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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 PROSPER trial. PROSPER was an international, phase 3, randomized, double-blind, placebo-controlled study which evaluated the efficacy and safety of Xtandi (enzalutamide) in men with non-metastatic (M0) castration-resistant prostate cancer (CRPC).<sup>1,2</sup> The PROSPER study enrolled 1401 chemo-naïve men with non-metastatic CRPC who were randomized to receive either enzalutamide + androgen deprivation therapy (ADT) or placebo + ADT.<sup>1,2</sup>

Specific Changes: Enzalutamide is an androgen receptor (AR) inhibitor that acts on multiple steps in the AR signaling pathway.<sup>3</sup> In prior studies, enzalutamide was shown to improve overall survival (OS) and radiographic progression-free survival (rPFS) in patients with metastatic (M1) CRPC.<sup>4,5</sup> Patients with non-metastatic CRPC and rapidly rising prostate-specific antigen (PSA) are at high risk for developing metastatic CRPC.<sup>2</sup> Preventing or delaying progression to metastatic disease continues to be an area of unmet clinical need for these patients.<sup>1</sup> The PROSPER study was conducted to determine if enzalutamide improved metastasis-free survival (MFS) in patients with non-metastatic CRPC compared to placebo.<sup>2</sup> We are submitting the PROSPER data to NCCN to support your evaluation of enzalutamide in the management of patients with non-metastatic CRPC.

The PROSPER study results were recently presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO-GU) in San Francisco, CA on February 8, 2018.<sup>2</sup>

FDA Clearance: Enzalutamide is currently approved for the treatment of patients with metastatic CRPC.<sup>3</sup> Enzalutamide does not have regulatory approval for use in men with non-metastatic CRPC.

Rationale: PROSPER was a randomized, double-blind, placebo-controlled international phase 3 study (MDV3100-14, NCT02003924) conducted to evaluate the efficacy and safety of enzalutamide in chemo-naïve patients with non-metastatic CRPC.<sup>2</sup> Study patients were randomized 2:1 to receive enzalutamide 160 mg orally once daily + ADT or placebo + ADT. The primary endpoint of the study was MFS which was defined as the time from randomization to radiographic progression or death within 112 days of treatment discontinuation. Key secondary endpoints included: time to PSA progression, time to first use of new antineoplastic therapy, OS, and PSA response.

During the study, enzalutamide treatment significantly prolonged median MFS (36.6 months vs 14.7 months [ $p < 0.0001$ ]) compared to placebo.<sup>2</sup> Patients receiving enzalutamide also had a significantly reduced relative risk (71%) of developing metastases or death compared to patients on placebo. Time to first use of new antineoplastic therapy (39.6 months vs 17.7 months [ $p < 0.0001$ ]) and time to PSA progression (37.2 months vs 3.9 months [ $p < 0.0001$ ]) were also significantly longer in the enzalutamide

treatment group compared to placebo.<sup>2</sup> In the first interim analysis, median OS was not reached in either treatment group and therefore was not statistically significant. However, there was a trend favoring enzalutamide; i.e. a 20% reduction in the relative risk of death with enzalutamide versus placebo (HR = 0.80 (0.58 - 1.09); p = 0.1519).<sup>7</sup>

The median duration of treatment was 18.4 months vs 11.1 months for enzalutamide vs placebo, respectively.<sup>2</sup> More adverse events (AEs) were reported with enzalutamide vs placebo (any Grade: 87% vs 77%; Grade  $\geq$  3: 31% vs 23%; serious: 24% vs 18%).<sup>2</sup> In the study, 9% of patients on enzalutamide discontinued treatment due to an adverse event vs 6% with placebo.<sup>7</sup> Adverse events seen in the PROSPER trial were generally consistent with those reported in prior enzalutamide clinical trials in patients with metastatic CRPC.<sup>2</sup>

Additional details regarding the PROSPER Study are available at:

[https://congress-download.pfizer.com/asco\\_gu\\_2018\\_383\\_enzalutamide\\_maha\\_hussain\\_3.html](https://congress-download.pfizer.com/asco_gu_2018_383_enzalutamide_maha_hussain_3.html)

We thank you for your time and consideration for the inclusion of Xtandi (enzalutamide) in the management of non-metastatic CRPC.

Sincerely,



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