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NCCN Guidelines Panel: Prostate Cancer

On behalf of Astellas and Pfizer, we respectfully request the NCCN Prostate Cancer Panel to review the enclosed data regarding the ARCHES trial. The ARCHES study assessed the efficacy and safety of enzalutamide plus androgen deprivation therapy (ADT) in men with metastatic hormone-sensitive prostate cancer (mHSPC), regardless of prior docetaxel use or disease volume.¹

Specific Changes: Enzalutamide is an androgen receptor (AR) inhibitor that acts on multiple steps in the AR signaling pathway.² In clinical studies, enzalutamide has demonstrated improvements in overall survival (OS) and radiographic progression-free survival (rPFS) in patients with metastatic castration-resistant prostate cancer (CRPC) before and after treatment with docetaxel^{3,4} and in metastasis-free survival (MFS) in chemotherapy-naïve patients with nonmetastatic CRPC.⁵

Results from the ARCHES study are now published in the Journal of Clinical Oncology.¹ We are submitting the data from ARCHES to support your evaluation and consideration of enzalutamide plus ADT for inclusion in the management of patients with mHSPC.

FDA Clearance: Enzalutamide is FDA approved for the treatment of patients with CRPC.² Enzalutamide does not have regulatory approval for use in men with mHSPC.

Rationale:

ARCHES is a multinational, double-blind, randomized, placebo-controlled, phase 3 study (NCT02677896).¹ Eligible patients included men (n=1150) with mHSPC, de novo or after biochemical recurrence, who were randomized 1:1 to enzalutamide 160 mg/day plus ADT (n=574) or placebo plus ADT (n=576). Patients were stratified according to disease volume (CHAARTED criteria; low vs. high) and prior receipt of docetaxel therapy (cycles received: 0, 1-5, or 6).

The primary endpoint was rPFS, defined as time from randomization to first objective evidence of radiographic disease progression, assessed centrally, or death (defined as death due to any cause within 24 weeks from study drug discontinuation), whichever occurred first. Key secondary endpoints included time to prostate-specific antigen (PSA) progression, time to initiation of new antineoplastic therapy, PSA undetectable rate, objective response rate (ORR), time to deterioration in urinary symptoms, and overall survival.

In the enzalutamide arm, 402 (70%) patients had distant metastases at initial diagnosis and 354 (61.7%) had high-volume disease. Prior treatment with docetaxel was reported as follows, 0 cycles: 471 (82.1%), 1-5 cycles: 14 (2.4%), and 6 cycles: 89 (15.5%) for the enzalutamide group. As of October 14, 2018, data

cutoff, median follow-up was 14.4 months. In the enzalutamide plus ADT group, the median duration of treatment was 12.8 months (range, 0.2 to 26.6 months) and 11.6 months (range, 0.2 to 24.6 months) in the placebo plus ADT group. At data cutoff, 292 radiographic disease progression events or deaths without radiographic disease progression within 24 weeks of treatment discontinuation had occurred (enzalutamide plus ADT, n=91 [15.9%] vs. placebo plus ADT, n=201 [34.9%]). Overall, the risk of radiographic disease progression or death was significantly reduced with enzalutamide plus ADT as compared with placebo plus ADT; by 61% (HR, 0.39; 95% CI, 0.30 to 0.50; $P<0.001$). In the enzalutamide plus ADT group, median rPFS was not reached (NR) (95% CI, NR to NR) versus 19.0 months (95% CI, 16.6 to 22.2 months) with placebo plus ADT. Similar significant improvement in rPFS was reported across all prespecified subgroups, including disease volume and prior docetaxel chemotherapy.

Significant improvement in secondary endpoints: time to PSA progression, time to initiation of new antineoplastic therapy, PSA undetectable rate, and objective response rate was observed in the enzalutamide plus ADT group. Enzalutamide in combination with ADT did not significantly affect time to deterioration in urinary symptoms. At this interim OS analysis, the data were immature with 84 deaths reported (enzalutamide plus ADT, n=39; placebo plus ADT, n=45). Median duration of OS was not reached (NR) in either treatment group (HR, 0.81; 95% CI, 0.53 to 1.25; $P=0.3361$). Adverse events (AEs) leading to discontinuation of treatment was 7.2% with enzalutamide plus ADT (n=572) and 5.2% in the placebo plus ADT group (n=574). Grade ≥ 3 AEs were reported in 24.3% of enzalutamide plus ADT patients and in 25.6% of patients who received placebo plus ADT. No unexpected AEs were reported.

We thank you for your time and consideration for the inclusion of enzalutamide in the management of metastatic hormone-sensitive prostate cancer.

Sincerely,



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Reference List

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