April 2, 2018

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109
Submitted via email: publiccomments@icer-review.org

RE: Draft Scoping Document for Non-metastatic Castration-resistant Prostate Cancer

Dear Dr. Pearson,

On behalf of Astellas Pharma Inc. (Astellas) and Pfizer Inc. (Pfizer), we are pleased to submit comments in response to the Institute for Clinical and Economic Review's (ICER) draft scoping document for the review of antiandrogen therapies for nonmetastatic castration-resistant prostate cancer (nmCRPC).[1] Prostate cancer affects the lives of millions of men in the United States (US). While research efforts over the past 2 decades have significantly improved treatment outcomes, important unmet needs remain, particularly among the nmCRPC population.

Since 2009, Astellas and Medivation, Inc. (a Pfizer company) have been dedicated to researching and understanding the clinical, economic, and quality of life (QoL) impacts on patients living with prostate cancer. Both companies have demonstrated this commitment through the robust clinical development of Xtandi® (enzalutamide) in the areas of greatest unmet need for patients with prostate cancer.[2]

The efficacy and safety profile of enzalutamide has been established in 3 randomized controlled clinical trials in mCRPC. Thousands of men with prostate cancer worldwide have enrolled in completed and on-going clinical trials. Globally, enzalutamide has been prescribed to more than 185,000 patients with mCRPC since its first regulatory approval in 2012.[2] The US Food and Drug Administration (FDA) has accepted for filing and granted Priority Review designation to our supplemental New Drug Application (sNDA) for Xtandi® (enzalutamide) in nmCRPC based on the phase 3 PROSPER trial.[3]

We appreciate ICER's efforts to seek input from a broad range of stakeholders as you seek to understand the value of treatments for nmCRPC. Based on Astellas and Pfizer's robust expertise in this area, we would like to offer the following perspectives and recommendations for ICER's consideration as it continues to further define and clarify the scope of the review.

The patient perspective is a critical consideration in the treatment of prostate cancer and should be incorporated to consider all elements of patient preferences and experience.

Ensuring a complete understanding of the patient experience with nmCRPC should be a key component, as it is fundamental to contextualizing the value of treatment. Because many patients with nmCRPC are asymptomatic, treatment goals often focus on delaying progression and maintaining current health status/QoL.[4] Moreover, progression to metastatic disease (measured by the endpoint of metastasis-free survival [MFS] in the PROSPER study) has been associated with a rapid and significant deterioration in

health-related quality of life (HRQoL), which continues to decline as the disease worsens.[3,5,6] Similarly, many men with nmCRPC are of working age, and the ability to maintain work productivity is an important consideration in treatment selection.[7] These, and other key considerations, are only understood through systematic and detailed discussions with patients, their caregivers, and their healthcare professionals.

Ensure that stakeholders understand that nmCRPC patients are a diverse group, and limited epidemiologic data make it a difficult population to characterize and quantify.

The exact proportion of patients diagnosed with CRPC at a nonmetastatic stage remains largely unknown.[8,9] Furthermore, the nmCRPC population is heterogeneous with regard to clinical characteristics and treatment outcomes,[10] as evidenced by large variations in clinical trial populations; thus, cross-trial comparisons are not straightforward.[3,11-15] As such, we expect that the uncertainty around this heterogeneous population will have implications throughout ICER's review.

Consider interventions and treatment options that are approved or nearing regulatory approval for nmCRPC.

The treatment paradigm in nmCRPC is rapidly evolving, with numerous investigational therapies on the horizon. We have concerns regarding both the appropriateness of selected treatment options because these factors may adversely affect the quality and relevance of ICER's review.

ICER has indicated its intent to include abiraterone acetate in its review, but the rationale for its inclusion is not clear. Abiraterone acetate is not approved by the FDA for use in nonmetastatic patients, is not recommended in guidelines for the treatment of nmCRPC,[16] and there is inadequate data in the nmCRPC population to support its use.[11] There are no ongoing publicly disclosed phase 2 or 3 trials for abiraterone acetate in the nmCRPC population.

At the time of this comment period, there are 2 second-generation antiandrogen therapies with available evidence of MFS for the treatment of nmCRPC: apalutamide,[17] which has recently received FDA approval, and enzalutamide,[18] which has been granted FDA Priority Review for an sNDA for the treatment of nmCRPC.[19] ICER should consider the data from these two drugs with published data in men with nmCRPC.

Carefully select outcomes that are operationally defined in a consistent manner and clinically meaningful to assess the value of nmCRPC therapies.

As noted previously, the heterogeneous nature of the nmCRPC population has resulted in important differences in populations across clinical trials. It is common for trials to include differing patient populations and select different primary and secondary outcomes, define outcomes dissimilarly, or use varying cutoff ranges, making comparisons of outcomes in a meta-analysis difficult. Thus, when comparing endpoints across trials, the variance in patient characteristics and clinical trial differences between the trials must be addressed.

- Enzalutamide and apalutamide included MFS as a primary endpoint; however, it is important to note that there were differences in how the trials defined these endpoints. They also differed in their patient inclusion criteria.[3,13-15] ICER should carefully consider how to address the differences in the interpretation of these endpoints to ensure appropriate comparisons.

- Because patients with nmCRPC are largely asymptomatic,[4] adverse event (AE) profiles of treatment can have a significant impact on physician and patient decisions around treatment selection. Therefore, it is important to have a clear understanding of AE definitions from each clinical trial and a transparent reconciliation of the differences in cut-off range measurements used across the trials for AEs.

Given treatment goals of the nmCRPC population, focus on measures such as delay of progression to chemotherapy and other antineoplastic treatments, in addition to traditional measures such as overall survival (OS).

- Nonmetastatic prostate cancer patients have an approximately 85% chance of surviving over a 10-year period.[20] While OS is an important endpoint, it should be considered together with patient and physician goals for treatment, along with the totality of outcomes and evidence. Because disease progression of the nmCRPC patient population is slower, the benefits of OS require robust clinical trial follow-up time.[20]
- Additionally, ICER should consider that MFS has been shown to be a strong correlate of OS among patients with high-risk localized prostate cancer.[20] Since OS data are not yet mature in either the PROSPER or SPARTAN trials, we recommend that ICER consider calculation of life-years gained and quality-adjusted life-years.
- In addition to the prevention of metastases to bone and other sites, the delay of progression to chemotherapy or other antineoplastic therapy is an important treatment consideration in the nonmetastatic space.[3,14] Therefore, such endpoints are critical to consider.[21]

As scientific leaders with an ongoing commitment to patients, Astellas and Pfizer appreciate the opportunity to make these recommendations to ICER as it continues shaping its review of nmCRPC therapies. Our clinical scientists and outcomes researchers would welcome an opportunity to discuss the scope and methodology of the planned review with you in more detail.

Best Regards,

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ERLEADA™ (apalutamide) ❖ ZYTIGA® (abiraterone acetate)

ICER SCOPING DOCUMENT - RESPONSE TO REQUEST FOR PUBLIC COMMENTS

The following information is provided in response to request for public comment and is not intended as an endorsement of any usage not contained in the Prescribing Information. For complete information, please refer to the full Prescribing Information for each product, including the following sections: INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, AND ADVERSE REACTIONS.

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BACKGROUND

Enclosed please find comments on the "Antiandrogen Therapies for Non-metastatic Castration-Resistant Prostate Cancer: Effectiveness and Value Draft Background and Scope" document, published on March 12, 2018. Comments below pertain to the respective sections and page numbers within the scoping document.

- **Page 1**: Suggest revising: "Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that progresses clinically, radiographically, or biochemically despite ADT that has achieved low levels of serum testosterone." to "Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that progresses clinically, radiographically, or biochemically despite ADT that has achieved **castrate** levels of serum testosterone."
- **Page 1**: Suggest revising: "Patients with metastatic disease who progress on ADT or who develop metastatic disease on ADT benefit from treatment with antiandrogen therapies. Antiandrogens include abiraterone (Zytiga®; Janssen Biotech, Inc.), enzalutamide (Xtandi®; Astellas Pharma, Inc.), and apalutamide (Erleada™; Janssen Biotech, Inc.)" to "Patients with **castration-resistant prostate cancer** can benefit from treatment with therapies such as abiraterone acetate (Zytiga®; Janssen Biotech, Inc.), enzalutamide (Xtandi®; Astellas Pharma, Inc.), and apalutamide (Erleada™; Janssen Biotech, Inc.)."
    - ERLEADA™ (apalutamide) is indicated for the treatment of patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC). ERLEADA is not indicated for the treatment of metastatic castration-resistant prostate cancer. There is an ongoing phase 3 study in metastatic castration-resistant prostate cancer (NCT02257736).
    - ZYTIGA® (abiraterone acetate) is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) and metastatic high-risk castration-sensitive prostate cancer (CSPC) (ZYTIGA PI).
- **Page 1**: Suggest revising: "Abiraterone inhibits testicular, adrenal, and tumor synthesis of androgens through inhibition of cytochrome P450 17A1; it must be administered with glucocorticoids." to "Abiraterone acetate (ZYTIGA) is converted to abiraterone *in vivo*. Abiraterone is an androgen biosynthesis inhibitor that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. ADT decreases androgen production in the testes but does not affect androgen production by the adrenals or in the tumor. ZYTIGA is administered in combination with prednisone." (ZYTIGA PI).
- **Page 1**: Abiraterone should be referred to as **abiraterone acetate** throughout the document.

- **Page 2**: Suggest revising: "Apalutamide and enzalutamide were evaluated in placebo-controlled randomized trials in patients with high-risk (as defined by rate of increase in PSA) nmCRPC." to "Apalutamide and enzalutamide were each separately evaluated in placebo-controlled randomized trials in patients with high-risk (as defined by **PSA doubling time [PSADT] ≤10 months**) NM-CRPC." (ERLEADA PI, Smith 2018, Hussain 2018).
- **Page 2:** Suggest revising: "Abiraterone has not been studied in this specific population but we have received expert input that it may have efficacy in patients with nmCRPC." to "Abiraterone acetate is not indicated for the treatment of patients with NM-CRPC. There are currently no phase 3, randomized clinical studies of abiraterone acetate in this patient population."

ANALYTIC FRAMEWORK

Figure 1.1

- **Page 3**: Suggest moving Metastasis-free survival from "Intermediate Outcomes" to "Key measures of Clinical benefit."
    - Metastasis-free survival (MFS) is an FDA-recognized registrational primary endpoint that was used in the apalutamide SPARTAN trial supporting full regulatory approval (ERLEADA PI, Smith 2018, Center for Drug Evaluation and Research 2018).
    - The appropriate primary efficacy endpoint to use in trials for study patients with NM-CRPC was addressed at two meetings of the FDA's Oncology Drugs Advisory Committee. The first meeting was non-product specific and discussed general issues related to the development of drugs for the treatment of NM-CRPC, while the second meeting was focused on the review of a specific drug for potential approval in the NM-CRPC setting. There was recognition that the transition to a state where the patient developed measurable metastatic disease represented a significant event for patients with NM-CRPC. A consensus emerged that an MFS endpoint would likely be clinically meaningful if it was of sufficient magnitude and was accompanied by data from supportive secondary endpoints such as overall survival (OS). Approval of apalutamide based on MFS, the primary efficacy endpoint of SPARTAN, established a new regulatory precedent for approval of treatments for NM-CPRC (Center for Drug Evaluation and Research 2018). MFS results were supported by consistency of effect on secondary efficacy endpoints. These included statistically significant and clinically meaningful improvements in median time to metastasis, median progression-free survival, and median time to symptomatic progression (P<0.001 for each endpoint). OS data are not mature yet, however, even at this early time point with 24% of events a strong trend in OS was observed (HR: 0.70, P=0.07) (ERLEADA PI, Smith 2018).

Populations

- **Page 4**: Suggest the following subgroups for analysis (ERLEADA PI, Smith 2018):
    - PSADT (≤6 months or >6 months)
    - Locoregional disease (N0 or N1)

Outcomes

- **Page 4**: Suggest revising and adding the following in the Key Harms section of Table 1.1:
    - Adverse events associated with death
        - Unexplained and unexpected deaths prior to metastasis
    - Mental impairment disorders
    - Hypertension

Other Benefits and Contextual Considerations

- **Page 6:** Suggest adding to **Potential Other Benefits**: This intervention offers patients with NM-CRPC the potential to delay progression to metastasis or death and the potential to delay the need for subsequent therapies in the treatment of mCRPC.
    - The SPARTAN trial is the only study in NM-CRPC that provided information on the second progression-free survival (PFS2), defined in the trial as time from randomization to investigator-assessed disease progression (PSA progression, detection of metastatic

disease on imaging, symptomatic progression, or any combination) during the first subsequent treatment for mCRPC or death from any cause.
    - PFS2 strongly supports the primary endpoint of MFS in NM-CRPC. It was demonstrated that treatment with ERLEADA provided clinically meaningful outcomes following second subsequent therapy.
    - In addition, PFS2 was important to patients because it illustrates that additional therapeutic options are still available to treat progressive disease.
- **Page 6:** Suggest adding to **Potential Other Benefits**: This intervention offers patients with NM-CRPC the potential to delay time to symptomatic progression and the potential to delay the need for additional therapies.
    - The SPARTAN trial provided information on time to symptomatic progression, defined in the trial as time from randomization to a skeletal-related event, pain progression, or worsening of disease-related symptoms leading to the initiation of a new systemic anticancer therapy or the time to the development of clinically significant symptoms due to local or regional tumor progression leading to surgery or radiation therapy.
    - Time to symptomatic progression strongly supports the primary endpoint of MFS in NM-CRPC and supports the maintained quality of life in these patients.

ECONOMIC MODELS FOCUSING ON COMPARATIVE VALUE

Scope of Comparative Value Analyses

- **Page 7**: **Comment:** When estimating the total treatment cost, we suggest considering the treatment duration.
- **Page 7**: **Comment:** Metastases avoided is proposed to be evaluated as a health outcome measure. In the SPARTAN trial, MFS was the primary endpoint and time to metastasis (TTM) was a secondary endpoint. The median time to MFS and the median TTM were the same for the apalutamide arm, 40.5 months (Smith 2018). This is because very few deaths contributed to MFS in the SPARTAN trial.
    - In the SPARTAN trial, MFS was defined as the time from the randomization to the first detection of distant metastasis on imaging (as assessed by means of blinded independent central review [BICR]) or death from any cause, whichever occurred first.
    - In the SPARTAN trial, TTM was defined as the time from the randomization to the first detection of distant metastasis involving the bone or soft tissue on imaging, as assessed by means of BICR.
- **Page 7**: **Comment:** In addition to the incremental cost per LY gained and incremental cost per QALY gained, we suggest calculating incremental cost per MFS gained. MFS has been shown to be a strong surrogate endpoint for overall survival in prostate cancer (Xie 2017). It is a composite endpoint capturing both survival and incidence of metastases, and is a primary endpoint for the SPARTAN and PROSPER registrational trials (Smith 2018, Hussain 2018).
- **Page 7**: **Comment**: Regarding the budgetary impact of apalutamide and enzalutamide, we recommend considering only the patient population (patients with NM-CRPC with PSADT ≤10 months) for which there is clinical evidence from SPARTAN and PROSPER, respectively (Smith 2018, Hussain 2018).

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March 29, 2018

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Submitted via email: publiccomments@icer-review.org

RE: Antiandrogen Therapies for Non-Metastatic Castration-Resistant Prostate Cancer: Effectiveness and Value Background *Draft Background and Scope Public Comment*

Dear Dr. Pearson,

For nearly 30 years the Prostate Conditions Education Council (PCEC) has been dedicated to saving lives through advancing the awareness and education of men, the women in their lives, as well as the medical community about prostate cancer treatment options. The Council – comprised of a consortium of leading physicians, health educators, scientists and prostate cancer advocates – is a global leading resource for information and access to therapies for prostate cancer.

On behalf of our patient centered organization we would like communicate the importance of incorporating "true" patient considerations into the Antiandrogen Therapies for Non-Metastatic Castration-Resistant Prostate Cancer Background and Scope, specifically as it relates to the value assessment. Any assessment of comparative clinical effectiveness and value that is designed to guide formulary or treatment decision-making impacts access to therapies, as such, a formal and transparent process should be taken into account to accommodate the patient perspective.

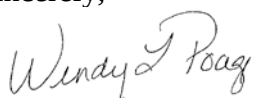
Clear transparency on the process for how patient and advocacy input are gathered and weighed is critical. This includes clearly stating the intent of patient and advocacy feedback, ensuring appropriate advocacy groups and patients are engaged with by ICER, the impact of their feedback and how it is processed as part of the overall value assessment. Additionally, it is critical to engage with multiple disease specific advocacy groups, and to disclose how many and which advocacy organizations and patients/caregivers are engaged with by ICER.

Input should be made by advocacy groups and patients early in the process including input on what questions that will be asked of advocates and patients, on the development of a standardized approach for both the review and collection of the feedback as well as details on how the information will be considered as part of the ICER review. These details should be clearly outlined in the Background and Scope document. This will ensure that advocates and the patient community are engaged in a meaningful manner and able to provide input on the outcomes that matter most to them. For example, the importance of therapeutic choice, the ability to switch to an alternative therapy when an existing therapy begins to fail, and cost.

We believe that improved details around the patient and advocacy input should be more clearly identified to ensure they are incorporated more appropriately into the review process and not simply listed under "other benefits or disadvantages" and "contextual considerations". Improving this process during the Background and Scope phase will allow ICER and its stakeholders to have more informed discussions and take into consideration the full context of how patient engagement is currently being considered into ICERs value assessment analyses.

Thank you for the opportunity to provide public comment on Antiandrogen Therapies for Non-Metastatic Castration-Resistant Prostate Cancer: Effectiveness and Value Background *Draft Background and Scope.*

Sincerely,



Wendy Poage, MHA