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DATA TO BE PRESENTED FROM PHASE 2 STUDY OF ENZALUTAMIDE IN ADVANCED ANDROGEN-RECEPTOR POSITIVE, TRIPLE-NEGATIVE BREAST CANCER

TOKYO, JAPAN – December 10, 2014 – Astellas Pharma Inc. (Tokyo: 4503), announced today that Stage 1 and preliminary Stage 2 data from a Phase 2 study evaluating the use of enzalutamide as a single agent for the treatment of advanced androgen receptor positive (AR+), triple negative breast cancer (TNBC) will be presented on December 12, 2014 at the 37th Annual San Antonio Breast Cancer Symposium. The abstract is as follows:

[P5-19-09] Stage 1 results from MDV3100-11: A 2-stage study of enzalutamide (ENZA), an androgen receptor (AR) inhibitor, in advanced AR+ triple-negative breast cancer (TNBC)

Traina TA, O'Shaughnessy J, Nanda R, Schwartzberg L, Abramson V, Cortes J, Peterson A, Tudor IC, Blaney M, Steinberg JL, Kelly C, Trudeau M, Awada A, Winer E, Hudis C, Schmid P, Yardley DA. Memorial Sloan Kettering Cancer Center, New York, NY; Texas Oncology, Baylor Charles A Sammons Cancer Center, Dallas, TX; Vall d'Hebron Institute of Oncology, Barcelona, Spain; Medivation Inc, San Francisco, CA; Astellas Pharma Global, Northbrook, IL; Memorial Sloan Kettering Cancer Center, London, United Kingdom; Sarah Cannon Research Institute, Nashville, TN; Tennessee Oncology PLLC, Nashville, TN; University of Chicago, Chicago, IL; University of Tennessee Health Science Center, Memphis, TN; Vanderbilt University, Nashville, TN; Mater Misericordiae University Hospital, Dublin, Ireland; Sunnybrook Health Science Centre, Toronto, ON, Canada; Jules Bordet Institute, Brussels, Belgium; Harvard University, Cambridge, MA

Background

TNBC is a heterogeneous disease with many subtypes that share one commonality; "triple-negative" breast tumors lack sufficient expression of a target (ER, PgR, HER2) associated with a therapeutic agent. AR expression occurs in a subset of TNBC and could identify patients (pts) that respond to AR inhibition. Preclinically, AR+ TNBC cell lines grow in response to AR stimulation and this growth is inhibited by ENZA. A phase 2 clinical study investigating bicalutamide in AR+ TNBC demonstrated a 19% clinical benefit rate at 24 weeks (CBR24) with no objective responses in 24 pts. ENZA is a potent AR inhibitor that improves overall survival in men with metastatic castration-resistant prostate cancer and is being evaluated in pts with advanced AR+ TNBC.

Methods

MDV3100-11 is an open-label, Simon 2-stage study evaluating ENZA (160 mg daily) in pts whose breast cancer expresses AR (>0% by IHC) but not ER, PgR or HER2 amplification (NCT01889238). There was no limit to prior therapies; bone-only non-measurable disease was allowed. Pts with CNS metastases or seizure history were excluded. Tissue was required; prescreening for AR was allowed. The primary

endpoint is CBR at 16 weeks (CBR16), defined as complete response (CR), partial response (PR), or stable disease (SD) ≥ 16 weeks per RECIST 1.1 in Evaluable pts. Evaluable pts were prespecified as those with tumors expressing $\geq 10\%$ AR by central review *and* who had assessment for response. ITT analyses include all pts. Secondary endpoints include CBR24, response rates, safety and tolerability. The analysis plan specified progression to Stage 2 if CBR16 is ≥ 3 of 26 Evaluable pts in Stage 1, and the null hypothesis (true CBR16=8%) is rejected if overall CBR16 is ≥ 9 in 62 Evaluable pts.

Results

Complete data on all Stage 1 pts (N=42) are reported herein; 16 were not evaluable (10 had AR $< 10\%$, 6 had AR $\geq 10\%$ but no response assessment). In the 26 Evaluable pts, median age was 62.5 years, 77% had measurable disease, 69% had ≥ 3 sites of metastases, 62% had visceral involvement, and 42% received ENZA in ≥ 3 rd line. CBR16 was 42% (11 of 26; 95%CI 24, 62) and CBR24 was 35% (9 of 26; 95%CI 18, 54), with 1 PR and 1 CR. Related adverse events (AEs) of any grade $\geq 10\%$ in the ITT were fatigue (29%), nausea (26%), decreased appetite (19%), diarrhea (14%), hot flush (12%) and vomiting (10%). Fatigue (7%) was the only Grade ≥ 3 related AE in $\geq 5\%$. Go to Stage 2 criteria were met, and enrollment is complete at 118. As of Sept 2014, 13 additional pts had clinical benefit at week 16 (including 3 PRs); data continue to mature.

Conclusion

The 42% CBR16 observed in Stage 1 alone was sufficiently high to reject the null hypothesis for the whole study. Data beyond Stage 1 are not mature; however, responses continue to be observed. AEs from ENZA in women with TNBC were generally mild and consistent with other studies of ENZA. These encouraging results suggest ENZA may provide meaningful benefit to pts with AR+ TNBC. Ongoing IHC and genomic analyses on 400 collected tissue samples will further inform how best to identify pts most likely to derive benefit from ENZA.

Poster Session: Advanced Therapy - Targeted (Friday, December 12, 2014 5:00 PM)

About the Phase 2 Study

The Phase 2 open label, single-arm study was initiated in June 2013 and completed enrollment in July 2014. 118 patients were enrolled in 2 Stages at sites in the United States, Canada and Europe. The primary endpoint of the trial is clinical benefit rate, defined as the proportion of patients with a best response of complete response, partial response or stable disease at ≥ 16 weeks. All patients receive enzalutamide at a dose of 160 mg to be taken orally once daily.

About XTANDI® (enzalutamide) capsules

XTANDI is approved by the U.S. Food and Drug Administration for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

Important Safety Information

Contraindications: XTANDI (enzalutamide) capsules can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. XTANDI is not indicated for use in women. XTANDI is contraindicated in women who are or may become pregnant.

Warnings and Precautions: In Study 1, conducted in patients with metastatic castration-resistant prostate cancer (CRPC) who previously received docetaxel, seizure occurred in 0.9% of patients who were treated with XTANDI and 0% treated with placebo. In Study 2, conducted in patients with chemotherapy-naïve metastatic CRPC, seizure occurred in 0.1% of patients who were treated with XTANDI and 0.1% treated with placebo. Patients experiencing a seizure were permanently discontinued from therapy and all seizure events resolved. There is no clinical trial experience re-administering XTANDI to patients who experienced a seizure, and limited clinical trial experience in patients with predisposing factors for seizure. Study 1 excluded the use of

concomitant medications that may lower threshold, whereas Study 2 permitted the use of these medications. Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity during which sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Adverse Reactions: The most common adverse reactions ($\geq 10\%$) reported from the two combined clinical trials that occurred more commonly ($\geq 2\%$ over placebo) in the XTANDI-treated patients 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.

Other Adverse Reactions include:

- **Laboratory Abnormalities:** In the two studies, Grade 1-4 neutropenia occurred in 15% of patients treated with XTANDI (1% Grade 3-4) and in 6% of patients treated with placebo (0.5% Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was 6% of patients treated with XTANDI (0.3% Grade 3-4) and 5% of patients on placebo (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of patients treated with XTANDI (0.2% Grade 3-4) and 16% of patients treated with placebo (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of patients treated with XTANDI (0.1% Grade 3-4) and 2% of patients treated with placebo (no Grade 3-4).
- **Infections:** In Study 1, 1% of XTANDI versus 0.3% of placebo patients and in Study 2, 1 patient in each treatment group (0.1%) had an infection resulting in death.
- **Falls:** In the two studies, falls including fall-related injuries occurred in 9% of XTANDI patients vs 4% treated with placebo. 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:** In the two studies, hypertension was reported in 11% of patients receiving XTANDI and 4% of patients receiving placebo. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in $< 1\%$ of XTANDI or placebo treated patients.

Drug Interactions:

- **Effect of Other Drugs on XTANDI** - Administration of strong CYP2C8 inhibitors can increase the plasma exposure to XTANDI. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI cannot be avoided, reduce the dose of XTANDI. Co-administration of XTANDI with strong or moderate CYP3A4 and CYP2C8 inducers may alter the plasma exposure of XTANDI and should be avoided if possible.
- **Effect of XTANDI on Other Drugs** -XTANDI is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. 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.

For Full Prescribing Information for XTANDI (enzalutamide) capsules, please visit www.XtandiHCP.com/PI

About Astellas Pharma Inc.

Astellas Pharma Inc. is a pharmaceutical company dedicated to improving the health of people around the world through provision of innovative and reliable pharmaceuticals. The organization

is committed to being a global category leader in Oncology and Urology, and has several oncology compounds in development in addition to enzalutamide. For more information on Astellas Pharma Inc., please visit our website at www.astellas.com/en.

About the Astellas/Medivation Collaboration

In October 2009, Medivation (NASDAQ: MDVN) and Astellas 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 advanced breast 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.

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