



August 9, 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 Evidence Report for Non-metastatic Castration-resistant Prostate Cancer

Dear Dr. Pearson,

On behalf of Astellas Pharma Inc. (Astellas) and Pfizer Inc. (Pfizer), we are writing in response to the Institute for Clinical and Economic Review's (ICER) draft evidence report for the review of antiandrogen therapies for non-metastatic castration-resistant prostate cancer (nmCRPC).¹

The efficacy and safety of Xtandi® (enzalutamide) was evaluated in four randomized controlled clinical trials in men with castration-resistant prostate cancer (CRPC).² Based on these studies, Xtandi® is FDA-approved for both nmCRPC and metastatic CRPC (mCRPC).³

Based on Astellas and Pfizer's role as scientific leaders in advanced prostate cancer, we have identified a number of concerns with the analysis and interpretation of data as presented in the draft evidence report. Most notably the draft evidence report: (1) does not appear to reflect an in-depth consideration of patient perspectives; (2) includes model decisions and assumptions that asymmetrically impact findings; and (3) lacks transparency on a number of key methodological elements and sources of input.

We offer the following perspectives and recommendations for ICER's consideration as it continues to refine and finalize its review of nmCRPC therapies. Comments provided within align with our previous response to the draft scoping document.²

The patient perspective is a critical consideration in the treatment of prostate cancer and should be more comprehensively incorporated into the analysis. Greater transparency is needed with respect to the details of ICER's patient engagement and the impact it had on the analysis.

Page 5 of the nmCRPC draft evidence report summarizes feedback from "*patients and patient groups.*" However, this brief section has a number of limitations. First, ICER does not specify which organizations were consulted. Patients with prostate cancer represent a large and diverse community, and the numerous groups representing this population may have different perspectives. As such, transparency around ICER's engagement with patients with prostate cancer and their advocates is critical to any interpretation of ICER's learnings. Second, the draft evidence report does not explain how patient and advocate feedback was obtained (e.g., structured interviews, formal public comment, or informal interactions). Transparency around the specific methods used is fundamental to any assessment of the validity of ICER's engagement strategy. Finally, no specific information is provided about how or where patient feedback was incorporated into the methodology and/or impacted the analysis. As such, it is not clear how ICER's

learnings from patient engagement ultimately shaped the methods used in the review, or its interpretation of the results.

In the Patient Participation Guide, ICER states that “*Patients are at the core of ICER’s mission to help provide an independent source of analysis of evidence on effectiveness and value to improve the quality of care that patients receive.*”⁴ However, in the case of the nmCRPC report, there is no clear evidence that substantive learnings from the patient engagement were incorporated into ICER’s process and findings. Therefore, the patient engagement section only serves as background information, and the goal of meaningful patient engagement is not met.

Decisions and assumptions made by ICER regarding model structure and inputs have an asymmetric impact on draft evidence report findings.

It is unclear why certain reported endpoints were included in the draft evidence report. The endpoint, *time to symptomatic progression*, which is only available in the SPARTAN clinical trial, was included in the base case.⁵ In contrast, a number of patient-relevant endpoints that were included in both the apalutamide and enzalutamide clinical trials were not included, such as: time to chemotherapy, time to PSA progression, and health related quality of life as measured by FACT-P and EQ-5D.^{5,6} Thus, the analytic team modeled *time to symptomatic progression* for enzalutamide, but ignored other empirical data on patient-relevant endpoints from the PROSPER trial. This approach suggests that the basic structure of the SPARTAN trial was adopted for the draft evidence report without consideration for the implications this may have for the rigor of the comparison. Inclusion of endpoints utilized in both trials would have provided an empirically-based and comprehensive analysis of the results. An analysis of consistent and patient relevant endpoints across the clinical trials for nmCRPC therapies was previously recommended in response to the draft scoping document.⁷

Endpoints that were included in ICER’s analysis did not account for heterogeneity in operational definitions across trials. The PROSPER and SPARTAN trials included metastasis-free survival (MFS) as the primary endpoint; but there are notable differences across clinical trials in both the definition of MFS and in the patient inclusion criteria.⁵⁻¹⁰ The draft evidence report does not consider differences in definition and interpretation of these endpoints, as well as the clinical trial study populations. For example, median baseline PSA doubling time was faster in PROSPER (3.8 months, range: 0.4, 37.4) compared to SPARTAN (4.4 months, range: 0.8, 10). Additionally, median MFS for the androgen deprivation therapy (ADT) placebo cohorts in PROSPER (14.7 months; range: 14.2, 15) and SPARTAN (16.2 months; range: 14.6, 18.4) months.^{5,6} These examples of heterogeneity among the clinical trial baseline characteristics question the validity of extrapolating overall survival and life-years gained outcomes differently for PROSPER and SPARTAN. Differences in the outcomes across the clinical trials may be attributed to the patient population heterogeneity. Therefore, an alternative, conservative base case would include consistent endpoints compared to ADT-placebo cohort and adjust accordingly through transparent sensitivity analyses.

A lack of transparency, unreferenced statements, and inconclusive results limit interpretation of ICER’s findings.

In the draft report, ICER makes a number of declarative statements that lack appropriate references or supporting information. For example:

- In the report, ICER noted that a lack of reliable clinical trial data led to the exclusion of abiraterone

acetate from the economic analysis for nmCRPC (page 19). However, page 2 states, “*Abiraterone acetate has not been studied in this specific population in a published randomized trial, but we have received expert input that it may have efficacy in patients with nmCRPC.*” While expert opinion can be an important source of information, ICER should be transparent about which experts offered this opinion, and the specific rationale underlying the statement. This is particularly important when the expert opinions elicited do not rely on FDA-approved indications or supporting clinical trial evidence. Additionally, in July 2018 the American Urology Association (AUA) updated treatment guidelines around the use of abiraterone acetate in nmCRPC stating, “*Clinicians may offer treatment with a second-generation androgen synthesis inhibitor (i.e. abiraterone plus prednisone) to select patients with non-metastatic CRPC at high risk for developing metastatic disease who do not want or cannot have one of the standard therapies [i.e. enzalutamide or apalutamide] and are unwilling to accept observation. (Option; Evidence Level Grade C).*” We strongly recommend that ICER’s discussion of abiraterone acetate be updated to reflect AUA’s guidelines.¹¹

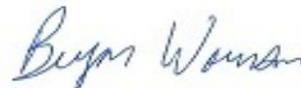
- In section 2.1 (page 7), multiple areas would benefit from additional transparency, including the inclusion/selection criteria of health plans for reviewing 2018 coverage policies (e.g., random selection, convenience sample).
- Statements on page 25 regarding the tolerability of apalutamide and enzalutamide may generate confusion without providing any supporting data. Specifically, “*(apalutamide) was **well-tolerated**, and quality of life remained stable for the duration of the SPARTAN trial*” may be interpreted as apalutamide having superior results vs. enzalutamide when compared to the statement, “*The side effect profile of enzalutamide is **relatively tolerable** and does not appear to negatively affect quality of life.*” We recommend using consistent terminology when describing similar results to avoid confusion or perceived bias.
- The draft evidence report inconsistently uses adverse event (AE) definitions (e.g., any grade and grade ≥ 3 AEs were used without appropriate identification and unclear sources).
- Page 60 states that the candidate budget impact analysis populations included “*adult males diagnosed with nmCRPC eligible for first-line therapy with antiandrogens.*” However, it is unclear if the analysis defined the eligible patient population as high-risk, consistent with the clinical trial inclusion criteria.

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 this feedback as you finalize the draft evidence report in more detail.

Best Regards,



Shontelle Dodson, PharmD
Senior Vice President
Medical Affairs, Americas
Astellas Pharma, Inc.



Bryon Wornson
Vice President, Oncology
Patient and Health Impact
Pfizer Inc.

References

1. ICER. Antiandrogen therapies for non-metastatic castration-resistant prostate cancer: effectiveness and value. https://icer-review.org/wp-content/uploads/2018/02/ICER_Prostate_Cancer_Draft_Evidence_Report_071218.pdf. July 12, 2018. Access July 12, 2018.
2. ICER. Antiandrogen therapies for non-metastatic castration-resistant prostate cancer: effectiveness and value. https://icer-review.org/wp-content/uploads/2018/02/MWCEPAC_PROSTATE_CANCER_DRAFT_SCOPE_03122018.pdf. March 12, 2018. Accessed March 12, 2018.
3. U.S. FDA Approves XTANDI® (enzalutamide) for the Treatment of Men with Non-Metastatic Castration-Resistant Prostate Cancer (CRPC) [press release]. <https://www.businesswire.com/news/home/20180713005429/en/U.S.-FDA-Approves-XTANDI%C2%AE-enzalutamide-Treatment-Men>. July 13, 2018. Accessed July 26, 2018.
4. ICER. Patient Participation Guide. <https://icer-review.org/patient-participation-guide>. Accessed July 26, 2018.
5. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378:1408-1418.
6. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med*. 2018;378(26): 2465-2474.
7. ICER. Prostate Cancer: Public Comments on Draft Scope. <https://icer-review.org/wp-content/uploads/2018/02/ProstateCancerDraftScopeComments.pdf>. April 2, 2018. Access August 2, 2018.
8. ClinicalTrials.gov. IMAAGEN: Impact of abiraterone acetate in prostate-specific antigen. <https://clinicaltrials.gov/ct2/show/NCT01314118>. Accessed March 28, 2018.
9. Luo J, Beer TM, Graff JN. Treatment of nonmetastatic castration-resistant prostate cancer. *Oncology (Williston Park)*. 2016;30(4):336-344.
10. Smith MR, Saad F, Hussain M, et al. ARASENS: a phase 3 trial of darolutamide in combination with docetaxel for men with metastatic hormone-sensitive prostate cancer (mHSPC). *J Clin Oncol*. 2018b;36:(Suppl 6S): abstr TPS383.
11. American Urological Association. Castration-Resistant Prostate Cancer. [http://www.auanet.org/guidelines/prostate-cancer-castration-resistant-\(2013-amended-2018\)](http://www.auanet.org/guidelines/prostate-cancer-castration-resistant-(2013-amended-2018)). Accessed August 2, 2018.



August 7, 2018

Institute for Clinical and Economic Review
2 Liberty Square, 9th Floor
Boston, MA 02109

Re: Comments on draft evidence document on “Androgen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer: Effectiveness and Value”

Bayer appreciates the opportunity to comment on ICER’s draft evidence document on “Androgen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer: Effectiveness and Value”.

Bayer is committed to helping patients with Prostate Cancer and recognizes the unmet need in the nonmetastatic Castration Resistant Prostate Cancer (nmCRPC) disease spectrum and the impact of anti-androgen therapies in substantially improving the clinical outcomes among these patients. With the rapidly evolving treatment landscape in nmCRPC, this draft evidence report showing the value of current treatments is very timely.

Our questions and recommendations on the draft scoping document are detailed below

- Section 1.4 Insights gained from discussions with patients and patient groups

We appreciate the transparent process to include patient’s views regarding their treatments.

However details on the patient representation or socio demographic profiles are not provided. It is also unclear if the inputs were collected from the population of interest i.e. nmCRPC or advanced PC patients in general. It will also be interesting to see the representation of minority subgroups in the discussion. Additional details on the patient population and methodology will be helpful.

Besides patient attributes, it is also important to understand caregiver’s insights to patient’s treatments as they are often key participants in treatment-decision making for cancer patients. We recommend adding this as a limitation as caregivers were not included in the discussion.

- Figure 3.1- ICER Evidence Rating Matrix

Abiraterone acetate is included as a comparator and was given a B+ evidence rating. We would like to underscore that the randomized trials supporting abiraterone in the review were largely focused on the metastatic CRPC (mCRPC) population. Also the IMAAGEN trial which is the key study for Abiraterone is only a phase II single arm study with only 131 patients. As mentioned in the report, abiraterone and enzalutamide may show similar efficacy in mCRPC, but we cannot be certain about the treatment efficacy in nmCRPC patient population due to lack of evidence. It would be helpful to understand the rationale behind the chosen rating given the limited evidence in nmCRPC.

- Outcome- Metastasis free survival (MFS)

Both SPARTAN and PROSPER considered MFS as the primary outcome and to date do not show a survival advantage. The ICER report mentions the abstract that was presented at ASCO 2018 that showed a positive association between overall survival and MFS from SPARTAN data. However there are other studies that show MFS as a relevant endpoint in prostate cancer trials which could be cited in the report.^{1, 2} More recently, the FDA has also published MFS as valid surrogate endpoint in prostate cancer trials.³ We think citing these studies would provide additional support to the strength of association.

- Adverse events

Bayer commends ICER for its inclusion of a spectrum of AEs within its evaluation. It may prove to be important to, over time, to further understand how safety and tolerability components may play out in this nonmetastatic stage of the disease. More specifically, individual grade 3-4 Adverse Events (AEs) that occur in at least 5% of patients and grade 2 fractures were included in the model. SPARTAN and PROSPER report high rates of fatigue. Additionally fatigue was also identified as a particularly common substantial side effect of apalutamide and enzalutamide in patient group discussions. Real world data studies in advanced prostate cancer have reported that patients treated with enzalutamide were more likely to experience central nervous system (CNS) events or fatigue.⁴ Providers may have concerns regarding adverse events, such as fatigue, pain, and possibly others potentially leading to dose reductions or treatment interruptions. We would therefore welcome, and advocate for, further development of evidence on how tolerability aspects of (pharmaco) therapies might influence therapy adherence and the overall well-being of the nonmetastatic PC patient.

Thank you again for the opportunity to offer our views on this draft evidence document. We look forward to further participation in the process

Sincerely,

Todd Williamson
VP, Data Generation & Observational Studies
Bayer U.S. LLC
100 Bayer Boulevard
Whippany, NJ 07981-0915

¹Xie W, Regan MM, Buyse M et al. Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer. *J Clin Oncol.* 2017; 35:3097-3104.

² Beaver JA, Kluetz P, Pazdur R. Metastasis-free Survival — A New End Point in Prostate Cancer Trials. *N Engl J Med* 2018; 378:2458-2460

³ Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure.

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm613636.htm>

⁴ Pilon D, Behl AS, Ellis LA, et al. Assessment of Real-World Central Nervous System Events in Patients with Advanced Prostate Cancer Using Abiraterone Acetate, Bicalutamide, Enzalutamide, or Chemotherapy. *Am Health Drug Benefits.* 2017; 10:143-153.

Tel: (862) 404-5418

Email: todd.williamson@bayer.com

Date: August 9, 2018

RE: ICER Prostate Cancer Draft Evidence Report – Response to Request for Public Comment

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.

CONTACT INFORMATION

Name	April Khetia, PharmD
Organization	Janssen Scientific Affairs, LLC.
City, State	Horsham, PA
Email Address	akhetia@its.jnj.com

EXECUTIVE SUMMARY

- The current Draft Evidence Report incorporates a more comprehensive listing of high-cost post-progression metastatic castration-resistant prostate cancer (CRPC) therapies with the addition of PROVENGE[®] (sipulecel-T) and XOFIGO[®] (radium Ra 223 dichloride), which, in part, has resulted in a lower incremental cost-effectiveness ratio compared to androgen deprivation therapy. With the exclusion of abiraterone acetate plus prednisone, the cost-effectiveness (CE) model now reflects only those products that are FDA-approved and indicated for non-metastatic CRPC (nmCRPC) and provides a CE model incorporating high-value evidence. Despite these changes, we believe the model structure can be further improved to reflect the true value of these nmCRPC therapies for the following reasons:
 - The model only reflects costs of nmCRPC therapies and post-progression metastatic CRPC therapies. The value for apalutamide and enzalutamide for patients with nmCRPC is to prevent progression to metastatic CRPC and reduce additional healthcare resource use (HRU) and costs associated with physical and functional deterioration that accompanies metastatic disease. The model currently does not reflect the full HRU and costs associated with progression to metastasis, which are exponentially higher than for nmCRPC (Li 2017, Valderrama 2017). Therefore, we recommend that lifetime post-progression HRU and costs of hospitalization, emergency room use, outpatient, ancillary pharmaceutical, supportive care costs, rehabilitation, and palliative care should be included in the model. Additionally, we believe that inclusion of mCRPC HRU and costs associated with disease progression will further decrease the ICER of both apalutamide and enzalutamide and will reduce the model sensitivity to treatment duration with these agents.
 - Given the recent FDA approval and updates to the XTANDI[®] (enzalutamide) Prescribing Information, we recommend that new information included in the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections are incorporated into the evaluation and modeling. The model should reflect the costs of monitoring and interventions to manage high-cost potential adverse events, including serious grade 3 and 4 adverse reactions associated with enzalutamide and apalutamide as well as post-progression metastatic CRPC therapies (See WARNINGS and PRECAUTIONS and ADVERSE REACTIONS sections of the ERLEADA and XTANDI PIs). Consideration should be given to continue to include these costs for the duration of time on therapy or for duration of the patient's lifetime in chronic diseases such as ischemic heart disease.
- ERLEADA[™] (apalutamide) is the first US FDA-approved therapy to treat patients with nmCRPC. As of the date of this submission, apalutamide is the only antiandrogen treatment option for this patient population with a Category 1 recommendation in the National Comprehensive Cancer Network (NCCN) Guidelines for Prostate Cancer (NCCN 2018). Apalutamide is also included as a *Standard* treatment option for asymptomatic nmCRPC based on Evidence Level Grade A in the American Urological Association (AUA) CRPC clinical guidelines (AUA 2018, Lowrance 2018). We recommend that the

category recommendations and evidence level ratings be specified when discussing each antiandrogen therapy in relation to clinical guidelines in the updated evidence report.

- Apalutamide has demonstrated improved median metastasis-free survival (MFS) by more than two years (24.3 months) in men with nmCRPC and a rapid PSA doubling time (≤ 10 months) compared to placebo. MFS results were supported by consistency of effect on secondary efficacy endpoints, including median time to symptomatic progression ($P < 0.001$) (Smith 2018). In addition to apalutamide + ADT providing a substantial net health benefit compared with ADT alone, tolerability has been supported by exploratory analyses of patient-reported outcomes revealing no notable adverse signals in symptom or functional effects despite the long treatment duration (Beaver 2018, Saad 2018). A manuscript of the health-related quality of life data from the SPARTAN study has been submitted to a peer-reviewed journal.
 - Additional information regarding the SPARTAN study, including the clinical study report, protocol, and statistical analysis plan, can be found on the FDA website: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/Erleada_210951_toc.cfm (scroll to the “Sponsor Clinical Study Reports ARN-509-003 SPARTAN NCT # 01946204” section).
- ZYTIGA[®] (abiraterone acetate) is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with *metastatic* CRPC and *metastatic* high-risk castration-sensitive prostate cancer (CSPC) (ZYTIGA PI). “Abiraterone acetate + prednisone” should be utilized within the document for ZYTIGA-specific information to align with the Prescribing Information. In addition, the phase 2, single-arm IMAAGEN study evaluated the combination of abiraterone acetate plus prednisone in patients with nmCRPC; dosing in combination with methylprednisolone was *not* studied.
- The use of abiraterone acetate plus prednisone for the treatment of nmCRPC is not currently included in any of the five CMS-recognized compendia, including the NCCN Compendium[®] (NCCN 2018).
- There are limited abiraterone acetate plus prednisone clinical study data in nmCRPC, and *no published randomized* study data in nmCRPC. Further, the numerous study limitations of the phase 2, *single-arm* IMAAGEN trial should be clearly outlined in the ICER assessment.
- Please see below our detailed feedback on the ICER prostate cancer draft evidence report.

INTRODUCTION

- **Page 1: Section 1.1:** ERLEADA is indicated for the treatment of patients with nmCRPC and not indicated for the treatment of metastatic CRPC (ERLEADA PI). There is an ongoing phase 3 study in metastatic CRPC (NCT02257736).
- **Page 2: Section 1.1:** Revise: "... (as defined by rate of increase in PSA) nmCRPC." to "More recently, apalutamide and enzalutamide have been evaluated in placebo-controlled randomized trials in patients with high risk (as defined by **PSA doubling time ≤ 10 months**) nmCRPC." (Smith 2018, Hussain 2018).
- **Page 2: Section 1.1:** Revise: "... (NCCN) guidelines were updated to suggest apalutamide or other antiandrogen therapies in men with nmCRPC, particularly with rapid increase in PSA..." to "In 2018, National Comprehensive Cancer Network (NCCN) guidelines were updated to **add apalutamide as an option in the Systemic Therapy for M0 Castration-Resistant Prostate Cancer (CRPC) treatment algorithm, especially if PSA doubling time ≤ 10 months (Category 1). In addition, regarding other secondary hormone therapy, the treatment algorithm was changed from especially if PSA doubling time < 10 months to especially if PSA doubling time ≤ 10 months (Category 2A).**" (NCCN 2018).
 - NCCN Category 1 and 2A: Based upon high-level evidence or lower-level evidence (Category 1 or 2A, respectively), there is uniform NCCN consensus that the intervention is appropriate.
 - Please note, the NCCN prostate cancer guidelines included in the References section are version 2.2018. The NCCN published v3.2018 on June 21, 2018.
- **Page 2: Section 1.1:** Revise: "... and American Urological Association guidelines were updated to recommend offering apalutamide or enzalutamide to men with nmCRPC at high risk of developing metastatic disease." to "American Urological Association guidelines **for CRPC** were updated to recommend offering apalutamide or enzalutamide (**Standard, Evidence Level Grade A**) with **continued androgen deprivation** to men with nmCRPC at high risk of developing metastatic disease." (AUA 2018, Lowrance 2018).
 - AUA Standard is defined as a directive statement that an action should (benefit outweighs risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A or B

evidence. Based on AUA nomenclature and methodology, AUA rates the quality of evidence as high, moderate or low (A, B or C). Please refer to the AUA CRPC clinical guidelines for complete definitions of AUA nomenclature and methodology.

- **Page 2-3: Section 1.2, Page 3: Figure 1.1, and Global comment:** Revise "abiraterone acetate + corticosteroid" to "abiraterone acetate + prednisone" to align with the ZYTIGA Prescribing Information throughout the document when information is specific to ZYTIGA, including the IMAAGEN study, as methylprednisolone was not utilized. The YONSA[®] (abiraterone acetate) Prescribing Information states: To avoid medication errors and overdose, be aware that YONSA tablets may have different dosing and food effects than other abiraterone acetate products. Recommended dose: YONSA 500 mg (four 125 mg tablets) administered orally once daily in combination with methylprednisolone 4 mg administered orally twice daily (YONSA PI).
- **Page 4: Table 1.1:** Add to the Key Harms column: **Cardiovascular-related adverse events (e.g. ischemic heart disease, coronary artery disorders, cardiac arrhythmias), Hypersensitivity.**
 - We recommend that new information included in the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS of the XTANDI PI sections are incorporated into the evaluation and modeling. Ischemic heart disease and Hypersensitivity are included in the WARNINGS AND PRECAUTIONS section of the XTANDI Prescribing Information, including the need to monitor for signs and symptoms of ischemic heart disease.
 - There are currently no such monitoring requirements related to ischemic heart disease included in the ERLEADA Prescribing Information (ERLEADA PI).
- **Page 4: Section 1.3:** The primary endpoint of SPARTAN and PROSPER, MFS, was defined differently in each clinical trial. Please differentiate the definition of MFS used in each trial:
 - SPARTAN: defined as the time from randomization to the time of first evidence of BICR-confirmed distant metastasis, defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcation, or death due to any cause, whichever occurred first (ERLEADA PI).
 - PROSPER: defined as the time from randomization to whichever of the following occurred first 1) loco-regional and/or distant radiographic progression per BICR or 2) death up to 112 days after treatment discontinuation without evidence of radiographic progression (XTANDI PI).

SUMMARY OF COVERAGE POLICIES & CLINICAL GUIDELINES

- **Page 7, Section 2.1:** Revise: "Apalutamide was not found in some formularies." to "Coverage for ERLEADA continues to increase since launch, with most national and regional plans covering it according to its FDA label across Commercial and Part D lives as of July 2018." (Data on file).
- **Page 7: Section 2.2:** Revise: "...especially with longer PSA doubling times (>10 months), and that secondary hormone therapy is an option mainly for with those with shorter PSA doubling times (≤10 months). The guidelines specifically mention that apalutamide can be considered, but also state that other secondary hormone therapies can be used." to "For men with castration-resistant prostate cancer and no signs of distant metastasis, the NCCN guidelines state that patients can consider observation especially **if PSA doubling time >10 months (Category 2A)** and that **other** secondary hormone therapy is an option **especially if PSA doubling time ≤10 months (Category 2A)**. The guidelines specifically mention that apalutamide **is an option especially if PSA doubling time ≤10 months (Category 1)**." (NCCN 2018)
- **Page 7-8: Section 2.2:** Revise: "...physicians offer apalutamide or enzalutamide with continued androgen deprivation to patients with nmCRPC at high risk for developing metastatic disease. For those who do not want or cannot have these therapies, physicians may recommend observation with continued androgen deprivation, or may offer treatment with a second-generation androgen synthesis inhibitor if the patient is not comfortable with observation. Systemic chemotherapy..." to "The AUA recommends that physicians offer apalutamide or enzalutamide (**Standard, Evidence Level Grade A**) with continued androgen deprivation to patients with nmCRPC at high risk for developing metastatic disease. For those **patients with nmCRPC at high risk for developing metastatic disease** who do not want or cannot have **the standard** therapies, physicians may recommend observation with continued androgen deprivation (**Recommendation, Evidence Level Grade C**) or may offer treatment with a second-generation androgen synthesis inhibitor **to select patients with nmCRPC at high risk for developing metastatic disease who do not want or cannot have one of the standard therapies and are unwilling**

to accept observation (Option, Evidence Level Grade C). Systemic chemotherapy or immunotherapy should not be offered **to patients with nmCRPC**, except in the context of a clinical trial **(Recommendation, Evidence Level Grade C).**" (AUA 2018, Lowrance 2018).

- AUA has specific definitions for a Standard, Recommendation, and Option based on levels of evidence. AUA also rates the quality of evidence as high, moderate or low (A, B or C). Please refer to the AUA CRPC clinical guidelines for complete definitions of AUA nomenclature and methodology.

COMPARATIVE CLINICAL EFFECTIVENESS

- **Page 12, Section 3.3:** Differentiate definition of MFS used in the SPARTAN and PROSPER clinical trials per comment related to Page 4: Section 1.3 in the Introduction section.
- **Page 13, Table 3.1:** Revise the following in the SPARTAN row, Patient Characteristics: N1: 17%, PSADT ≤ 6 months: 72%, median time from initial diagnosis to randomization: 7.9 years (Smith 2018).
- **Page 13, Table 3.1:**
 - **Global Comment:** IMAAGEN-remove the abstract citation reference "15" and utilize the full publication citation: Ryan CJ, Crawford ED, Shore ND, et al. The IMAAGEN study: effect of abiraterone acetate and prednisone on prostate-specific antigen and radiographic disease progression in patients with non-metastatic castration-resistant prostate cancer. *J Urol.* 2018;200(2):344-352.
 - Change "Median time to radiographic progression: 41.4 mo" to "Median time to radiographic progression: **Not Reached (estimated 41.4 mo [n=15]).**" (Ryan 2018).
- **Page 14, Section 3.3:** Revise: "...enrolled 51 patients with high-risk nonmetastatic disease. This trial assessed 12-week PSA response and safety." to "We also identified a small, single arm Phase II study of apalutamide + ADT that enrolled 51 patients with high-risk nonmetastatic **CRPC. Among the endpoints studied included** 12-week PSA response and safety." (Smith 2016).
- **Page 14, Section 3.3:** Change the citation number from "11" to "38" for the following sentence: "At the time of data cut-off, only 24% of the events needed for final analysis had occurred." (ERLEADA PI).
- **Page 15, Section 3.3:** Revise: "Time to symptomatic progression was also longer with apalutamide (HR: 0.44; 95% CI 0.29 to 0.66)." to "**Median** time to symptomatic progression was also longer with apalutamide (HR: 0.45; 95% CI 0.32 to 0.63)." Please also update Table 3.3 accordingly (Smith 2018).
- **Page 15, Table 3.2:** Revise the following for Loco-regional disease: N0: apalutamide + ADT median (mo): NE, placebo + ADT median (mo): 39, and HR to 0.72 (0.47 to 1.10). Revise the following for Loco-regional disease: N1: HR to 0.52 (0.19 to 1.42). Revise the following for PSA doubling time ≤ 6 mo: apalutamide + ADT median (mo): NE and placebo + ADT median (mo): 39 (J&J PRD 2018).
- **Page 16, Section 3.3:** Revise: "...Quality of Life (EQ) visual-analogue scale (VAS)." to "The SPARTAN trial measured patient-reported outcomes from the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire and the European Quality of Life-5 Dimensions (**EQ-5D-3L**) questionnaire (consists of EQ-5D descriptive system and the EQ visual-analogue scale)." (Smith 2018, Saad 2018).
- **Page 16, Section 3.3:** Provide results from SPARTAN patient-reported outcomes data presented during the 2018 European Association of Urology Congress: FACT-P total and subscale scores and EQ-5D-3L scores indicated that overall HRQoL over time was maintained in both the apalutamide group and placebo group (median treatment exposure: 16.9 months vs 11.2 months, respectively). Group means at baseline for FACT-G (apalutamide, 84.1 [standard deviation (SD) 14.4]; placebo, 83.4 [SD 14.2]) were consistent with the FACT-G population norm (80.9 [SD 17.4]) for adult men (Saad 2018).
- **Page 16, Section 3.3:** Revise: "...however, that the FACT-P is unresponsive to drug or disease effects and that the prostate-specific domain includes items that are more relevant to early stage prostate cancer." to "The FDA noted, **exploratory analyses of patient-reported outcomes indicated apalutamide did not appear to adversely affect functional outcomes as measured by the FACT-P and appeared well-tolerated over the long duration of therapy compared to placebo.**" (CDER 2018, Beaver 2018).
- **Page 18, Section 3.3:** Revise: "Median time to radiographic evidence of disease progression was not reached in a single study of the regimen, although a sensitivity analysis projected time to progression to be approximately 41 months." to "... to be approximately 41 months **in 15 patients.**" (Ryan 2018).
- **Page 19, Section 3.3:** Revise: "...progression was 24 months." to "In the Phase II study of apalutamide, median time to PSA progression, **a secondary study endpoint**, was 24 months." (Smith 2016).

- **Page 19, Section 3.3:** Revise: "In the IMAAGEN study of abiraterone acetate, median time to PSA progression was 28.7 months." to "In the IMAAGEN study of abiraterone acetate **plus prednisone**, median time to PSA progression, **a secondary study endpoint**, was 28.7 months." (Ryan 2018).
- **Page 22: Section 3.3:** MFS is referred to as an imaging-based surrogate outcome, however it is an accepted FDA regulatory endpoint. MFS was the primary endpoint of SPARTAN, the pivotal clinical trial used to support the FDA-approval of apalutamide. The appropriate primary efficacy endpoint to use in trials for study patients with nmCRPC was addressed at 2 meetings of the FDA's Oncology Drugs Advisory Committee. Approval of apalutamide based on MFS established a new regulatory precedent (CDER 2018, Beaver 2018).

LONG-TERM COST EFFECTIVENESS

- **Page 27, Table 4.1:** Revise median diagnosis to randomization time for apalutamide from 7.95 months to **7.95 years** and 7.85 months to **7.85 years** for continued ADT (Smith 2018).
- **Page 37, Table 4.7:** Janssen recommends that cardiovascular-related adverse events (e.g. ischemic heart disease, coronary artery disorders, cardiac arrhythmias) be included as a key harm of interest in this assessment. The 10-year risk of incident atherosclerotic cardiovascular disease in a 70-year old non-Hispanic diabetic white male with risk factors including untreated hypertension and/or dyslipidemia is at least 30% (U.S. HSS 2013). Costs related to monitoring a large population of patients for cardiovascular-related adverse events could include additional clinical assessments during the history and physical examination, specific blood tests, electrocardiograms, and exercise ECG testing (Fihn 2012). The CE model should also include the costs of the potential interventions, that can be costly such as myocardial perfusion imaging, cardiac catheterization with coronary angiography, percutaneous coronary intervention (coronary stents and angioplasties), or coronary bypass surgeries (Fihn 2014). Cost information is available on the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project website (HCUP 2015).
- **Page 37, Table 4.7:** Severe rash for continued ADT in SPARTAN should be 0.3%. Hypertension for continued ADT in SPARTAN should be 11.8% (Smith 2018).
- **Page 39, Section 4.2:** Revise: "...of which 165 (52.5%) received subsequent treatment for mCRPC, and the remainder received no treatment; we assumed similar proportions for enzalutamide patients. For the placebo arm (continued ADT), 279 patients discontinued treatment, of which 161 (77.7%) received subsequent treatment for mCRPC and the remainder received no treatment." to "For the apalutamide arm, 314 patients discontinued initial treatment, of which 165 (52.5%) received subsequent **approved** treatment for metastatic CRPC; we assumed similar proportions for enzalutamide patients. For the placebo arm (continued ADT), 279 patients discontinued treatment, of which **217** (77.7%) received subsequent **approved** treatment for metastatic CRPC." (Supplement to Smith 2018).
- **Page 44, Economic Inputs:** Please use real-world estimates for healthcare resource utilization and costs incurred in the nmCRPC state and the metastatic CRPC state because the costs of these two health states are significantly different with metastatic CRPC costs being exponentially higher than nmCRPC (Li 2017, Valderrama 2017).
- **Page 45-46, Tables 4.16 and 4.17:** Revise <6 months to **≤6 months** (Smith 2018).

POTENTIAL BUDGET IMPACT

- **Page 60, 7.2 Methods:** Regarding the budgetary impact of apalutamide and enzalutamide, we recommend considering only the patient population (patients with nmCRPC with PSADT ≤10 months) for which there is clinical evidence from SPARTAN and PROSPER, respectively (Smith 2018, Hussain 2018). The distribution of PSA doubling time in men with nmCRPC has been reported (Howard 2017).
- **Page 63, Figure 7.1:** We were not able to reproduce budget impact results shown in Figure 7.1. Please consider making the underlying assumptions immediately transparent.

APPENDICES

- **Page 71, Appendix C:** NCT03523338 is one ongoing study for apalutamide in patients with nmCRPC. For information about all ongoing studies for apalutamide, please visit www.clinicaltrials.gov.
- **Page 76, Table D1:** Revise SPARTAN entry in Interventions & Dosing Schedule column: "Apalutamide and placebo were administered orally according to a **continuous daily dosing regimen** until **protocol-defined** progression, adverse events, or withdrawal of consent." (Smith 2018).

REFERENCES

- American Urological Association. Castration-resistant prostate cancer: AUA Guideline. www.auanet.org. Accessed August 6, 2018.
- Beaver JA, Kluetz PG, Pazdur R. Metastasis-free survival-a new end point in prostate cancer trials. *N Engl J Med*. 2018;378(26):2458-2460.
- Center for Drug Evaluation and Research. NDA/BLA Multi-Disciplinary Review and Evaluation (Summary Review, Office Director, Cross Discipline Team Leader Review, Clinical Review, Non-Clinical Review, Statistical Review and Clinical Pharmacology Review) NDA 210951 - ERLEADA (apalutamide) - Reference ID: 4221387. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210951Orig1s000MultidisciplineR.pdf. Published March 19, 2018. Accessed July 23, 2018.
- Data on File. Janssen Biotech, Inc.
- ERLEADA™ (apalutamide) [Prescribing Information]. Horsham, PA: Janssen Products, LP. February 2018. https://www.janssenmd.com/pdf/erleada/erleada_pi.pdf.
- Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;64(18):1929-1949.
- Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60(24):2564–2603.
- Hospital Inpatient National Statistics. Healthcare Cost and Utilization Project (HCUP) [database online]. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2015. <https://hcupnet.ahrq.gov/>. Accessed July 25, 2018.
- Howard LE, Moreira DM, Hoedt AD et al. Thresholds for PSA doubling time in men with non-metastatic castration-resistant prostate cancer. *BJU Int*. 2017;120(5B):E80-E86.
- Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2018;378(26):2465-2474.
- J&J PRD. Clinical Study Report: A multicenter, randomized, double-blind, placebo-controlled, phase III study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer selective prostate AR targeting with ARN-509 (SPARTAN) Protocol ARN-509-003; Phase 3 JNJ-56021927 (apalutamide); 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/rev_210951_arn-509-003_CSR_Redacted.pdf. Updated March 29, 2018, Accessed July 23, 2018.
- Li TT, Shore ND, Mehra M, et al. Impact of subsequent metastases on costs and medical resource use for prostate cancer patients initially diagnosed with localized disease. *Cancer*. 2017;123(18):3591-3601.

Lowrance WT, Murad MH, Oh WK, et al. Castration-Resistant Prostate Cancer: AUA Guideline Amendment 2018. In press. *J Urol* 2018.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]): Prostate Cancer (Version 3.2018). National Comprehensive Cancer Network. www.nccn.org. Published June 21, 2018, Accessed July 23, 2018.

NCCN Drugs and Biologics Compendium[®] Abiraterone Acetate monograph. National Comprehensive Cancer Network (NCCN). www.nccn.org. Accessed July 23, 2018.

Ryan CJ, Crawford ED, Shore ND, et al. The IMAAGEN study: effect of abiraterone acetate and prednisone on prostate-specific antigen and radiographic disease progression in patients with non-metastatic castration-resistant prostate cancer. *J Urol*. 2018;200(2):344-352.

Saad F, Small EJ, Hadaschik BA, et al. Patient-reported outcomes in SPARTAN, a phase 3, double-blind, randomized study of apalutamide plus androgen deprivation therapy (ADT) vs placebo plus ADT in men with nonmetastatic castration-resistant prostate cancer. Poster presented at: the European Association of Urology (EAU) Congress; March 16-20, 2018; Copenhagen, Denmark.

Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418.

Smith MR, Antonarakis ES, Ryan CJ, et al. Phase 2 study of the safety and antitumor activity of apalutamide (ARN-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant prostate cancer cohort. *Eur Urol*. 2016;70(6):963-970.

Supplement to: Smith MR, Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418.

Valderrama A, Tangirala K, Babajanyan S, et al. Treatment, healthcare resource utilization, and costs associated with non-metastatic and metastatic castration-resistant prostate cancer: a claims analysis [abstract]. *J Clin Oncol*. 2017;35(suppl): Abstract e18341.

U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. Evidence Report: Assessing Cardiovascular Risk - Systematic Evidence Review from the Risk Assessment Work Group 2013. <https://www.nhlbi.nih.gov/health-topics/assessing-cardiovascular-risk>. Published November 2013. Accessed July 31, 2018.

XTANDI[®] (enzalutamide) [Prescribing Information]. Northbrook, IL: Astellas Pharma US, Inc. July 2018.

YONSA[®] (abiraterone acetate) [Prescribing Information]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc. May 2018.

ZYTIGA[®] (abiraterone acetate) [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. April 2018. http://www.janssenmd.com/pdf/zytiga/ZYTIGA_PI.pdf.

Sun Pharmaceutical would like to thank ICER for the opportunity to provide input on the Midwest CEPAC draft evidence report on antiandrogen therapies for nonmetastatic castration-resistant prostate cancer.

We believe that descriptions and mentions of Yonsa need to be clearer and more consistent, particularly relative to Zytiga. While it is correct that Yonsa and Zytiga are both formulations of abiraterone acetate, it is important to recognize their differences. They are distinct from each other in three primary ways as described below. Due to these and other differences, the US Food and Drug Administration have determined that Yonsa and Zytiga are not interchangeable, meaning they cannot be substituted for each other without the involvement of a physician.

1. Yonsa is combined with methylprednisolone at 4mg[1]; Zytiga is combined with prednisone at 5mg.[2]
2. Yonsa is administered as a 500 mg dosage[1]; Zytiga is administered at a 1000 mg dosage, though they both have similar absorption.[2]
3. Though outcomes are similar, the better absorption of Yonsa means that Yonsa achieves higher concentrations in the body at a lower dosage than Zytiga.[3]

Given these distinctions, we recommend that ICER incorporate Yonsa in the report in the following ways:

- To the list of interventions of page 3
- In the search terms for the systematic review and in the studies selected on page 11
- To Table 4.8 Drug Costs on page 38 for a WAC per 125mg pill price of \$76.74

References

1. Sun Pharmaceutical Industries. *Highlights of prescribing information* 2018 [cited 2018 July 17,]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210308s000lbl.pdf.
2. Janssen Pharmaceuticals. *Highlights of prescribing information*. 2018 [cited 2018 July 17,]; Available from: <http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ZYTIGA-pi.pdf>.
3. Prescribers' Digital Reference (PDR). *Abiraterone Acetate - Drug Summary*. 2018 [cited 2018 July 17,]; Available from: <http://www.pdr.net/drug-summary/Zytiga-abiraterone-acetate-266.5987>.

To Whom It May Concern:

On behalf of the American Urological Association (AUA) I would like to thank you for the opportunity to review the ICER draft evidence report on *Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer: Effectiveness and Value*. We commend ICER on the development of such a comprehensive document to aid in the improvement of patient outcomes.

Leadership from our Castration-Resistant Prostate Cancer Guideline Panel reviewed the draft report on behalf of AUA and agreed that this is a very impressive document. While a topic so focused in the urologic space would have benefitted from inclusion of a urologic health services representative, the cost effectiveness analysis was extremely rigorous and described by our panel as one of the most impressive documents seen relating to advanced prostate cancer medication. The literature/data review and analysis of key clinical outcomes will surely benefit future research in this space. The development team should also be recognized for the inclusion of quality of life data, which reviewers often ignore in favor of hard outcomes. Such information is both important and interesting, particularly in this patient population.

We would again like to stress the importance of inclusion of a multidisciplinary stakeholder population in order to accurately represent the perspective of those most frequently interacting with the given patient space. This will not only broaden the expertise of the panel but also increase the transparency of a development process that will surely affect such physicians and their patients. To this end, AUA would like to make a formal request to be included as a stakeholder on future documents with significant urologic focus such as this.

Thank you once again for allowing us to comment, and congratulations on the construction of such an important and impactful document.

Sincerely,



David F. Penson
Hamilton and Howd Chair in Urologic Oncology
Professor and Chair, Department of Urologic Surgery
Vanderbilt University Medical Center

August 7, 2018

Steven D. Pearson, MD, MSc
President Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor Boston, MA 02109

Dear Dr. Pearson:

CancerCare, joined by the Men's Health Network, is writing in response to requests for comments on ICER's Draft Evidence Report on treatments for high risk prostate cancer. We represent the voices of millions of cancer patients, survivors, and family members who are challenged each day by the financial burdens associated with cancer and its treatment. In the current environment of rising health care costs and cost shifting, we believe it is essential that the issue of value be focused on what is important to patients, rather than payer and provider priorities. To that end, please consider these concerns:

1. The ICER analysis is derived largely from clinical trial data, with minimal attempt to include real world evidence/data. Randomized Clinical Trials (RCTs) provide limited data, represent only a small segment of the population and do not represent how patients respond to these treatments in the real-world. They don't reflect patients' values and preferences, and are limited to the endpoints measured in the RCT's. In order for the impact to be fairly and accurately assessed, patient and clinical data registries should be examined.
2. While this ICER report includes almost one full page of insights from patients and patient groups, there is little transparency regarding how much of this feedback has been accepted and incorporated into the draft report. ICER should be transparent about the evidence on which its assessments are based.
3. Several variables important to patients, their families and caregivers are not considered in the comparative effectiveness analysis (e.g., potential to significantly reduce caregiver or broader family burden). The Value-Based Price Benchmarks section (#6) is blank and will be included in the revised evidence report released in late August. It remains to be seen if this will adequately incorporate patient priorities. Past experience suggests this might not be, and we hope you will incorporate quality of life outcomes that are truly patient-centric

4. ICER continues to include a budget impact threshold analysis. This arbitrarily establishes budget caps for societal expenditures on medical innovations and fundamentally ignores the value of innovation in healthcare and the value of care provided to individual patients.
5. A health sector and societal perspective are included in this report however the focus remains on drugs. For patients and society as a whole, costs extend much more broadly than this single element of healthcare. ICER analyses should consider the values associated with a broader continuum of care, since the use of drugs never occurs outside of this context.

We appreciate the opportunity to share these concerns with you, and hope that you will adjust your analyses to reflect what is important to patients. After all, each and every one of us stands in the shoes of a cancer patient or caregiver who deserves and is entitled to be treated as an individual, not a population.

Sincerely,

Ellen Miller Sonet

Ellen Miller Sonet, JD, MBA
Chief Strategy and Policy Officer
CancerCare
P: 212-712-8351 Email: esonet@cancerca.org



Headquarters Office:
734 15th Street, NW, Suite 300, Washington DC 20005
202.659.9709 Phone 202.974.7999 Fax 888.793.9355 Toll Free

New York City Office:
165 West 46th Street, Suite 1002, New York, NY, 10036
917.305.1200 Phone 212.967-8717 Fax 888.445.3248 Toll Free

Research & Training Institute:
4100 Chamounix Drive, Fairmount Park, Philadelphia, PA 19131
267.295.3000 Phone 215.883.2580 Fax

August 9, 2018

Steven Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

Re: Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer:
Effectiveness and Value Draft Evidence Report

Dear Dr. Pearson,

On behalf of the Cancer Support Community (CSC), an international nonprofit organization that provides support, education, and hope to cancer patients, survivors, and their loved ones, we appreciate the opportunity to respond to the request for comments regarding the Institute for Clinical and Economic Review's (ICER) Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer: Effectiveness and Value Draft Evidence Report. As the largest direct provider of social and emotional support services for people impacted by cancer, and the largest nonprofit employer of psychosocial oncology professionals in the United States, CSC has a unique understanding of the cancer patient experience. Each year, CSC serves more than one million people affected by cancer through its network of 44 licensed affiliates, more than 120 satellite locations, and a dynamic online community of individuals receiving social support services. Overall, we deliver more than \$40 million in free, personalized services each year to individuals and families affected by cancer nationwide and internationally.

Additionally, CSC is home to the Research and Training Institute—the only entity of its kind focused solely on the experiences of cancer patients and their loved ones. The Research and Training Institute has contributed to the evidence base regarding the cancer patient experience through its Cancer Experience Registry, various publications and peer-reviewed studies on distress screening, and the psychosocial impact of cancer and cancer survivorship. This combination of direct services and research uniquely positions CSC to provide valuable patient- and evidence-informed feedback on value frameworks such as ICER's Value Framework. CSC is pleased to offer the following comments on this Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer: Effectiveness and Value Draft Evidence Report.

Unrealistic Timeframe to Respond

The timeframe to read, consider, and respond to ICER documents continues to pose a challenge to many organizations and individuals who wish to respond. Four weeks to read, analyze, and respond to a document of this complexity is extraordinarily challenging for many individuals and

organizations. We ask that a minimum of 60 days is allowed for comments on any document included in the value assessment process.

Concept of Value

As we have noted in previous comments, it is critical to clearly delineate the differences between the concept of “value” as it pertains to medical treatments and devices, and assessment based primarily on the financial implications of those treatments and devices. ICER identifies the “primary anchor” of the value framework, which is “long-term value for money.” This is bolstered by the complementary perspective of “short-term affordability.” Although cost-effectiveness is a reasonable endpoint in the value discussion, the use of budget impact is inappropriate.

We continue to believe that any value framework cannot be a one-size-fits-all approach and the concept of value must be broader than budget impact and cost containment. Patients make different determinations regarding what they value most throughout their illness and care journeys.

While the short- and long-term financial impacts of drugs and devices are clearly important to consider, there are other aspects of value that are critical to include in any comprehensive “value assessment.” Meaningful patient and stakeholder representation is vital to all institutions determining value, including ICER. It would be helpful for ICER to not only post public comments but also transparently describe how they identify groups and individuals to provide feedback and which groups and individuals provided feedback on the documents and reports.

CSC recommends the following:

1. Limit inclusion of budget impact in the final value assessment, but rather report it as one endpoint.
2. Recognize value beyond 5-year timeline including late and long-term benefits and effects.
3. Allow sufficient time for new therapies to be studied in both clinical and real-world populations before rendering a value assessment.
4. Include and apply weights to user preferences. Ensure that user preferences are appropriately reflected in final assessment.
5. Ensure that outcomes reflect patient experiences and preferences and include value endpoints that are important to patients as reported by patients.
6. Utilize patient registries and survey databases to explore and incorporate patient experience data.
7. Incorporate review and approval from multidisciplinary, disease-specific experts as well as patients who have experienced the disease state under review.

Evidence

As we have noted in previous comment letters, evidence informing ICER’s value assessments cannot be limited solely to clinical and financial impact. The same holds true for evidence from randomized controlled trials (RCTs). RCTs are widely deemed the gold standard of research, allowing for limited bias and increased usefulness in judging clinical effectiveness. However, it

is also not always possible to perform an RCT nor can an RCT encompass all of the available and relevant evidence from various sources. We commend ICER for promulgating a policy on inclusion of grey literature, but this alternative source of information must rise to a minimum of peer-reviewed and published literature which will exclude many sources of legitimate data.

Conway and Clancy (2009) state that “clinicians and patients need to know not only that a treatment works on average but also which interventions work best for specific types of patients.” The National Health Council (2016) outlines “patient-centered data sources” as integral to a patient-centered value model. They note that the value model should incorporate a variety of credible data sources that allow for timely information and account for the diversity of patient populations. This information should come from real-world settings and be reported by patients directly. Patient registries and survey databases could provide opportunities to better understand patient experiences from a wide-range of individuals. While we appreciate ICER’s use of health-related quality of life, we ask that additional patient- defined outcomes be included in the assessment.

Insights Gained from Discussions with Patients and Patient Groups

While we appreciate the inclusion of insights gained from discussions with patients and patient groups, the information provided is limited. We also believe that insights gained from patient experience data should be included in the body of the report and given the same amount of weight as the clinical and economic data.

Patient experience data including quality of life information regarding a host of factors is vital to an assessment regarding prostate cancer treatment. We commend ICER for inclusion of this information particularly regarding psychosocial impacts, fatigue, and financial toxicities. However, as we report below, there are other factors that are important to consider and we urge ICER to review measures and findings which fully capture the patient experience.

In 2017, we learned from our prostate cancer specialty registry that many patients report a substantially worse quality of life than the national average for fatigue (20% of respondents), anxiety (18%), physical functioning (14%), depression (12%), and social functioning (11%). Patients report that treatment is not the only source of stress and that “watching and waiting” can produce elevated levels of worry and anxiety. We found the following factors to be the top concerns across prostate cancer patients in our registry: 1) intimacy, sexual function, and/or fertility; 2) eating and nutrition; 3) exercising and being physically active; 4) worrying about the future and what lies ahead; 5) worrying about family, children, and/or friends; 6) sleep problems; 7) feeling sad or depressed; 8) feeling irritable; 9) moving around (walking, climbing stairs, lifting, etc.); and 10) feeling too tired to do the things they need or want to do.

From our Prostate Cancer Specialty Registry Report (2017), we gained significant insights into the patient experience. These include the following that we believe are important to this report:

- 20% of patients report worse fatigue than the national average
- 38% of patients are at risk for clinical depression

- 51% are concerned about sexual intimacy and function yet 24% said they did not feel comfortable speaking with anyone on their health care team about sexual side effects. Another 65% reported that they did not engage in sexual intercourse
- 50% felt they were not sufficiently knowledgeable about erectile dysfunction prior to treatment
- 51% are concerned about eating and nutrition
- 45% are concerned about exercising and remaining physically active
- While 84% were involved in treatment decision making, only 48% felt fully prepared to make a decision

When selecting a prostate cancer treatment option, we found the following factors as “most important” to patients: 1) higher chance for survival; 2) higher chance for cure; 3) doctor’s recommendation; 4) fewer side effects; 5) high chance to preserve sexual function; 6) higher chance to preserve urinary continence; and 7) family’s recommendation.

We recognize that many men survive prostate cancer, yet the impact on their overall lives and wellbeing can be significant as noted by the 57% of respondents who felt that their lives changed for worse compared to their lives prior to diagnosis. Decisional regret was a theme for the patients who participated in this study.

Potential Other Benefits and Contextual Considerations

While we appreciate ICER’s inclusion of potential other benefits and contextual considerations, it appears after ICER has made its conclusion. While it’s unclear the weight that the considerations had in the conclusion, from an optics perspective, it appears that these considerations are an afterthought rather than a critical component of the overall evidence report. We ask that these considerations be included prior to the conclusion, both in terms of ICER’s process as well as the visual representation in the report.

Voting Questions

We appreciate ICER’s inclusion of “potential other benefits” but ask that they are given the same weight as clinical evidence. We recommend re-titling this section “Patient Experience Evidence and Benefits” and indicating an equal level of importance to clinical evidence. We also ask for clarification and a definition of “reduced complexity” in question 6a. Further, we strongly urge ICER to include sexual dysfunction, urinary continence, and social and emotional health in this section. We also encourage ICER to include a component in this section inquiring whether the intervention meets any current unmet needs for specific populations of prostate cancer patients.

Finally, we seek clarification regarding the scoring process of the draft voting questions. Are certain questions given more weight than others? How is the final determination of value determined and by whom?

We appreciate the opportunity to provide feedback on ICER’s Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer: Effectiveness and Value Draft Evidence Report. Please feel free to contact me at 202.650.5369 or efranklin@cancersupportcommunity.org if you have questions or if we can serve as a resource.

Sincerely,

A handwritten signature in black ink, appearing to read "Elizabeth Franklin". The signature is fluid and cursive, with the first name being more prominent.

Elizabeth Franklin, LGSW, ACSW
Executive Director, Cancer Policy Institute
Cancer Support Community Headquarters

References

Cancer Support Community. (2017). *Prostate cancer specialty registry report 2017*. Retrieved from https://www.cancersupportcommunity.org/sites/default/files/uploads/our-research/2017_Report/the_prostate_specialty_report_7-10.pdf.

Conway, P. H. & Clancy, C. (2009). Comparative-effectiveness research—
Implications of the federal coordinating council's report. *New England Journal of Medicine*, 361, 328-330.

The National Health Council. (2016). *The patient voice in value: The national health council patient-centered value model rubric*. Retrieved from <http://www.nationalhealthcouncil.org/sites/default/files/Value-Rubric.pdf>



August 9, 2018

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Evidence Report “Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer: Effectiveness and Value”

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with life-threatening conditions and chronic diseases for them to have access to vital therapies and services. Access to treatments is a matter of survival for those patients, and a requirement for them to have better and more productive lives. We believe access spans affordability, insurance coverage, and physical access, and one of our main areas of work is analyzing information and publicly communicating those analyses.

We appreciate the opportunity to provide our comments on ICER’s July 12th draft evidence report, “Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer: Effectiveness and Value.” As we’re confident you understand, treatment options for prostate cancer presents patients with a complex array of possibilities. This has led to many shared decision support programs being developed specifically for prostate cancer.ⁱ We point this out at the beginning of our comments to highlight the very personal nature of making treatment decisions for prostate cancer, and the importance of communications and collaboration between a patient and their clinical team.

Our specific patient-focused comments about this draft report are below, organized into sections about Individualized Treatment Approaches for Prostate Cancer and Data Uncertainty; Patient-Oriented Information and Perspectives; and QALYs and Budget Impact Analyses.

Individualized Treatment Approaches for Prostate Cancer and Data Uncertainty

As we stated above, treatment options for prostate cancer are varied, and are based upon many different clinical and patient characteristics.ⁱⁱ Therefore, we believe ICER’s analysis is too narrow and its economic conclusions are too sweeping and general. In addition, the draft evidence report’s reliance on four individual studies spanning three different therapies – with none of the studies including all three therapies – presents a significant degree of uncertainty. For rare or unusual conditions, such a limited data analysis would be understandable, but for a condition as common as prostate cancer, this raises many concerns – particularly since ICER’s literature review found 2,307 publications potentially relevant to the analysis.ⁱⁱⁱ

We also want to highlight the references ICER makes to the increased incidence of and mortality from prostate cancer among African Americans. This is of great concern, and we believe is an area in need of more research. Therefore, we are encouraged that the NIH has recently launched

a new initiative to identify genetic and other markers to better understand the “biological and non-biological factors associated with aggressive prostate cancer in African-American men.”^{iv} The advancement of the factors that predispose to prostate cancer will likely lead to greater understanding of better treatments, as well as greater individualization of therapeutic choices – such as has been done with other cancers based on genetic characteristics of both the tumor and the patient. We encourage this research and urge ICER to structure its analyses, conclusions and recommendations to support that type of research and specific actions of payors and clinicians – rather than continue to conduct overly generalized assessments.

Patient-Oriented Information and Perspectives

We appreciate ICER noting the different measures of patient reported outcomes in the trials they analyzed, (e.g., FACT-P, EQ VAS, and QLQ-PR25), and recognizing that this data is often not considered a primary endpoint in such studies. This is a challenge we hope regulators (including the U.S. Food and Drug Administration) and payers are addressing. Therefore, we would also hope that ICER would seek additional patient reported information – including going beyond the four studies it deemed acceptable for its economic analysis – to provide a more robust assessment of patient perspectives and concerns.

Another area of concern is ICER’s lack of examination of patient’s actual costs. Because approximately 60% of people with prostate cancer are over age 65,^v and thus likely have Medicare for their health insurance coverage, doing subgroup cost modeling that includes patient costs would be very appropriate and useful. This is especially true because unlike most private insurance, Medicare beneficiaries do not have annual out-of-pocket limits unless they are enrolled in a Medicare Advantage plan, have certain Medigap coverage, or if they are also eligible for Medicaid, which may essentially provide them with an annual cost ceiling. In addition, with the Federal Government examining ways to reorganize Medicare’s benefits (e.g., changes to the Medicare Part D benefit structure, and potentially moving some medications from Part B to Part D coverage), this type of sub-group analysis would be both timely and appropriate. Therefore, we believe this aspect of patient perspectives should be explicitly considered at the September 13th Public Meeting and during the voting of the Midwest CEPAC for the question under Potential Other Benefits i.e., “There are additional contextual considerations that should have an important role in judgments of the value of this intervention: _____.” And further, because of the disproportionate impact of prostate cancer for African Americans, we urge the discussion concerning the question as to whether “This intervention will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.”

QALYs and Budget Impact Analyses

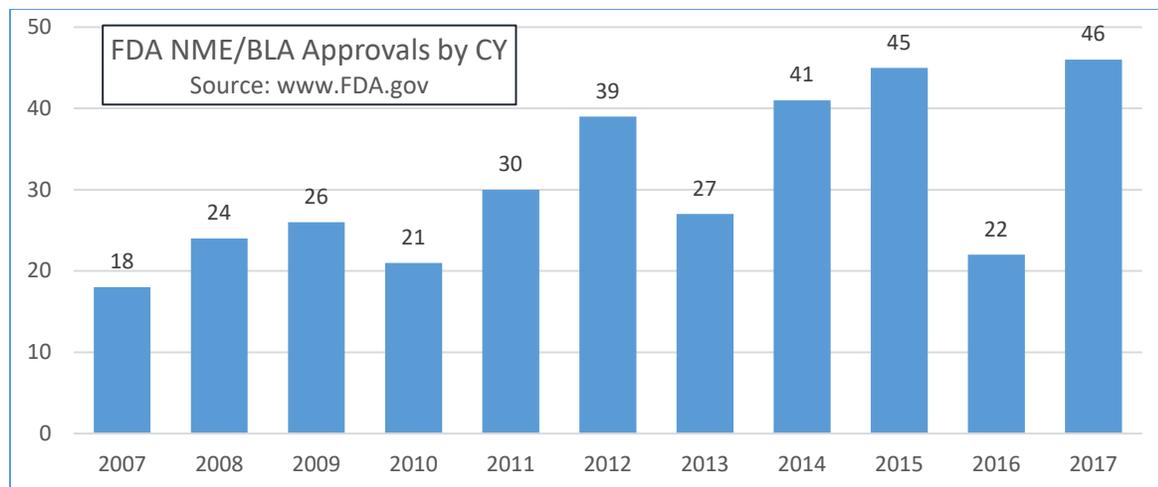
We note that ICER uses a patient population estimate of 59,000 in the budget impact analysis, but we believe that number represents the total population of individuals with nmCRPC, while the clinical trials used for the medicines evaluated looked at a subgroup of those people who had rapidly rising PSA levels, i.e., “the trial population was enriched with patients deemed to have high risk given their PSA doubling time.”^{vi} Therefore, while we recognize that the FDA approved labeling does not restrict the indication to that subgroup, as Beaver et al., noted “The trial population is clearly described in the labeling, so decisions about what PSA doubling time justifies treatment are left to physicians and patients.”^{vii} Therefore, we believe that a more

accurate real-world budget impact analysis would use a number representative of the subgroup from the trials, i.e., a number smaller than the 59,000 used by ICER.

We've previously questioned ICER's use of QALYs and Budget Impact Analysis methodology. For this draft evidence report for some prostate cancer treatments, we note some new wrinkles that we would appreciate ICER explaining:

The budget impact analysis presented in Section 7.3 use three price point options: WAC, Discounted WAC, and \$50,000/QALY, however, in other recent assessments ICER has done it has used the three budget impact points of \$50,000/QALY, \$100,000/QALY and \$150,000/QALY. Excluding those two higher amounts per QALY seems inconsistent with ICER's own framework principles as described in the updated framework document^{viii} that states, "ICER will present information that will allow stakeholders to ascertain the potential budget impact of a new service according to a wide range of assumptions on price and uptake. **Prices modeled in the potential budget impact analysis will include: WAC, estimated net price from SSR data, and prices to achieve cost-effectiveness thresholds of \$50,000, \$100,000, and \$150,000 per QALY.**"^{ix} [emphasis added] We recognize that using those higher QALY thresholds in the budget impact assessment section would reduce the percentage of potential populations eligible to be treated under ICER's budget impact threshold number of \$991 million per year for the entire U.S. health care system, but we believe that for consistency and sake of comparison ICER should be consistent in its methodology.

Another change in this draft evidence report is the inclusion of the number of FDA approvals for 2017, as well as other input data changes announced by ICER^x. As we've previously noted, using a 2-year average for FDA approvals may not be an appropriate reference for ICER's budget impact analyses. As illustrated in the chart below, there is great variability in the number of annual approvals by the FDA. Therefore, we would appreciate ICER explaining why a 2-year average of FDA approval numbers is the right metric for determining a budget threshold amount.



As is obvious to most experts and lay observers, there are benefits of more approvals by the FDA. First, more approvals by the FDA creates more treatment options for patients – whether they are clustered around a few conditions or for a wide variety of illnesses. This is a particularly

important point for prostate cancer because it is estimated there will be about three million people in the U.S. with prostate cancer by 2020, with about 260,000 with localized disease newly diagnosed per year.^{xi} And further, highlighting the need for new treatments for nmCPRC, the authors of the study cited by ICER concluded that “developing interventions for non-metastatic castration-resistant prostate cancer (nmCRPC) should be a priority for clinical research.”^{xii}

And lastly, if there are several approvals of new treatments for the same condition, that helps promote price and other forms of competition that can benefit patients and help reduce overall costs. We note that the rhetoric around such developments has done a complete reversal in the past 20-plus years, i.e., in the 1990s R&D spending by multiple companies to develop treatments for the same condition was criticized as wasteful because it only led to so-called “me-too” medicines. In contrast, the development of multiple medicines in a class – if not specifically those that utilize the same mechanism of action – is now considered crucial for promoting not only more patient choices but market competition to reduce overall costs. It clearly can’t be both wasteful and economically valuable, but in the context of ICER’s budget impact analysis, more drug approvals are treated as an input without regard to whether they are all directed towards different conditions or many compete with each other and thus would not be used simultaneously. Further, ICER’s budget impact process seems to be directed towards a national spending target that is hypothetically under a single organization’s control. Additionally, we note that using the number of FDA approvals as an input is also problematic when more than one newly approval medicine are required to be used together – as was the case this year with the simultaneous approvals of encorafenib and binimetinib for melanoma with specific genetic markers.^{xiii} Will ICER consider that as one approval or two for the purposes of modeling so-called budget impact since they are not indicated for use except with each other in combination therapy?

Additional Notes:

- In Table 4.7 we wonder why fatigue is not included as an adverse event input since that was identified as a common adverse event in table 3.5 and it is certainly a very important aspect of treatment for patients.
- In Table 4.9 the differential duration of therapy seems to be due to the different trials as the source of data. Since that 1.5 months difference is used in ICER’s economic analysis and there seems to be no direct comparator studies to determine if that difference is real or a result of the two different studies structural parameters or patient populations, would it not have been better to use a single number for both – perhaps an average of the two?
- We read with interest the recent NEJM perspectives about Metastasis-Free Survival as a clinical endpoint for evaluating prostate cancer treatments^{xiv} and would appreciate ICER reflecting on those perspectives during the Public Meeting and in its final report.
- Transgender women can develop prostate cancer.^{xv} Therefore rather than use the pronoun men, we believe the report would be more accurate to refer to people, patients, or individuals.

Conclusions & Recommendations

Patients Rising Now believes that ICER's draft report on some treatment options for a subpopulation of people with prostate cancer inadequately reflects patients' perspectives and is also inconsistent with ICER's own practices concerning budget impact analysis.

We believe it is critical that patients' voices be part of defining and assessing the value of their treatment plans along with the cost of all aspects of their care. Without comprehensive evaluations of all treatment options, patients are presented with siloed or fragmented contexts for making decisions, which should include patient's direct out of pocket costs. Because the majority of people with prostate cancer in the U.S. will have Medicare as their primary insurance, the economic analysis from the perspective of individuals covered by Medicare – as well as the Veterans Administration – would be a useful and insightful component that ICER in its uniformed assessment does not do. The U.S. health care system is criticized for many things, but we should not add to the list that it sacrifices quality or specificity of individual care on the altar of uniformity, siloed vision, or illusionary cost-effectiveness calculations masquerading as comprehensive value analyses.

Sincerely,



Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

ⁱ <https://www.ncbi.nlm.nih.gov/pubmed/29473938>, and <https://www.onclive.com/insights/prostate-shared-care/shared-decision-making-for-prostate-cancer>

ⁱⁱ NCCN Guidelines Version 3.2018 Prostate Cancer

ⁱⁱⁱ Draft Evidence Report – Antiandrogens for Nonmetastatic Castration-Resistant Prostate Cancer, p. 11

^{iv} <https://www.nih.gov/news-events/news-releases/nih-prostate-cancer-foundation-launch-large-study-aggressive-prostate-cancer-african-american-men>

^v <https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html>

^{vi} Beaver, JA, et al., Metastasis-free Survival — A New End Point, in Prostate Cancer Trials,” NEJM 6/28/18, p. 2459

^{vii} Ibid.

^{viii} Overview of the ICER value assessment framework and update for 2017-2019.

^{ix} Overview of the ICER value assessment framework and update for 2017-2019, pp 24-25.

^x ICER Value Framework Overview of Conceptual Elements and Procedures Related to Value Assessment Reports and Appraisal Committee Voting at Public Meetings, January, 2018, slide 21.

^{xi} Scher HI, et al., Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS One. 2015;10(10):e0139440

^{xii} Ibid., p. 2

^{xiii} <https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm592464.htm>

^{xiv} Beaver op cit., pp. 2458-60

^{xv} <https://www.ncbi.nlm.nih.gov/pubmed/28882782>, [https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(15\)00439-8/fulltext](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00439-8/fulltext), and <https://prostatecanceruk.org/prostate-information/are-you-at-risk/trans-women-and-prostate-cancer>

August 9, 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: Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer: Effectiveness and Value

Dear Dr. Pearson:

ZERO - The End of Prostate Cancer appreciates the opportunity to provide comments on the Institute for Clinical and Economic Review's (ICER's) draft evidence report for the review of antiandrogen therapies for nonmetastatic castration-resistant prostate cancer (nmCRPC).

ZERO is the leading national nonprofit with the mission to end prostate cancer. We fight to advance research, improve the lives of men and families, and inspire action against a disease that kills a man every 18 minutes. As a key focal point of our mission, ZERO organizes and manages national efforts to protect and grow federal research funding that has led to several key prostate cancer treatments for extending and improving the lives of men, including enzalutamide and abiraterone.

As we stated in our letter dated June 11, 2018, ZERO is concerned over the lack of transparency regarding the engagement of patients, advocacy groups, and caregivers in the review process. While Section 1.1 of the draft report summarizes comments from patients and patient groups, it is unclear to what extent ICER used the patient and patient group feedback in drafting its report. Without explanation, we question whether patient and patient group's input impacted ICER's approach to the report.

Additionally, after reviewing the draft evidence report, ZERO is unconvinced any organization should use the report to make coverage or formulary decisions.

First, we are concerned that ICER is citing "expert opinion" in its evaluation of abiraterone. ICER describes itself as a "non-profit research organization that evaluates medical evidence." As its name implies, expert opinion is not medical evidence. To be clear, ZERO is not making a statement about abiraterone. We are pointing out the inconsistency of an evidence based organization publishing a report that partially relies on expert opinion rather than a strong evidence base.

Main Office/Mid-Atlantic Chapter

515 King Street
Suite 420
Alexandria, VA 22314
202-303-3115

California Chapter

3357 Cahuenga Blvd.
West #44
Los Angeles, CA 90068
213-481-5254

Midwest Chapter

3501 N. Southport Ave.
#485
Chicago, IL 60657
312-561-6629

Texas Chapter

5570 FM 423
Suite 250 – 194
Frisco, TX 75034
469-240-1216

In addition to the above, we are unclear how ICER could include a therapy without a strong evidence base in the non-metastatic castration resistant patient population in its comparative clinical effectiveness evaluation. ICER recognizes the “lack of comparative evidence” and that “not all data available are reassuring that abiraterone acetate is non-inferior to apalutamide and enzalutamide in men with nmCRPC.” Yet, the report provides a B+ rating. Without the evidence, this commentary and rating potentially do a disservice to abiraterone. Perhaps the evidence will show it has a superior net benefit if the authors wait until evidence has been developed. Again, we question the utility of a report that draws conclusions absent of such evidence.

Similarly, one of the two expert reviewers of the ICER report is a lead author of one of the primary studies that ICER evaluated. While we trust his experience and unbiased position, ICER’s utilization of this expert calls in to question the report’s methodology.

Lastly, we believe that ICER has vastly overestimated the population that the U.S. will treat for nmCRPC. For example, as imaging improves clinicians will be able to identify more men as metastatic. These men will not be treated as part of the nmCRPC pie. The rationing of care to only 11% to 30% of the population due to this overestimation is dangerous for patient access to these therapies.

Our conclusion upon reviewing the draft evidence report is that it is of limited utility to insurers in its current form. Due to the subjectivity of expert opinions, assumptions made about comparative effectiveness, and overestimation of the treatment population, a nuanced understanding of the report is required of users of the report. We are concerned that insurers will only look at topline conclusions of the report when making coverage and formulary decisions, which could have a negative impact on patient access.

Thank you for consideration of our comments. We look forward to working with ICER as this process continues to unfold.

In the meantime, please do not hesitate to contact me at Jamie@zerocancer.org or 202-303-3105.

Be Well,



Jamie Bearse
President & CEO
ZERO - The End of Prostate Cancer