.[7] For more information on the ARCHES (NCT02677896) trial, go to www.clinicaltrials.gov.

About ENZAMET
ENZAMET is a trial sponsored by the University of Sydney with trial sites in Australia, Canada, Ireland, New Zealand, UK and United States. The trial evaluates the potential of enzalutamide plus androgen deprivation therapy (ADT) versus a conventional non-steroidal anti androgen (NSAA) plus ADT in 1,125 men with mHSPC. The primary endpoint for the trial is overall survival (OS).[8] Additional details about ENZAMET (NCT02446405) are available on www.clinicaltrials.gov. Astellas provided funding and support for the ENZAMET trial.

About metastatic Hormone-Sensitive Prostate Cancer (mHSPC)
In men with prostate cancer, the disease is considered metastatic once the cancer has spread outside of the prostate gland to other parts of the body.[9] Men are considered hormone (or castration) sensitive if their disease still responds to medical or surgical treatment to lower testosterone levels.[9] mHSPC is fatal, with a median survival of approximately 3–4 years for men starting treatment with ADT.[10]

About Enzalutamide
Enzalutamide is an oral, once-daily androgen receptor (AR) signaling inhibitor. Enzalutamide targets the AR and exerts its effects on the AR signaling pathway:[4]

- Inhibits androgen binding: Androgen binding induces a conformational change that triggers activation of the receptor[4]

As a consequence of inhibiting androgen binding, enzalutamide:

- Prevents nuclear translocation: Translocation of the AR to the nucleus is an essential step in AR-mediated gene regulation[4]
- Impairs DNA binding: Binding of the AR to the DNA is essential for modulation of gene expression[4]

Important Safety Information for Enzalutamide
For important Safety Information for enzalutamide please see the full Summary of Product Characteristics at: https://www.medicines.org.uk/emc/product/3203

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. For more information, please visit our website at https://www.astellas.com/en.

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 commercialise enzalutamide. The companies jointly commercialise enzalutamide in the United States and Astellas has responsibility for manufacturing and all additional regulatory filings globally, as well as commercialising enzalutamide outside the United States.

Cautionary Note
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.

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References

[1] European Medicines Agency. European Medicines Agency post-authorisation procedural advice for users of the centralised procedure. Available at: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en-0.pdf. Last accessed June 2019.

[2]Armstrong AJ et al. Phase 3 study of androgen deprivation therapy (ADT) with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer (mHSPC): the ARCHES trial. American Society of Clinical Oncology Genitourinary Cancer Symposium (ASCO-GU) Abstract. Available at: https://meetinglibrary.asco.org/record/170727/abstract. Last accessed June 2019.

[3] Davis I, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. NEJM. 2019:[Epub ahead of print]. DOI: 10.1056/NEJMoa1903835.

[4] European Medicines Agency. Summary of Product Characteristics: Xtandi 40 mg soft capsules. http://ec.europa.eu/health/documents/community-register/2018/20181023142671/anx_142671_en.pdf. Last accessed June 2019.

[5] US FDA. Highlights of prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203415s014lbl.pdf. Last accessed June 2019.

[6] Astellas Press Release. Astellas Announces Marketing Approval in Japan for XTANDI® (enzalutamide) Capsules, an Advanced Prostate Cancer Treatment. Available at: https://www.prnewswire.com/news-releases/astellas-announces-marketing-approval-in-japan-for-xtandi-enzalutamide-capsules-an-advanced-prostate-cancer-treatment-252021811.html. Last accessed June 2019.

[7] Clinicaltrials.gov. A Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Patients with Metastatic Hormone Sensitive Prostate Cancer (mHSPC) (ARCHES). Available at: https://clinicaltrials.gov/ct2/show/NCT02677896. Last accessed June 2019.

[8] Clinicaltrials.gov. Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer (ENZAMET). Available at: https://clinicaltrials.gov/ct2/show/NCT02446405?cond=ENZAMET&rank=1. Last accessed June 2019.

[9] Cancer.net. Prostate Cancer: Types of Treatment (03-2018). https://www.cancer.net/cancer-types/prostate-cancer/types-treatment. Last accessed June 2019.

[10] Mottet N, et al. Updated Guidelines for Metastatic Hormone-sensitive Prostate Cancer: Abiraterone Acetate Combined with Castration Is Another Standard. Eur Urol. 2018;3:316-321