

Name: Andree Amelsberg, MBA, MD
Title: Executive Medical Director Oncology
Company: Astellas Scientific and Medical Affairs, Inc.
Address: 1 Astellas Way
Northbrook, IL 60062
Phone: (224) 205-5774
Email: andree.amelsberg@astellas.com
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NCCN Guidelines Panel: Prostate Cancer

On behalf of Astellas Pharma and Medivation, Inc., please find below data published in abstract form regarding the results of the Phase 3 PREVAIL trial, which investigated XTANDI® (enzalutamide) capsules in the treatment of men with chemotherapy-naïve metastatic prostate cancer after progression on androgen deprivation therapy.

Specific Changes: For your information, we are providing data on the use of enzalutamide in the treatment of men with chemotherapy-naïve metastatic castrate-resistant prostate cancer (mCRPC) that was recently presented at the ASCO Genitourinary Cancers Symposium in San Francisco, CA, January 30 to February 1, 2014.¹

FDA Clearance: On March 18, 2014, Astellas Pharma and Medivation Inc. announced the submission of a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) seeking approval of enzalutamide for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) who have not received chemotherapy.

The FDA has not approved enzalutamide for the treatment of men with asymptomatic or mildly symptomatic metastatic prostate cancer whose disease progressed despite treatment with androgen deprivation therapy (luteinizing hormone-releasing hormone (LHRH) analogue or after bilateral orchiectomy) who had not yet received chemotherapy. Enzalutamide is currently approved by the FDA for the treatment of men with mCRPC, who previously received docetaxel.² Please refer to the enclosed enzalutamide prescribing information for more information about enzalutamide.³

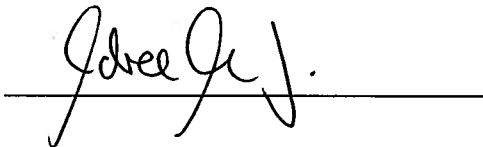
Rationale for request: The phase 3 international, randomized double-blind PREVAIL trial evaluated enzalutamide 160 mg daily versus placebo in chemotherapy-naïve men with metastatic prostate cancer that had progressed despite androgen deprivation therapy and were asymptomatic or mildly symptomatic from their disease. The study met its co-primary endpoints of overall survival (OS) and radiographic progression-free survival (rPFS) in the intent-to-treat (ITT) population. In a total of 1717 men randomized (1715 treated) between September 2010 and September 2012, a pre-specified interim analysis of OS at 540 deaths (71% of the 765 deaths specified for the final analysis) demonstrated a statistically significant benefit for enzalutamide over placebo in OS, with a 29% reduction in risk of death (HR 0.71; 95% CI:[0.60, 0.84]; p< 0.0001) and a statistically

significant benefit for enzalutamide over placebo in rPFS, with an 81% reduction in risk of radiographic progression or death (HR 0.19; 95% CI: [0.15-0.23], $p < 0.0001$). The estimated median OS was 32.4 months (mo) (95% CI:[30.1, not reached]) in the enzalutamide arm vs 30.2 mo (95% CI:[28.0, not reached]) for placebo. The estimated median rPFS was not reached (95% CI:[13.8, not reached]) in the enzalutamide arm vs 3.9 mo (95% CI:[3.7, 5.4]) for placebo. Treatment with enzalutamide demonstrated a statistically significant benefit in the pre-specified secondary endpoints presented. The most common adverse events ($\geq 20\%$ overall and $\geq 2\%$ in the enzalutamide arm over placebo) reported in the enzalutamide arm during the PREVAIL study were fatigue, back pain, constipation, arthralgia adverse events.¹

Additional details of the PREVAIL study and reported data can be obtained by accessing the following link: <http://www.congressposterlink.com/ASCOGU/Beer-Prevail.pdf>¹

Additional data on the use of enzalutamide in the treatment of men with chemotherapy-naïve mCRPC was previously reported by Scher et al, and is currently described in the NCCN Guidelines and Compendia.^{4,5}

Respectfully submitted,



Andree Amelsberg, MD, MBA
Executive Medical Director Oncology
Astellas Scientific & Medical Affairs, Inc.



Hank Mansbach, MD
Vice President, Medical Affairs
Medivation, Inc

Encl: XTANDI[®] (enzalutamide) capsules Prescribing Information

Reference List

1. Beer TM, Armstrong AJ, Sternberg CN, et al. Enzalutamide in men with chemotherapy-naïve metastatic prostate cancer (mCRPC): Results of phase III PREVAIL study. Proceedings of the 2014 American Society of Clinical Oncology Genitourinary Cancers Symposium, San Francisco, CA. [Poster - Abstract LBA1]. 2014. <http://www.congressposterlink.com/ASCOGU/Beer-Prevail.pdf>.
2. Scher HI, Fizazi K, Saad F, et al. Enzalutamide (formerly MDV3100) prolonged survival in men with prostate cancer following chemotherapy. 1-46. 4-13-2012.
3. XTANDI [package insert]. Northbrook, IL: Astellas, Inc. and San Francisco, CA: Medivation, Inc.
4. Scher HI, Beer TM, Higano CS et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. Lancet 2010; 375(9724):1437-1446.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology - Prostate Cancer Version 4.2013. www.nccn.org. Accessed 8-22-13.