INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Antiandrogen Therapies for Nonmetastatic Castration-Resistant Prostate Cancer

Response to Public Comments on the Draft Evidence Report

August 24, 2018

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Manufacturers		
Astellas and Pfizer		
1.	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." 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.	ICER does not provide details on individual patient engagement so as to maintain patient confidentiality. Although stakeholder engagement affected multiple aspects of the review, the discussions of limitations in the data on efficacy in the subgroup of black men, and aspects of Potential Other Benefits and Contextual Consideration were influenced by input from patients and patient groups.
2.	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 SPRATAN clinical trial, was included in the base case. 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. Thus, the analytic team modeled time to symptomatic progression for enzalutamide, but ignored other empirical data on patient-relevant endpoints	In Table 4.2, Key Model Assumptions, we note that patient characteristics across clinical trials were similar, and MFS for the continued ADT arm in the SPARTAN and PROSPER trials were similar. In SPARTAN and PROSPER, hazard ratios for the primary outcome were similar for patients with longer or shorter PSA doubling times, suggesting that PSA doubling time is not an effect modifier. In a scenario analysis, we employed a three-state partitioned survival model that does not differentiate between asymptomatic and

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	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.	symptomatic progression; the results indicate that the inclusion of time to symptomatic progression for all comparators had a small impact on quality of life estimates, no impact on cost or life years, and an unremarkable impact on the antiandrogen ICERs versus continued ADT. For time to chemotherapy, we note that PROSPER studied time to antineoplastic therapy, while SPARTAN studied time to cytotoxic chemotherapy, and that the Kaplan-Meier data for these two different outcomes were quite different, leading us to conclude that the definitions of subsequent treatments were different. Therefore, we used real-world data combined with a timing estimate derived from PROSPER (a similar timing estimate was not available from SPARTAN), and modeled subsequent treatment equivalently for antiandrogens.
3.	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. 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	In SPARTAN and PROSPER, hazard ratios for the primary outcome were similar for patients with longer or shorter PSA doubling times, suggesting that PSA doubling time is not an effect modifier. Viewed in isolation, the median metastasis-free survival estimates between trials do seem to indicate that SPARTAN and PROSPER trials may have enrolled different populations. However, Figure 4.2 of the report clearly shows that the antiandrogen arms and the placebo arms are very closely aligned, particularly over the first three years. Thus, we believe the differences in median MFS are likely due to data censoring, not underlying population differences. Regarding overall survival, we did not model these differently between antiandrogens. We opted to use real-world data due to the current immaturity of overall survival data from the trials. In the model, the proportion of patients who die following metastasis was calculated using a monthly transition probability derived from five-year survival rates for mCRPC from SEER.

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4.	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.	ICER is transparent about which stakeholders, including clinical experts, provided input to ICER, but does not attribute statements to individual experts.
5.	• 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).	We have made revisions in this section to clarify methodology.
6.	• 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.	These statements have been revised to use consistent terminology.
7.	• 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).	We have reviewed the "Harms" discussion in Section 3.3 and think we have clearly differentiated grade 3-5 adverse events from any grade adverse events. However, we have added additional citations to this section to more clearly identify sources of AE data.

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8.	• 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.	While the clinical trials may have included a high-risk population, the prescribing information based on the FDA approval does not indicate a high-risk population among nmCRPC.
Bayer		
1.	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.	Please see Response 1 to Astellas and Pfizer.
2.	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.	Input from patient groups provided information from the caregiver perspective.
3.	In Figure 3.1: 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.	We have expanded the discussion explaining the B+ rating for abiraterone acetate.
4.	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. More recently, the FDA has also published MFS as valid surrogate endpoint in prostate cancer trials. We think citing these studies would provide additional support to the strength of association.	We are uncertain that other data on the association between MFS and OS apply to the particular situation of nmCRPC.
5.	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	We agree that studies looking at this information would be valuable. If new therapies enter this space, it would be valuable for trials to include measures of quality of life and the effects of fatigue on quality of life, and to compare new therapies directly with existing therapies so as to

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	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. 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.	determine whether there are important differences on these patient-important outcomes.
Janssen		
1.	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).	That section of the report says explicitly that apalutamide is not approved for mCRPC.
2.	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).	Thank you, but we discuss the specifics of this issue elsewhere.
3.	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.	Thank you, but we are comfortable with the existing wording.
4.	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	Thank you, but we are comfortable with the existing wording.

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	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.	
5.	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).	We have revised "abiraterone acetate + corticosteroid" to "abiraterone + prednisone."
6.	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).	We have included data related to ischemic heart disease in the "Harms" discussion of Section 3.3.
7.	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	We have revised Section 1.3 to clarify that MFS has been defined differently in individual clinical trials.

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	and/or distant radiographic progression per BICR or 2) death up to 112 days after treatment discontinuation without evidence of radiographic progression (XTANDI PI).	
8.	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).	The section reflects information found thorough a scan of select policies publicly available at the time of report publication.
9.	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)	Thank you, but we are comfortable with the existing wording.
10.	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.	Thank you, but we are comfortable with the existing wording.

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	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.	
11.	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.	We have revised Section 3 to include the specific definitions of MFS from SPARTAN and PROSPER.
12.	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).	Thank you. We have made these corrections.
13.	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)	We have made the suggested changes.
14.	Page 14, Section 3.3: Revise: "…enrolled 51 patients with high-risk nonmetastastic 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 nonmetastastic CRPC. Among the endpoints studied included 12-week PSA response and safety." (Smith 2016).	We have revised the language to read "We also identified a small, single-arm Phase II study of apalutamide + ADT that enrolled 51 patients with high-risk nonmetastatic CRPC. This trial assessed 12-week PSA response as the primary endpoint."
15.	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).	We have changed the citation.
16.	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).	Thank you. We have made these corrections.
17.	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).	Thank you. We have made these corrections.
18.	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	We have changed EQ-VAS to EQ-5D-3L.

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	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).	
19.	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).	Thank you. We reviewed these data and do not think they would materially change our summary of the evidence or conclusions. Our report states "Between baseline and 29 months of follow-up, patients in both treatment groups maintained stable quality of life on both instruments."
20.	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).	We think it is important to highlight the limitations of the FACT-P and have not changed the language noting the FDA's concerns. However, we have included additional language to the discussion to note that exploratory analyses of patient-reported outcomes suggested that apalutamide was well-tolerated and did not appear to adversely affect functional outcomes.
21.	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).	Thank you, but we are comfortable with the existing wording.
22.	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).	Thank you, but we are comfortable with the existing wording.
23.	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).	Thank you, but we are comfortable with the existing wording.
24.	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).	Thank you. We are aware of the FDA guidance on this.
25.	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).	Thank you, we will address this error in the report.

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26.	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).	We have added a cardiovascular adverse event to the model. However, we note that this did not have a meaningful impact on the results.
27.	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).	Thank you, we will address this error in the report.
28.	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).	Thank you, we will address this error in the report.
29.	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).	Metastatic disease treatment costs are based on real-world usage estimates. This was noted in the Assumptions table, but we have now made this more explicit in the "Economic Inputs: Post-Progression Costs" section of the report.
30.	Page 45-46, Tables 4.16 and 4.17: Revise <6 months to ≤6 months (Smith 2018).	We have clarified this in the report, thank you.
31.	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	While the clinical trials may have included a high-risk population, the prescribing information based on the FDA approval does not indicate a high-risk population among nmCRPC. At least initially, it is likely that not

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	distribution of PSA doubling time in men with nmCRPC has been reported (Howard 2017).	all patients with nmCRPC would be treated with antiandrogen therapy. We expect input at the meeting of the Midwest CEPAC on estimating the likely proportion of patients with nmCRPC whom clinicians would want to treat with antiandrogen therapy.
32.	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.	An explanation of our budget impact threshold including sources used to arrive at this threshold have been detailed in the budget impact methods in Section 7.2. Additionally, you can refer to a peer-reviewed publication on this at: www.valueinhealthjournal.com/article/S1098-3015(18)30021-4/pdf
33.	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.	Thank you. NCT03523338 was included in the Draft Evidence Report and was identified through a search of ongoing studies on www.clinicaltrials.gov. Although several studies of apalutamide are currently ongoing, we felt study NCT03523338 most closely represented the study population of interest for our review.
34.	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).	We have made the suggested change to Table D1.
Sun Pharma		
1.	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; Zytiga is combined with prednisone at 5mg. (2) Yonsa is administered as a 500 mg dosage; Zytiga is administered at a 1000 mg dosage, though they both have similar absorption. (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. 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	Thank you. We agree that the way in which Yonsa was included was confusing. We have chosen to explicitly remove Yonsa from the scope of the assessment for reasons of clarity, as now described in that section.

#	Comment	Response/Integration
	• To Table 4.8 Drug Costs on page 38 for a WAC per 125mg pill price of $76.74	
Clinical Societies		
David F. Penson, MD, MPH, Chair of Science and Quality, American Urological Association		
1.	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.	Thank you.
2.	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.	The AUA should have been included as a stakeholder for this report. We apologize for the oversight.
Patient Organizations		
Ellen Miller Sonet, JD, MBA, Chief Strategy and Policy Officer, Cancer*Care* joined by Men's Health Network		
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.	We would very much appreciate high quality real-world evidence on outcomes seen with the treatments under review.
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.	Please see Response 1 to Astellas and Pfizer.
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	We did not find high quality evidence on these outcomes. We agree that they are important.

#	Comment	Response/Integration
	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.	ICER's budget impact threshold serves to alert policy makers when growth of the percentage of health resources allocated to drugs is growing faster than the national economy. Assumptions in our approach when arriving at this threshold favors innovation by assuming that all net health budget impact for drug spending can be allocated to new drugs alone, requiring an assumption that the background spending on existing drugs is net neutral.
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.	The societal perspective accounts for productivity loss costs to patients and their informal care givers.
Elizabeth Franklin, LGSW, ACSW, Executive Director of Cancer Policy Institute, Cancer Support Community		
1.	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.	We understand that the time frame for ICER reports is tight for all involved. However, they are needed to make ICER reports timely while including as much developing evidence as possible.
2.	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.	Please see Response 1 to Astellas and Pfizer.
3.	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)	Thank you for your comments.

#	Comment	Response/Integration
	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.	
4.	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.	ICER is willing to use high quality evidence of the sort suggested. If it is felt that such evidence exists, and we missed it in our systematic review, please make us aware of the evidence so that it can be included.
5.	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.	The information is included in the body of the report and also the executive summary.
6.	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:	Thank you for sharing these insights. We have included several of the findings from the Prostate Cancer Specialty Survey Report 2017 in the "Insights Gained from Discussions with Patients" summary.

#	Comment	Response/Integration
	• 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	
7.	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.	These considerations do not appear after a "conclusion." ICER's value framework includes inputs of comparative effectiveness and cost effectiveness along with potential other benefits and contextual considerations.
8.	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?	The Midwest CEPAC will decide how to weigh various pieces of the value assessment framework when it meets on September 13th and votes on issues of comparative effectiveness and value. Most commonly, reduced complexity has applied to therapies that are easier to administer or are taken less frequently (such as emicizumab compared with bypassing agents for hemophilia A with inhibitors). Sexual dysfunction, urinary incontinence, and social and emotional health are not "potential other benefits" but are typically measured as part of health-related quality of life and thus included in the primary analyses of comparative effectiveness and cost effectiveness.
Terry Wilcox, Co-Founder and Executive Director, Patients Rising Now		
1.	As we stated above, treatment options for prostate cancer are varied, and are based upon many different clinical and patient characteristics. 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	We agree that it is unfortunate that none of the trials directly compared antiandrogen therapies.

#	Comment	Response/Integration
	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.	
2.	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. 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.	We agree that studies examining why some group are at higher risk for more aggressive prostate cancer would be of benefit.
3.	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.	Please Response 1 to Cancer*Care* and Men's Health Network above.
4.	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, 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	We agree that understanding patients' out-of-pocket expenditure serves to understand the direct financial burden of disorders and associated treatments for patients. Our estimate of net price paid to the manufacturer includes patient costs, however, the net price data currently does not allow parsing out patient costs. We are happy to consider any methods or databases that focus on average out-of-pocket expenditure for patients, if available.

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	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."	
5.	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." 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." 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 agree that decisions about what treatment to use lies with the physicians and patients and hence do not want to underestimate the actual size of the population eligible for treatment. We expect input at the meeting of the Midwest CEPAC on estimating the likely proportion of patients with nmCRPC whom clinicians would want to treat with antiandrogen therapy.
6.	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 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." [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	We have included justification (in Section 7.3) for not including the budget impact at the $100,00 and $150,000 per QALY threshold for both drugs.

#	Comment	Response/Integration
	sake of comparison ICER should be consistent in its methodology.	
7.	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 . 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.	We believe that using a one-year timeline would cause too much volatility, while using an average over three years or more might not align with current trends in policy around FDA approvals. We acknowledge that there is variability in the number of approvals, but would also like to point out that health system budgets are finite and do not necessarily increase in line with the annual number of approvals. We continuously monitor approval trends and, based on our observation and analysis of these trends, will consider revisions to this metric in our next value framework update.
8.	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. 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?	Our cost inputs for the budget impact model are sourced from the cost-effectiveness model which takes into account all treatment-related costs, when available. Thus, if a newly approved drug can only be used in combination with another drug, the costs of the second drug are also considered, in both models.
9.	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.	We agree that fatigue is an important issue to patients, however the impacts of fatigue are unlikely to meaningfully alter the results of the model.

#	Comment	Response/Integration
10.	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?	Duration of therapy was reported in the trials, and we consider this to be the best estimate available for each antiandrogen. We recognize there is uncertainty in the "true" treatment duration for each agent, so in sensitivity analyses, uncertainty in time to subsequent treatment calculations is linked to variation of MFS curves.
11.	We read with interest the recent NEJM perspectives about Metastasis-Free Survival as a clinical endpoint for evaluating prostate cancer treatments and would appreciate ICER reflecting on those perspectives during the Public Meeting and in its final report.	Thank you. We agree this is an important issue.
12.	Transgender women can develop prostate cancer. Therefore, rather than use the pronoun men, we believe the report would be more accurate to refer to people, patients, or individuals.	Thank you. We are generally referring to sex rather than gender in this report, and have the added concern that transgender women may have been taking hormonal therapies that would make it uncertain whether results from the clinical trials of antiandrogens could be generalized. We have chosen not to change the wordings in the Evidence Report, but will seek additional input prior to the Final Report with dual goals of being clear and inclusive.
Jamie Bearse, President and CEO, Zero – The End of Prostate Cancer		
1.	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	Please see Response 1 to Astellas and Pfizer above.
2.	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.	The report refers to expert opinion on an issue not assessed by the report: the comparability of abiraterone acetate and enzalutamide in mCRPC.
3.	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	Please see Response 3 to Bayer above.

#	Comment	Response/Integration
	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	
4.	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.	ICER reviewers are not required to be free of conflicts of interest. The authors of the paper, including the lead evidence author, are free of such conflicts.
5.	Lastly, we believe that ICER has vastly overestimated the population that the US 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.	While the clinical trials may have included a high-risk population, the prescribing information based on the FDA approval does not indicate a high-risk population among nmCRPC. At least initially, it is likely that not all patients with nmCRPC would be treated with antiandrogen therapy. We expect input at the meeting of the Midwest CEPAC on estimating the likely proportion of patients with nmCRPC whom clinicians would want to treat with antiandrogen therapy.
6.	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.	We agree that readers of ICER's reports should attend to the details. We try in the summary sections to highlight the most important issues for all stakeholders.