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

Final Evidence Report

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David Rind served as the lead author for the report. Patricia Synnott led the systematic review and authorship of the comparative clinical effectiveness section. Varun Kumar was responsible for oversight of the cost-effectiveness analyses and developed the budget impact model. Erin Lawler authored the section on coverage policies and clinical guidelines. Dan Ollendorf and Steve Pearson provided methodologic guidance on the clinical and economic evaluations. The role of the University of Washington (UW) modeling group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of UW. ICER would also like to thank Ellie Adair, Laura Cianciolo, Geri Cramer, Ariel Jurmain, Shelly Kelly, Sonya Khan, Aqsa Mugal, Madeline O'Grady, and Matt Seidner for their contributions to this report. None of the authors above disclosed any conflicts of interest.

About ICER

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The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The Midwest CEPAC is an independent committee of medical evidence experts from across the Midwest, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about Midwest CEPAC is available at https://icer-review.org/programs/midwest-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/prostate-cancer-stakeholder-list/.

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List of Acronyms Used in this Report

ADT	Androgen deprivation therapy
AE	Adverse event
AUA	American Urological Association
BPI-SF	Brief Pain Inventory—Short Form
CRPC	Castration-resistant prostate cancer
EQ VAS	European Quality of Life Visual Analog Scale
EQ-5D-3L	European Quality of Life-5 Dimensions-3 Level Questionnaire
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Level Questionnaire
FACT-P	Functional Assessment of Cancer Therapy—Prostate
FDA	US Food and Drug Administration
GnRH	Gonadotropin releasing hormone
HR	Hazard ratio
ICERs	Incremental cost-effectiveness ratios
mCRPC	Metastatic castration-resistant prostate cancer
MFS	Metastasis-free survival
NCCN	National Comprehensive Cancer Network
nmCRPC	Nonmetastatic castration-resistant prostate cancer
PFS	Progression-free survival
PSA	Prostate specific antigen
QALY	Quality-adjusted life year
QLQ-PR25	Quality of Life Questionnaire—Prostate
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
USPSTF	United States Preventive Services Task Force
WAC	Wholesale acquisition cost

Executive Summary

Background

Prostate cancer is the second most common cause of cancer death among men in the US (after lung cancer).[1] Estimates suggest that in 2018, approximately 165,000 new cases of prostate cancer will be diagnosed, and approximately 30,000 will die from prostate cancer.[1] Prostate cancer disproportionately affects black men, with an incidence rate that is approximately 60% higher and a mortality rate that is approximately 110% higher than the overall rates in US men.[2]

Prostate cancers are generally responsive to androgens and, at least initially, typically respond to androgen deprivation therapy (ADT).[3] ADT involves medical or surgical castration. Medications used for ADT include gonadotropin releasing hormone (GnRH) agonists, such as leuprolide, goserelin, and triptorelin,[4] and GnRH antagonists, such as degarelix.[5]

ADT is used in a number of clinical settings.[6] Prostate cancer that has not been treated with ADT or that is responding to ADT is called "castration sensitive". Over time, most cancers that were castration sensitive become castration resistant. Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that progresses clinically, radiographically, or biochemically despite ADT that has achieved low (castrate) levels of serum testosterone.[6]

Patients with metastatic disease by conventional imaging (e.g., CT, bone scan, MRI) who progress on ADT or who develop metastatic disease on ADT benefit from treatment with antiandrogen therapies, with improvement in overall survival.[3] Antiandrogens include abiraterone acetate (Zytiga®; Janssen Biotech, Inc. and Yonsa®; Sun Pharma, Inc.), enzalutamide (Xtandi®; Astellas Pharma, Inc.), and apalutamide (Erleada™; Janssen Biotech, Inc.). Abiraterone is an androgen biosynthesis inhibitor and must be administered with corticosteroids.[3,7-9] Enzalutamide and apalutamide are androgen receptor inhibitors that bind to the ligand-binding domain of the androgen receptor.[10,11] Apalutamide is not FDA-approved for metastatic CRPC (mCRPC).

The management of patients without metastatic disease by conventional imaging who progress on ADT (nonmetastatic castration-resistant prostate cancer; nmCRPC) has been less clear; progression typically involves increases in the biochemical marker prostate specific antigen (PSA). Until recently, such patients were most often managed with continued ADT and surveillance for the development of metastases. More recently, apalutamide and enzalutamide have been evaluated in placebo-controlled randomized trials in patients with high risk (as defined by rate of increase in PSA) nmCRPC. In 2018, National Comprehensive Cancer Network (NCCN) guidelines were updated to suggest apalutamide, enzalutamide, or other antiandrogen therapies in men with nmCRPC, particularly with rapid increases in PSA,[6] and American Urological Association guidelines were

updated to recommend offering apalutamide or enzalutamide to men with nmCRPC at high risk of developing metastatic disease.[12] Apalutamide was approved in February 2018 by the US FDA for treatment of nmCRPC,[13] and the label for enzalutamide was broadened to include this same indication in July of 2018.[14] 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. A Phase II trial suggested efficacy in this population,[15] and a trial comparing abiraterone acetate and enzalutamide in both mCRPC and nmCRPC is under way.[16]

Insights Gained from Discussions with Patients and Patient Groups

Patients and patient groups stressed the serious risks of morbidity and mortality in men with CRPC and how this affects men and their families, the psychological effects of prostate cancer on a man's sense of self, the substantial side effects of therapies for prostate cancer, and the sense that burdensome therapy has failed when PSA levels begin to rise leading some to question their prior decisions about therapy.

In a 2017 survey report from the Cancer Support Community, 49 patients rated the following factors to be among the "most important" considerations when selecting a treatment for their prostate cancer: higher chance for survival (27%), higher chance for cure (20%), recommendations from a doctor (16%), and fewer side effects (14%).[17]

In our discussions with patient groups, we heard that the tolerability of ADT and antiandrogen therapies is highly variable from person to person. Fatigue was called out as a particularly common substantial side effect of apalutamide and enzalutamide.

Patient groups and clinicians stressed the psychological benefits of having a therapeutic course of action available in the face of PSA evidence of progression, in contrast to the difficulties of waiting for the development of detectable metastases. The connection was made between this and the overall value of hope in patients with a life-threatening disease.

Patient groups also stressed the important financial toxicities of therapies for prostate cancer and reported that some men choose to forgo such therapies because of this. In the survey cited above, more than 50% of respondents reported having monthly prostate cancer-related out-of-pocket costs of more than $100, with 25% of respondents reporting over $500 of out-of-pocket costs per month; these figures were broadly consistent with those reported in a larger survey (n=1,252) of cancer survivors.[17,18]

We also heard about the disproportionate effects of prostate cancer on black men in the US. These include the higher incidence and mortality rates described above, but financial toxicity and its effects on choices about undergoing and adhering to therapies may also be greater in black men.

We also heard from patient groups that, not surprisingly, the use of the term "castration" in discussions of treatments (e.g., "medical castration") and stages (e.g., "castration-resistant") of prostate cancer creates issues for patients who are already dealing with a serious illness. Despite this, because it is the standard language used in oncology and the research literature, we have chosen to use the word throughout this report. However, we wish to acknowledge the issues this creates and the potential future need for alternative terminology that men with prostate cancer would find more acceptable.

ICER looks forward to continued engagement with stakeholders throughout its review.

Potential Cost-Saving Measures in Prostate Cancer

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). During stakeholder engagement and public comment periods, ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for men with prostate cancer that could be reduced, eliminated, or made more efficient.

The American Board of Internal Medicine's Choosing Wisely® campaign encourages specialty societies to identify areas of low-value care that could be reduced or eliminated. Recommendations from the American Urological Association (AUA) and other clinical societies include limiting treatment of men with low-risk localized prostate cancer without discussing active surveillance as part of the shared-decision-making process.[19]

Comparative Clinical Effectiveness

Our literature search identified 2,307 potentially relevant references, of which six references (four publications, one conference presentation, and one FDA Multidisciplinary Review packet) relating to four individual studies met our inclusion criteria.

Two of the four selected studies were Phase III randomized controlled trials (RCTs) of apalutamide and enzalutamide, respectively;[11,20] the remaining two studies were single-arm Phase II clinical studies of apalutamide and abiraterone acetate.[21,22]

Although metastatic castration-resistant prostate cancer was not of focus for this review, there have been several good-quality placebo-controlled trials of enzalutamide and abiraterone acetate conducted in this population (Appendix Table D2).[10,23-25] We report survival and safety data from these trials in order to supplement the sparse evidence identified through our literature search and provide additional efficacy evidence on these agents.

Clinical Benefits

Apalutamide

Mature overall survival data are not yet available; however, available data suggest a trend toward longer survival with apalutamide. Time to symptomatic progression was prolonged by apalutamide, as was the primary outcome of metastasis-free survival (MFS). Clinical benefits were observed across all subgroups of interest. Quality of life scores remained stable during the Phase III SPARTAN trial with no notable differences between treatment groups.

Evidence on apalutamide was primarily derived from the Phase III SPARTAN trial.[11] This study was a multinational trial that randomized 1207 men with nonmetastatic castration-resistant prostate cancer and a prostate-specific doubling time of 10 months or less to apalutamide (n=806) or placebo (n=401); all patients continued to receive background ADT.

Overall Survival

In an interim analysis of the SPARTAN trial, the median overall survival was not reached in the apalutamide group, while the placebo group had a median survival of 39 months.[11] The hazard ratio for overall survival was 0.70 (95% CI 0.47 to 1.04).

Disease Progression

The primary endpoint of the SPARTAN trial was MFS. At final analysis, the median MFS was 40.5 months in the apalutamide group and 16.2 months in the placebo group (HR 0.28; 95% CI 0.23 to 0.35; p<0.001).[11] Time to symptomatic progression was also longer with apalutamide (HR 0.45; 95% CI 0.32 to 0.63) and there were improvements in PFS and PSA progression.

Health-Related Quality of Life

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-3 Levels (EQ-5D-3L) questionnaire. Between baseline and 29 months of follow-up, patients in both treatment groups maintained stable quality of life on both instruments.[11]{Saad, 2018, 862}

Enzalutamide

Mature overall survival data are not yet available; however, available data suggest a trend toward longer survival with enzalutamide. Data on symptomatic progression have not been reported; the primary outcome of MFS was longer in those taking enzalutamide. Patient-reported outcomes showed no significant differences in quality of life between treatment groups.

Evidence on enzalutamide was primarily derived from the PROSPER trial.[20] This study was a placebo-controlled multinational Phase III trial that randomized 1401 men with nonmetastatic castration-resistant prostate cancer and a rapidly rising PSA to enzalutamide (n=933) or placebo (n=468); all patients continued to receive background ADT.

Overall Survival

Median overall survival was not reached in the PROSPER trial's first interim analysis.[20] At the time of data cutoff, the hazard ratio for survival was 0.80 (95% CI 0.58 to 1.09; p=0.1519).

Although not a population of focus for this review, a survival benefit with enzalutamide has been observed in patients with metastatic castration-resistant prostate cancer, both in chemotherapy-naïve patients[26] and in patients previously treated with chemotherapy.[23]

Disease Progression

The PROSPER trial evaluated MFS as a primary endpoint. Final analyses showed a median MFS of 36.6 months (95% CI 33.1 to NR) for the enzalutamide arm versus 14.7 months (95% CI 14.2 to 15.0) for the placebo arm; the difference was statistically significant with a hazard ratio of 0.29 (95% CI 0.24 to 0.35; p<0.0001).[20]

Progression events occurred in 219 (23%) of the enzalutamide-treated patients, of which 187 (85%) were due to progression and 32 (15%) were attributed to death without documented radiographic progression. In the placebo arm, progression events occurred in 228 (49%) patients, of which all but 4 (2%) were attributed to radiographic progression. The lower proportion of deaths in the placebo group was likely due to more rapid disease progression. Enzalutamide also significantly delayed PSA progression.

We did not identify any data related to symptomatic progression or progression-free survival from the PROSPER trial.

Health-Related Quality of Life

The PROSPER trial assessed health-related quality of life and pain using several instruments. No statistically significant or clinically meaningful differences between the enzalutamide and placebo arms have been reported.[20,27]

Abiraterone Acetate

Overall survival with abiraterone acetate + prednisone has not been evaluated in patients with nonmetastatic castration-resistant prostate cancer. 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. We did not identify any quality of life data for abiraterone acetate + prednisone in the population of focus. We are uncertain whether the efficacy of abiraterone acetate in men with nmCRPC is comparable to the efficacy of apalutamide and enzalutamide.

Our review of abiraterone acetate + prednisone was primarily informed by the IMAAGEN trial.[22] This single-arm Phase II study evaluated abiraterone acetate + prednisone in 131 patients with high-risk nonmetastatic prostate cancer. The trial's primary endpoint was the proportion of patients achieving at least a 50% reduction in PSA during six cycles of therapy (treatment cycles were 28 days in duration).

We chose not to include Yonsa®, the newly approved formulation of abiraterone acetate which has bioavailability differences from Zytiga®, is administered with methylprednisolone, and for which there are no published trial data in patients with prostate cancer. This decision was made to simplify the discussion in the report, given the absence of additional outcomes data to inform any evaluations. This decision should not be taken to mean that ICER believes that different formulations of abiraterone acetate have different clinical effects.

Overall Survival

Overall survival was not assessed in the Phase II IMAAGEN trial. Although not a population of focus for this review, a survival benefit with abiraterone acetate has been observed in patients with metastatic castration-resistant prostate cancer, both in chemotherapy-naïve patients[28] and in patients previously treated with chemotherapy.[25]

Disease Progression

In the IMAAGEN trial, 31 (23.7%) patients had confirmed radiographic evidence of disease progression.[22] Median time to radiographic evidence of disease progression was not reached, however a sensitivity analysis that included 15 unconfirmed progressions estimated median time to progression to be 41.4 months (95% CI 27.6 to NE). The median time to PSA progression was 28.7 months (95% CI 21.2 to 38.2).

Health-Related Quality of Life

Health-related quality of life was not evaluated in the IMAAGEN trial.

Comparing Abiraterone Acetate to Apalutamide and Enzalutamide

As noted, we have limited evidence on the efficacy of abiraterone acetate in patients with nmCRPC that would allow us to judge the efficacy of this agent relative to apalutamide and enzalutamide, and differences in trial populations and study designs precluded formal quantitative comparisons.

In randomized trials in men with **mCRPC** who had or had not received prior chemotherapy, treatment with enzalutamide and abiraterone acetate had similar reductions in mortality compared with placebo (HR 0.77 and HR 0.81 in chemotherapy-naïve, respectively; HR 0.63 and 0.65 in chemotherapy-experienced, respectively).[23,25,26,28] In single arm studies of apalutamide and abiraterone acetate in men with **nmCRPC**, median times to PSA progression were also similar (24 months and 28.7 months, respectively).[21,22]

While these suggest that the effects of abiraterone acetate are similar to those of other antiandrogen therapies in men with nmCRPC, not all data support this hypothesis. In the randomized trials in men with nmCRPC (SPARTAN and PROSPER), the median time to PSA progression with apalutamide was not reached and with enzalutamide was 37.2 months.[11,29] These appear longer than the time discussed above with abiraterone acetate (28.7 months) and could reflect differences in study design, random statistical variation, or true differences in efficacy.[30]

Although we think there is reason to believe that treatment with abiraterone acetate + prednisone in men with nmCRPC achieves similar outcomes to treatment with apalutamide or enzalutamide, the above results create sufficient uncertainty that we chose not to model the use of abiraterone acetate in the economic analyses described in Section 4.

Harms

Despite spending a longer time on study therapy, rates of serious adverse events with apalutamide and enzalutamide + ADT were similar to those reported in patients taking placebo + ADT. There may be an increased risk for falls, fractures, and ischemic heart disease with apalutamide and enzalutamide. Patients taking abiraterone acetate should be monitored for mineralocorticoid excess, adrenocortical insufficiency, and hepatoxicity. Fatigue is common with all three agents.

Adverse event (AE) frequencies and rates of Grade 3-4 (severe and life-threatening) events are reported by regimen in Table ES1.

Table ES1. Adverse Events of Apalutamide, Enzalutamide, and Abiraterone Acetate

	Apalutamide[11,31,32] (%)		Enzalutamide[10,29,33] (%)		Abiraterone acetate[22,34] (%)	
Median Duration of Treatment	16.9 months		18.4 months		22.1 months	
Grade ≥3 AEs	45		31		57	
SAEs	25		24		44	
AEs Leading to Discontinuation	11		9		15	
AEs Associated with Death	1		3		5	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fracture	12	3	10	2	NR	NR
Falls	16	2	11	1	6†	0†
Fatigue	30	1	33	3	40	1
Ischemic Heart Disease	4	1	3	1	NR	NR
Hypertension	25	14	12	5	42	24
Rash	24	5	NR	NR	8‡	0‡
Hypothyroidism	8	0	NR	0*	NR	NR
Seizure	<1	0	<1	<1	NR	NR
Hypokalemia	NR	NR	NR	NR	34	7
Peripheral Edema	11	0	12*	<1*	25	2

AEs: adverse events, NR: not reported, SAE: serious adverse event

*safety data from the PREVAIL trial from Beer et al. (2014). Other enzalutamide data reported from PROSPER trial.

†safety data from the COU-AA-302 trial from Ryan et al. (2013)

Controversies and Uncertainties

Men with mCRPC are treated with antiandrogen therapy.[6] Although not defined as metastatic disease, rising PSA levels are a marker for disease progression and likely micrometastases. As such, the treatment strategy evaluated in this report essentially involves using the same medications that would be given for mCRPC at an earlier stage of disease progression. Antiandrogen medications have important side effects. Thus, their use earlier in disease management must demonstrate improvements in patient-important outcomes such as survival and quality of life, and not simply an imaging-based surrogate outcome such as MFS. The current trials showed no improvements in quality of life, and survival data are immature such that only trends toward improved survival have been demonstrated to date. However, time to symptomatic progression is a patient-important outcome, and apalutamide showed a clear benefit. Additionally, an analysis presented at the 2018 Annual Meeting of the American Society of Clinical Oncology concluded that MFS is positively correlated with overall survival in patients with high-risk, nonmetastatic castration-resistant prostate cancer.[35]

The FDA indications for apalutamide and enzalutamide do not limit their use to high-risk patients alone, although only men with a PSA doubling time of 10 months or less were eligible for the

SPARTAN and PROSPER trials. The benefit provided by early treatment with antiandrogens in men with longer PSA doubling times remains uncertain.

Black men were underrepresented in the SPARTAN trial of apalutamide and PROSPER trial of enzalutamide, accounting for just 6% and 2% of participants, respectively. As noted in Section 1 of this report, African Americans have an incidence of prostate cancer that is 60% higher and a mortality rate that is approximately 110% higher than the overall rates in US men.[2] In the SPARTAN trial, the point estimate for the hazard ratio for MFS among African American men was somewhat higher (0.63 [95% CI 0.23 to 1.72] vs. 0.28 [95% CI 0.23 to 0.35] for the entire group), although given the small sample size and wide confidence interval, we cannot determine whether apalutamide has a differential effect on black men.[11] We did not identify any data related to outcomes in this subgroup from the PROSPER trial. In the single-arm IMAAGEN study of abiraterone acetate, 19 patients (14.5%) were black, and the times to PSA progression and radiographic progression were similar among black and non-black men.[22] Additional data demonstrating the generalizability of the randomized trial results to the subgroup of black men would be helpful.

Finally, head-to-head studies of the therapies of interest have not been performed and there are insufficient data available to indirectly compare these regimens using network meta-analysis. While we heard from clinical experts that abiraterone acetate and enzalutamide have comparable effectiveness in metastatic castration-resistant prostate cancer, it is difficult to determine how these agents compare in the nonmetastatic population without more robust, comparative data. Thus, the comparative effectiveness of the antiandrogens relative to each other cannot be determined at this time.

Summary and Comment

Apalutamide

Compared to ADT alone, apalutamide led to statistically significant delays in disease progression. Although overall survival data are not yet mature, interim analyses indicate a trend toward improved survival. Apalutamide prolonged time to symptomatic progression and improved median MFS by more than two years (24.3 months). The therapy was well-tolerated, and quality of life remained stable for the duration of the SPARTAN trial. In men with nmCRPC and a rapid PSA doubling time (≤10 months), we have high certainty that apalutamide + ADT provides a substantial net health benefit compared with ADT alone ("A").

Enzalutamide

Evidence from the PROSPER trial indicate that enzalutamide delays disease progression. Although overall survival data are preliminary and not yet mature, there was also a trend toward improved survival. Data are not available on symptomatic progression, but median MFS was prolonged

substantially. The side effect profile of enzalutamide is relatively tolerable and does not appear to negatively affect quality of life. Given the evidence that MFS is correlated with overall survival,[35] and the similar results in SPARTAN and PROSPER, in men with nmCRPC and a rapid PSA doubling time (≤10 months), we have high certainty that enzalutamide + ADT provides a substantial net health benefit compared with ADT alone ("A").

Abiraterone Acetate + Prednisone

Due to the lack of direct comparative evidence, we have less certainty of the net health benefit of abiraterone acetate + prednisone. As discussed in detail above, evidence suggests that treatment outcomes with abiraterone acetate and enzalutamide are similar in men with mCRPC, however not all data available are reassuring that abiraterone acetate is non-inferior to apalutamide and enzalutamide in men with nmCRPC. Despite this, mean time to PSA progression in the IMAAGEN trial (28.7 months)[22] was much longer than the times seen for PSA progression in the placebo arms of the SPARTAN and PROSPER trials (3.7 and 3.9 months, respectively).[20,21] As such, in men with nmCRPC and a rapid PSA doubling time (≤10 months), compared with ADT alone, we have moderate certainty that abiraterone acetate + ADT provides a small or substantial net health benefit and high certainty of at least a small net health benefit ("B+").

Comparisons Among the Agents

In the absence of head-to-head comparisons, we have insufficient data ("I") to conclude that the net health benefit of any of the three antiandrogens evaluated in men with nmCRPC is superior/inferior to either of the other two antiandrogens.

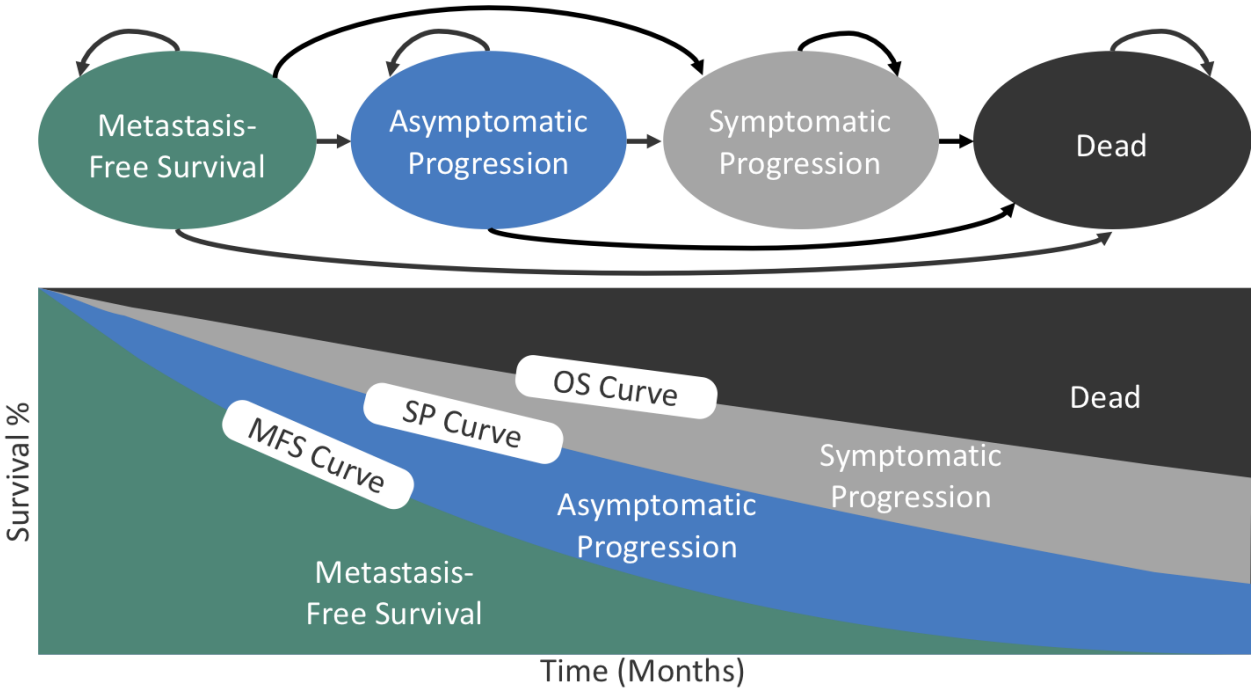
Long-Term Cost Effectiveness

We conducted an economic evaluation to estimate the cost-effectiveness of antiandrogen therapies as first-line treatment in adult men diagnosed with nmCRPC who have a rapidly rising PSA (doubling time of 10 months or less), from a US health sector perspective. Costs and outcomes in the model were discounted at 3% annually, and the model had one-month cycle lengths and was run for a lifetime horizon.

Our model compared (1) apalutamide (Erleada™; Janssen Biotech, Inc.) plus ADT or (2) enzalutamide (Xtandi®; Astellas Pharma, Inc. and Pfizer, Inc.) plus ADT to continued ADT alone. Our *de novo* model comprised four health states; metastasis-free survival (MFS), asymptomatic progression (PSA doubling time ≤10 months but not experiencing other symptoms), symptomatic progression, and death (Figure ES1). Using a hybrid approach, we combined a partitioned survival modeling approach to transition patients among MFS, asymptomatic progression and symptomatic

progression health states, with a Markov modeling approach to transition patients from metastatic CRPC (mCRPC) to death.

Figure ES1. Model Framework



Time to symptomatic progression was not a trial outcome in PROSPER.[20] To accommodate the four health state model structure, we estimated an enzalutamide "time to symptomatic progression" hazard ratio versus continued ADT based on PROSPER trial outcomes and the observed differences between apalutamide and continued ADT from the SPARTAN trial.[11] Overall survival was modeled using a combination of trial-reported outcomes and real-world 5-year survival data for mCRPC from the Surveillance, Epidemiology, and End Results (SEER) Program.[36] A complete list of model choices and assumptions along with respective rationales can be found in section 4.2 of this report.

Each antiandrogen regimen was administered within the metastasis-free survival health state, and treatment duration was based on trial-reported median durations of therapy. Treatment regimen post-progression was based on recently published real world data (Appendix Table E3).[37,38] We obtained the average discount from WAC to achieve net price for enzalutamide and abiraterone acetate from the SSR Health database, and applied this discount to the most recent WAC for these drugs to arrive at a net price. Apalutamide was only recently approved by the FDA and hence no data on discounts for the drug exists in the SSR database. We hence applied the enzalutamide's discount (29%) to apalutamide's WAC to arrive at its net price

Health state utilities were sourced from published literature, with MFS-related utilities being sourced from a Canadian-cost-effectiveness analysis of PSA-based screening. Utilities for symptomatic and asymptomatic disease were sourced from a U.K.-specific questionnaire administered to men with mCRPC.[39] The EQ-5D-5L utilities stratified by prostate cancer disease states from this study were selected for our model. We also included disutilities associated with fracture in this population. We also modeled adverse events (AE) occurring in >5% and attributed relevant costs and disutilities of these AEs.

Details regarding inputs, model assumptions and their rationale, sensitivity analyses, and scenario analyses are available in Section 4 of the report.

Base-Case Results

Apalutamide and enzalutamide resulted in increased life years, increased QALYs, increased time in MFS and asymptomatic progression, and increased costs compared to continued ADT. The gain in QALYs for antiandrogens was approximately 1.5 years, driven primarily by gains in time spent in MFS compared to continued ADT. Although antiandrogens increased treatment costs prior to metastasis, the delay of metastasis compared to continued ADT alone resulted in a savings in post-progression treatment costs.

Table ES2. Base-Case Results for Antiandrogen Therapies Compared to ADT

Treatment	Drug Cost (nmCRPC)	Post-Progression Treatment Costs	Total Cost	Life Years	QALYs	ICER vs. continued ADT
Continued ADT	$4,500	$427,000	$475,000	6.77	5.51	
Apalutamide + ADT	$195,000	$342,000	$583,000	8.45	7.10	$68,000
Enzalutamide + ADT	$209,000	$345,000	$601,000	8.40	7.01	$84,000

QALYs: quality-adjusted life years, ICER: incremental cost-effectiveness ratio
Costs are rounded to the nearest $1,000; total costs include drug costs.

Sensitivity and Scenario Analyses

Results from our one-way sensitivity analyses shows that the parameters with the greatest impact on incremental cost-effectiveness ratios were duration of therapy, the cost of the antiandrogen, time to subsequent therapy, utility for MFS, and effectiveness of therapy.

Results from our probabilistic analysis showed that for both antiandrogens only a small percentage of all simulations fell below the $50,000 per QALY cost-effectiveness threshold, while over 80% and nearly 100% of simulations for enzalutamide and apalutamide respectively fell below the $100,000 per QALY cost-effectiveness threshold.

Including patient and caregiver productivity costs in the modified societal perspective analysis increased the total expected costs in all strategies and did not have a substantial impact on the incremental cost-effectiveness ratios.

Based on concerns raised by clinical experts and members of the Midwest CEPAC at the Public Meeting, we conducted a scenario analysis in which duration of treatment was based on duration of MFS. In this scenario analysis, the incremental cost-effectiveness ratios of both apalutamide and enzalutamide exceeded $150,000 per QALY. Longer term data on duration of treatment should clarify the true cost-effectiveness of these therapies.

Threshold Analyses

The unit prices at which antiandrogens would reach cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained are presented below.

Table ES3. Threshold Analysis Results

	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY
Apalutamide + ADT	$11,079	$7,866	$6,638	$10,014	13,391
Enzalutamide + ADT	$11,065	$7,847	$5,685	$8,895	$12,105

ADT: androgen deprivation therapy, QALY: quality-adjusted life year

*WAC prices for the two investigational drugs were not available as of the date of this report.

Summary and Comment

Our analysis indicates that the long-term cost-effectiveness of apalutamide and enzalutamide, compared to continued ADT without antiandrogen therapy, in patients with nmCRPC fell below $100,000 per QALY gained. The findings remained robust in most sensitivity and scenario analyses. While the antiandrogens are also indicated for treatment in the mCRPC population, our evaluation did not consider the long-term value of these therapies in the mCRPC population. Our results are to be interpreted as reflecting value when used early in the disease path for CRPC, in the non-metastatic phase of disease.

Our model was limited by the lack of long-term survival data; we had to extrapolate these estimates from short-term outcomes. Although we used real-world longer-term data from patients with mCRPC to estimate overall survival, it is uncertain whether survival after mCRPC in patients who are naïve to antiandrogen therapy is similar to survival after progression on antiandrogen therapy.

The findings of our analysis suggest that both antiandrogen therapies result in longer life years and greater QALYs at a higher cost compared to continued ADT alone. Based on the current data and model assumptions, the incremental cost-effectiveness of these antiandrogen therapies versus continued ADT is expected to fall within commonly cited thresholds of $50,000 to $150,000 per QALY gained. Longer term data on duration of treatment and overall survival should clarify the true cost-effectiveness of these therapies.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

Potential Other Benefits

Table ES4. Potential Other Benefits

Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	NA
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	Given the disproportionate impact of prostate cancer on black men, improved therapy for nmCRPC has the potential to reduce health disparities across racial and socio-economic categories in the US.
This intervention will significantly reduce caregiver or broader family burden.	NA
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	NA
This intervention will have a significant impact on improving return to work and/or overall productivity.	NA
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	Although we have no evidence from clinical trials, we heard from patient groups and clinical experts that there may be psychological benefits to having a therapy available for men who are experiencing rising PSA test results.

Contextual Considerations

Table ES5. Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	NA
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	NA
This intervention is the first to offer any improvement for patients with this condition.	NA
Compared to waiting to add antiandrogen therapy with either abiraterone acetate or enzalutamide until the development of detectable metastatic disease, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	NA
Compared to waiting to add antiandrogen therapy with either abiraterone acetate or enzalutamide until the development of detectable metastatic disease, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	In the absence of more mature survival data, there is significant uncertainty about the survival benefit, if any, of treating men with nmCRPC with antiandrogen therapy.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	NA

Value-Based Benchmark Prices

ICER's value-based price benchmarks are meant to showcase drug prices that are required to align with value, defined as a willingness-to-pay (WTP) price range of between $100,000 to $150,000 per QALY. In cases where prices fall outside the upper bound and sometimes within this range, we present value-based prices.

For the antiandrogens, we did not estimate value-based prices that would meet WTP thresholds because the analysis in this report effectively compares earlier use of these agents (i.e., in nmCRPC) to later use of these and other drugs (in mCRPC), making problematic any attempt to understand the effects of price premiums.

Potential Budget Impact

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact for each antiandrogen therapy relative to continued ADT alone. We used the WAC, estimated net price and price to reach the $50,000 per QALY threshold price in our estimates of budget impact. We did not estimate potential budgetary impact at the prices that would meet thresholds of $100,000 and $150,000 per QALY. While theoretically the current price of antiandrogens could increase and meet these thresholds, this analysis effectively compares earlier use of the drug (i.e., in nmCRPC) to later use of this and other drugs (in mCRPC), making problematic any attempt to understand the budgetary effects of price premiums.

The candidate population in the budget impact model that was eligible for treatment with antiandrogens comprised adult males diagnosed with nmCRPC eligible for first-line therapy with antiandrogens. This reflects the labeled indication for apalutamide and enzalutamide, although the trials examined patients with more rapid PSA doubling times. We estimated an annual incident population of approximately 59,000 patients eligible for treatment with either antiandrogen therapy.

For apalutamide, the per patient budget impact results using its WAC ($133,000 per year), discounted WAC ($94,400 per year), and the price to reach $50,000 per QALY for apalutamide ($79,700 per year) compared to ADT alone are presented in Table ES6.

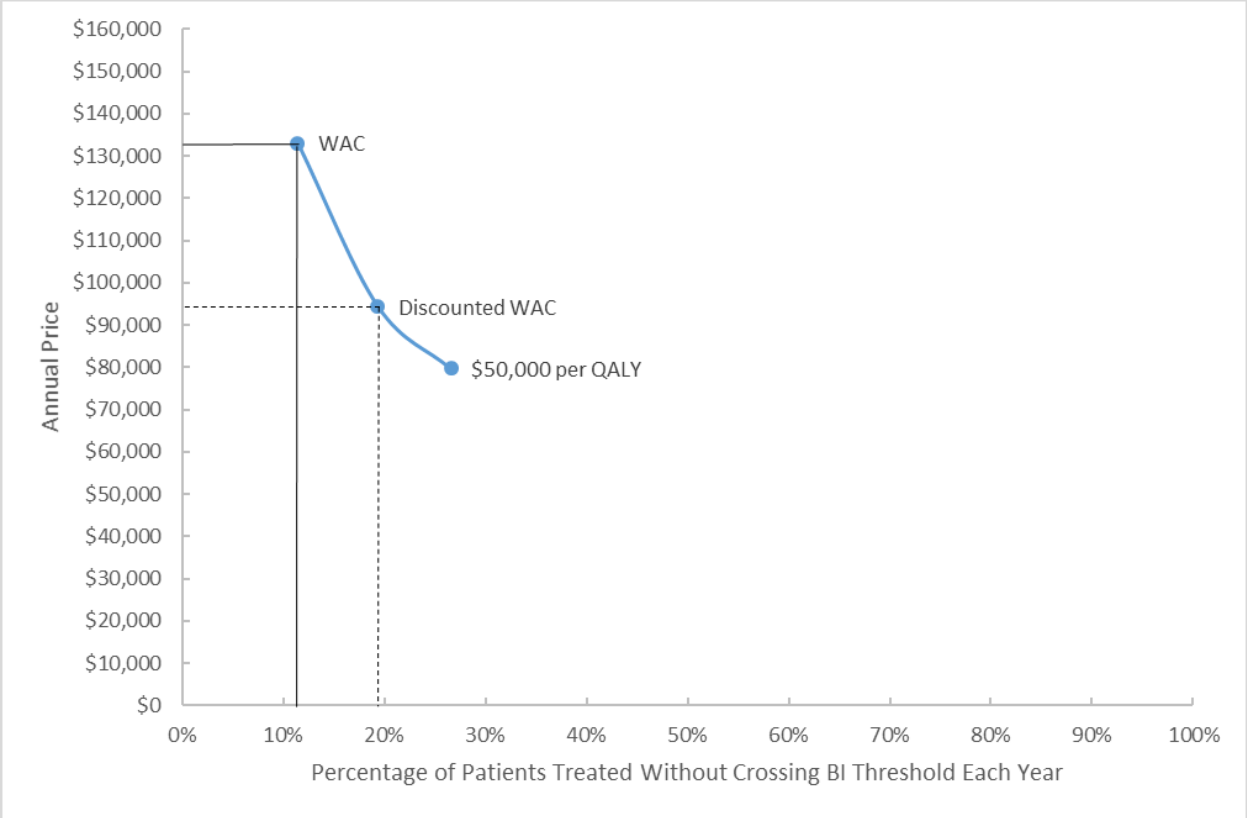
Table ES6. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Apalutamide

	Average Annual Per Patient Budget Impact		
	WAC	Discounted WAC	$50,000/QALY
Apalutamide	$91,058	$68,201	$59,297
ADT	$29,073		
Difference	$61,985	$39,128	$30,224

ADT: androgen deprivation therapy, QALY: quality-adjusted life year, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

As shown in Figure ES2, approximately 11% of eligible patients could be treated in a given year without crossing the ICER annual budget impact threshold of $991 million at apalutamide's WAC and approximately 19% of patients at the discounted WAC.

Figure ES2. Potential Budget Impact Scenarios at Different Prices of Apalutamide to Treat Adult Males with nmCRPC



For enzalutamide, the per-patient budget impact calculations based on its WAC ($132,800 per year), discounted WAC ($94,200 per year), and the price to reach $50,000 per QALY for enzalutamide ($68,200 per year) compared to ADT are presented in Table ES7.

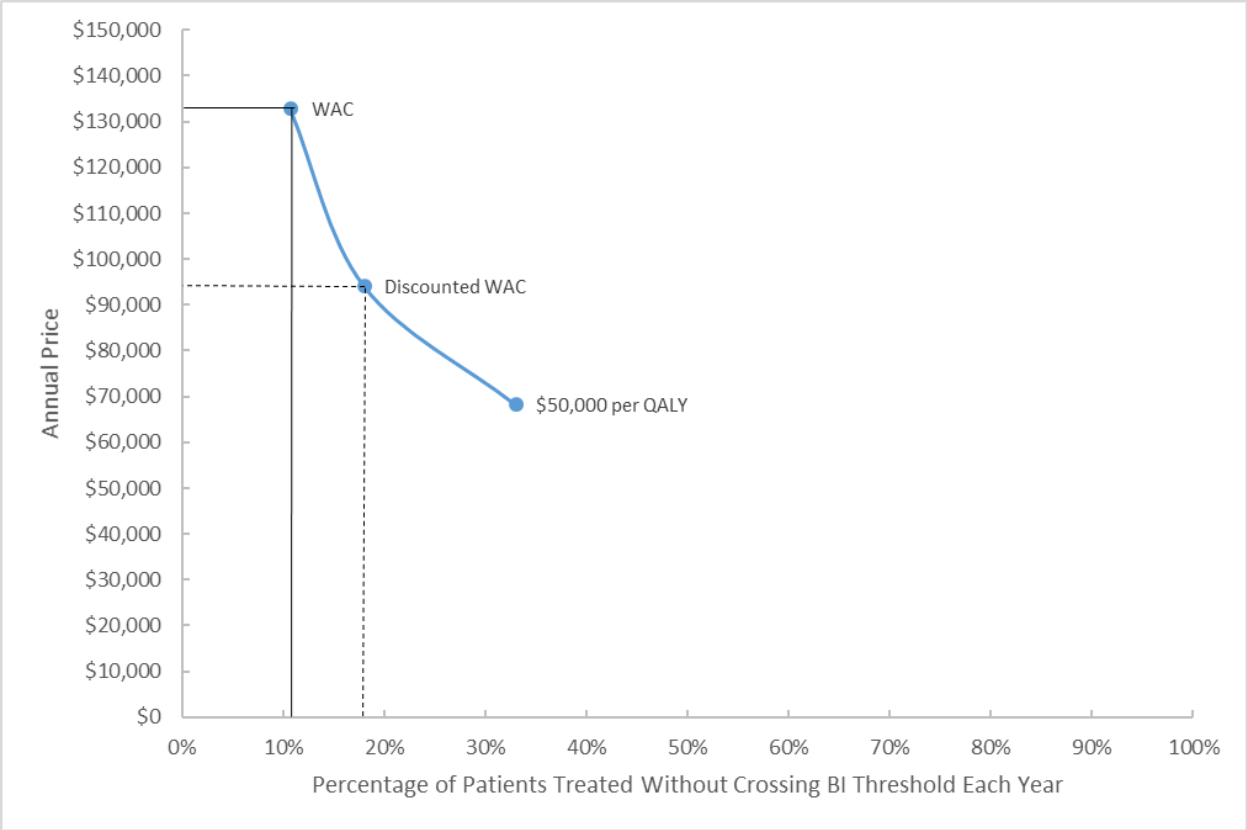
Table ES7. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Enzalutamide

	Average Annual Per Patient Budget Impact		
	WAC	Discounted WAC	$50,000/QALY
Enzalutamide	$93,824	$70,033	$54,048
ADT		$29,073	
Difference	$64,751	$40,959	$24,975

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

As shown in Figure ES3, approximately 11% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $991 million at enzalutamide's WAC and approximately 18% of patients at the discounted WAC.

Figure ES3. Potential Budget Impact Scenarios at Different Prices of Enzalutamide to Treat Adult Males with nmCRPC



As illustrated in the above analysis, treating the entire eligible nmCRPC eligible population with either antiandrogen therapy would result in a substantial budget impact. However, at the September 13th, 2018 Midwest CEPAC meeting, clinical experts indicated that these antiandrogen therapies will initially likely be prescribed only in an nmCRPC sub-population with rapid PSA doubling times, and not the larger nmCRPC population indicated by the drugs' FDA labels. ICER is therefore not issuing an access and affordability alert at this time, but recommends that health systems likely to be covering large numbers of affected patients, such as the Veterans' Administration, pay close attention to actual use and costs of antiandrogen treatment

Midwest CEPAC Votes

The Midwest CEPAC Panel deliberated on key questions raised by ICER's report during the public meeting on September 13th, 2018. The results of these votes are presented below and additional deliberation surrounding the votes can be found in chapter eight of this report.

All voting questions pertain to the following patient population: For each question, we are considering men with high risk (PSA doubling time ≤10 months) nonmetastatic castration-resistant prostate cancer being treated with androgen deprivation therapy. The comparator is waiting to add antiandrogen therapy with either abiraterone acetate or enzalutamide until the development of detectable metastatic disease.

Clinical Effectiveness

1) Is the evidence adequate to demonstrate a net health benefit of treating with apalutamide?

Yes: 10 votes	No: 1 vote

2) Is the evidence adequate to demonstrate a net health benefit of treating with enzalutamide?

Yes: 8 votes	No: 3 votes

3) Is the evidence adequate to demonstrate a net health benefit of treating with abiraterone acetate?

Yes: 2 votes	***No: 10 votes***

4) Is the evidence adequate to distinguish the net health benefits of apalutamide and enzalutamide?

Yes: 0 votes	***No: 11 votes***

5) Is the evidence adequate to demonstrate that abiraterone acetate has comparable efficacy to apalutamide and enzalutamide?

Yes: 0 votes	***No: 11 votes***

Potential Other Benefits

6) Does treating patients with antiandrogen therapies offer one or more of the following "potential other benefits?" (select all that apply)

Potential Other Benefits	Number of Votes
This intervention offers reduced complexity that will significantly improve patient outcomes.	0 / 11
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	0 / 11
This intervention will significantly reduce caregiver or broader family burden.	0 / 11
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	2 / 11
This intervention will have a significant impact on improving the patient's ability to return to work or school and/or their overall productivity.	0 / 11
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention	3 / 11

7) Are any of the following contextual considerations important in assessing antiandrogen therapies' long-term value for money? (select all that apply)

Potential Other Contextual Considerations	Number of Votes
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	3 / 11
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	4 / 11
This intervention is the first to offer any improvement for patients with this condition.	0 / 11
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	3 / 11
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	8 / 11
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	3 / 11

Long-term Value for Money

8) In men with high risk (PSA doubling time ≤10 months) non-metastatic castration resistant prostate cancer being treated with androgen deprivation therapy, given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering potential other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with apalutamide compared with waiting to add antiandrogen therapy with either abiraterone acetate or enzalutamide until the development of detectable metastatic disease?

Low: 2 votes	***Intermediate: 7 votes***	High: 2 votes

9) In men with high risk (PSA doubling time ≤10 months) non-metastatic castration resistant prostate cancer being treated with androgen deprivation therapy, given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering potential other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with enzalutamide compared with waiting to add antiandrogen therapy with either abiraterone acetate or enzalutamide until the development of detectable metastatic disease?

Low: 2 votes	***Intermediate: 8 votes***	High: 1 vote

Key Policy Recommendations

Payers and Clinicians

- The FDA approved indications for apalutamide and enzalutamide are broad and do not include limitations related to the rapid PSA doubling times that were part of the eligibility criteria for pivotal studies. Since benefits for patients have not been directly demonstrated among patients with slower PSA doubling times, payers may therefore consider limiting coverage to patients similar to those in the clinical trials. One clinical expert expressed that such an approach would not be viewed as clinically inappropriate by some clinicians but that many would consider intrusion into their clinical decision-making offensive.
- If apalutamide and enzalutamide are considered for treatment of men with nmCRPC and longer PSA doubling times, clinicians should practice shared decision-making with their patients and make them aware that the clinical trials only examined men with doubling times ≤10 months.

Payers

- The evidence base is not adequate to distinguish the clinical benefits or risks of apalutamide and enzalutamide in treating nmCRPC. Since lower prices benefit patients as well, payers may consider negotiating preferential price discounts linked to formulary tiering or step therapy favoring the less expensive option.
- Since price appears to be aligned with the added benefits from early treatment, payers should work to design and implement benefit designs that would cover antiandrogen therapy in a way that reduces financial toxicity for patients.

Federal Government

- There are no financial incentives for the manufacturer of abiraterone acetate, which is going off patent soon, to perform trials of abiraterone acetate that might undermine interest in newer agents. If clinical equivalence could be demonstrated, however, there could potentially be substantial savings for both payers and patients. The Japanese government is sponsoring a trial of abiraterone among men with CRPC. Funding for a similar trial in the US should actively be considered by the Patient-Centered Outcomes Research Institute (PCORI) or the NIH.

Manufacturers and Researchers

- Manufacturers and researchers should collaborate to ensure that future clinical trials of treatments for men with nmCRPC or mCRPC use identical endpoints to allow for clear comparison of drug effectiveness. All trials in nmCRPC should also include patient-important endpoints such as time to symptomatic progression and should be powered to measure changes in overall survival.
- Data from the large trials of apalutamide and enzalutamide should be analyzed jointly to better inform the understanding of whether metastasis-free survival is a valid surrogate for overall survival in men receiving antiandrogen therapy for nmCRPC.

1. Introduction

1.1 Background

Prostate cancer is the second most common cause of cancer death among men in the US (after lung cancer), and, aside from non-melanoma skin cancers, the most common cancer in men.[1] Estimates suggest that in 2018, approximately 165,000 new cases of prostate cancer will be diagnosed, and approximately 30,000 will die from prostate cancer.[1] Prostate cancer disproportionately affects black men, with an incidence rate that is approximately 60% higher and a mortality rate that is approximately 110% higher than the overall rates in US men.[2]

Prostate cancers are generally responsive to androgens and, at least initially, typically respond to androgen deprivation therapy (ADT).[3] ADT involves medical or surgical castration. Medications used for ADT include gonadotropin releasing hormone (GnRH) agonists, such as leuprolide, goserelin, and triptorelin,[4] and GnRH antagonists, such as degarelix.[5]

ADT is used in a number of clinical settings, including disseminated prostate cancer, high-risk prostate cancer treated with radiation therapy, and prostate cancer treated with radical prostatectomy found to have positive pelvic nodes.[6] Prostate cancer that has not been treated with ADT or that is responding to ADT is called "castration sensitive". Over time, most cancers that were castration sensitive become castration resistant. Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that progresses clinically, radiographically, or biochemically despite ADT that has achieved low (castrate) levels of serum testosterone.[6]

Patients with metastatic disease by conventional imaging (e.g., CT, bone scan, MRI) who progress on ADT or who develop metastatic disease on ADT benefit from treatment with antiandrogen therapies, with improvement in overall survival.[3] Antiandrogens include abiraterone acetate (Zytiga®; Janssen Biotech, Inc. and Yonsa®; Sun Pharma, Inc.), enzalutamide (Xtandi®; Astellas Pharma, Inc.), and apalutamide (Erleada™; Janssen Biotech, Inc.). Abiraterone is an androgen biosynthesis inhibitor that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17), which is expressed in testicular, adrenal, and prostatic tumor tissues; abiraterone acetate must be administered with corticosteroids (typically prednisone or methylprednisolone).[3,7-9] Enzalutamide and apalutamide are androgen receptor inhibitors that bind to the ligand-binding domain of the androgen receptor.[10,11] Apalutamide is not FDA-approved for metastatic CRPC (mCRPC).

The management of patients without metastatic disease by conventional imaging who progress on ADT (nonmetastatic castration-resistant prostate cancer; nmCRPC) has been less clear; progression typically involves increases in the biochemical marker prostate specific antigen (PSA). Until

recently, such patients were most often managed with continued ADT and surveillance for the development of metastases. More recently, apalutamide and enzalutamide have been evaluated in placebo-controlled randomized trials in patients with high risk (as defined by rate of increase in PSA) nmCRPC. In 2018, National Comprehensive Cancer Network (NCCN) guidelines were updated to suggest apalutamide, enzalutamide, or other antiandrogen therapies in men with nmCRPC, particularly with rapid increases in PSA,[6] and American Urological Association guidelines were updated to recommend offering apalutamide or enzalutamide to men with nmCRPC at high risk of developing metastatic disease.[12] Apalutamide was approved in February 2018 by the US FDA for treatment of nmCRPC,[13] and the label for enzalutamide was broadened to include this same indication in July of 2018.[14] 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. A Phase II trial suggested efficacy in this population,[15] and a trial comparing abiraterone acetate and enzalutamide in both mCRPC and nmCRPC is under way.[16]

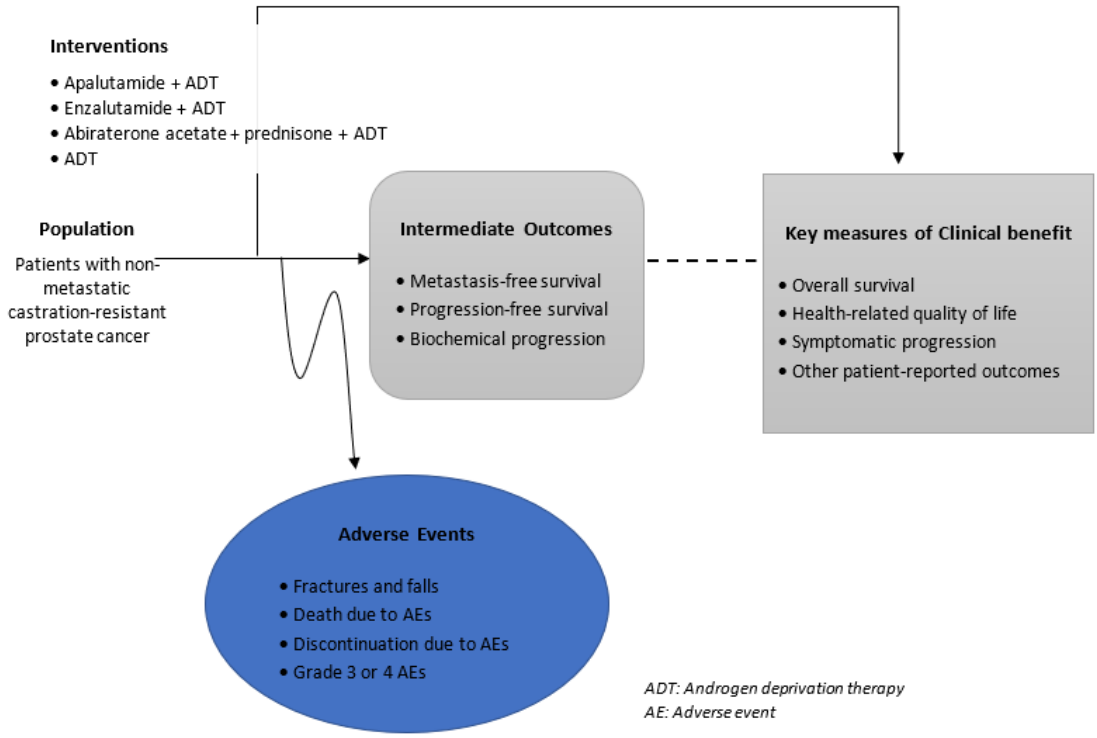
1.2 Scope of the Assessment

This review evaluated the comparative clinical effectiveness of apalutamide, enzalutamide, and abiraterone acetate plus prednisone for the treatment of men with nonmetastatic castration-resistant prostate cancer. Evidence was collected from available randomized controlled trials and non-randomized clinical trials. We did not restrict studies according to number of patients or study setting. We supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.1.

Figure 1.1. Analytic Framework



Populations

The population of focus for this review is men with nonmetastatic castration-resistant prostate cancer. We sought subgroup data based on rate of doubling of PSA levels, including those with doubling times greater than 10 months, and extent of disease at baseline.

Interventions

The interventions of interest for this review are:

- Apalutamide (Erleada™; Janssen Biotech, Inc.)
- Enzalutamide (Xtandi®; Astellas Pharma, Inc. and Pfizer, Inc.)
- Abiraterone acetate (Zytiga®; Janssen Biotech, Inc.) + prednisone

Patients continued treatment with ADT.

We chose not to include Yonsa®, the newly approved formulation of abiraterone acetate which has bioavailability differences from Zytiga®, is administered with methylprednisolone, and for which there are no published trial data in patients with prostate cancer. This decision was made to

simplify the discussion in the report, given the absence of additional outcomes data to inform any evaluations. This decision should not be taken to mean that ICER believes that different formulations of abiraterone acetate have different clinical effects.

Comparators

We examined studies comparing apalutamide, enzalutamide, and abiraterone acetate to continued ADT without antiandrogen therapy.

Outcomes

The outcomes of interest are described in Table 1.1.

Table 1.1. Key Outcomes and Harms

Outcomes	Key Harms
Overall survival	Adverse events associated with death
Metastasis-free survival	Grade 3 or 4 adverse events
Progression-free survival	Adverse events leading to discontinuation
Symptomatic progression	Fracture
PSA progression	Falls
Health-related quality of life	Rash
	Fatigue
	Hypothyroidism
	Seizure
	Cardiovascular-related adverse events

Timing

Evidence on intervention effectiveness and harms were derived from studies of any duration.

Settings

All relevant settings were considered, including inpatient, clinic, and outpatient settings.

1.3 Definitions

Androgen deprivation therapy (ADT) – Medical or surgical castration (i.e., orchiectomy). Medications used for ADT include GnRH agonists, such as leuprolide, goserelin, and triptorelin,[4] and GnRH antagonists, such as degarelix.[5]

Castration-resistant prostate cancer (CRPC) – Prostate cancer that progresses clinically, radiographically, or biochemically despite ADT that has achieved low (castrate) levels of serum testosterone.[6]

Metastasis-free survival (MFS) – The time from randomization to the first detection of metastasis on imaging or death from any cause; definitions of MFS have varied in individual clinical trials, differing most notably in the location of where the first detection of metastasis must occur (i.e., distant or loco-regional) and in the timeframe in which death from any cause must occur (see Section 3.3).

Overall survival – The length of time from randomization until death due to any cause.

Progression-free survival (PFS)– The time from randomization to the first detection of local or distant metastatic disease or death from any cause.

Prostate-specific antigen (PSA) – A protein produced by cells of the prostate gland. The level of PSA present in the blood may be elevated in men with prostate cancer, may decline with treatment, and may rise again when treatment loses effectiveness.[40]

Time to symptomatic progression – The time from randomization to any of the following: a) a skeletal-related event (i.e., pathologic fracture, spinal cord compression, or surgical or radiation therapy of the bone); b) pain progression or worsening of disease symptoms requiring use of a new systemic anti-cancer therapy; c) development of clinically significant symptoms due to local or regional tumor progression requiring surgery or radiation therapy.[32]

1.4 Insights Gained from Discussions with Patients and Patient Groups

Patients and patient groups stressed the serious risks of morbidity and mortality in men with CRPC and how this affects men and their families, the psychological effects of prostate cancer on a man's sense of self, the substantial side effects of therapies for prostate cancer, and the sense that burdensome therapy has failed when PSA levels begin to rise leading some to question their prior decisions about therapy.

In a 2017 survey report from the Cancer Support Community, 49 patients rated the following factors to be among the "most important" considerations when selecting a treatment for their prostate cancer: higher chance for survival (27%), higher chance for cure (20%), recommendations from a doctor (16%), and fewer side effects (14%).[17]

In our discussions with patient groups, we heard that the tolerability of ADT and antiandrogen therapies is highly variable from person to person. Fatigue was called out as a particularly common substantial side effect of apalutamide and enzalutamide.

Patient groups and clinicians stressed the psychological benefits of having a therapeutic course of action available in the face of PSA evidence of progression, in contrast to the difficulties of waiting for the development of detectable metastases. The connection was made between this and the overall value of hope in patients with a life-threatening disease.

Patient groups also stressed the important financial toxicities of therapies for prostate cancer and reported that some men choose to forgo such therapies because of this. In the survey cited above, more than 50% of respondents reported having monthly prostate cancer-related out-of-pocket costs of more than $100, with 25% of respondents reporting over $500 of out-of-pocket costs per month; these figures were broadly consistent with those reported in a larger survey (n=1,252) of cancer survivors.[17,18]

We also heard about the disproportionate effects of prostate cancer on black men in the US. These include the higher incidence and mortality rates described above, but financial toxicity and its effects on choices about undergoing and adhering to therapies may also be greater in black men.

We also heard from patient groups that, not surprisingly, the use of the term "castration" in discussions of treatments (e.g., "medical castration") and stages (e.g., "castration-resistant") of prostate cancer creates issues for patients who are already dealing with a serious illness. Despite this, because it is the standard language used in oncology and the research literature, we have chosen to use the word throughout this report. However, we wish to acknowledge the issues this creates and the potential future need for alternative terminology that men with prostate cancer would find more acceptable.

ICER looks forward to continued engagement with stakeholders throughout its review.

1.5. Potential Cost-Saving Measures in Prostate Cancer

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). During stakeholder engagement and public comment periods, ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for men with prostate cancer that could be reduced, eliminated, or made more efficient.

The American Board of Internal Medicine's Choosing Wisely® campaign encourages specialty societies to identify areas of low-value care that could be reduced or eliminated. Recommendations from the American Urological Association (AUA) and other clinical societies include limiting treatment of men with low-risk localized prostate cancer without discussing active surveillance as part of the shared-decision-making process.[19]

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for antiandrogen therapies, we reviewed publicly available coverage policies and formularies for the Illinois state Medicaid program,[41] Centers for Medicare and Medicaid Services (CMS), regional commercial plans available in individual marketplaces in Illinois from Blue Cross Blue Shield of Illinois[42] and Cigna,[43] and major commercial national plans including Anthem[44] and UnitedHealthcare.[45] We also reviewed Medicare Part D coverage from Cigna and Humana.[46,47]

We did not locate any CMS National or Local Coverage Determination policies on antiandrogen therapies. The Illinois state Medicaid program does not list any of the three agents on its preferred drug list.[41]

With the exception of United HealthCare, which includes only abiraterone acetate, the drug formularies for each commercial plan and each Medicare Part D plan include both abiraterone acetate and enzalutamide on a specialty tier with requirements for prior authorization. While the specific criteria were not publicly available for most of the plans reviewed, Anthem specifies that both therapies are covered for mCRPC; abiraterone acetate may also be covered for high-risk castration-sensitive disease and must be used in combination with prednisone.

Apalutamide was not found in some formularies. Anthem's policy notes that it is covered for patients with nmCRPC when used in combination with GnRH, or for patients who have previously undergone a bilateral orchiectomy. Medicare Part D plans surveyed did include apalutamide, with requirements for prior authorization.

This information is reflective of coverage policies publicly available at the time of publication.

2.2 Clinical Guidelines

National Comprehensive Cancer Network (NCCN) Guidelines (Updated 2018)[6]

For men with castration-resistant prostate cancer and no signs of distant metastasis, the NCCN guidelines state that patients can consider observation, 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 and

enzalutamide can be considered, but also state that other secondary hormone therapies can be used.

American Urological Association (AUA) (Updated 2018)[48]

The AUA recommends that 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 or immunotherapy should not be offered, except in the context of a clinical trial.

3. Comparative Clinical Effectiveness

3.1 Overview

To inform our analysis of the comparative clinical effectiveness of antiandrogens in the treatment of nonmetastatic castration-resistant prostate cancer, we abstracted evidence from available clinical studies, whether in published or unpublished form (e.g., conference abstracts or presentations, FDA review documents). Therapies of interest included the second-generation antiandrogens apalutamide, enzalutamide, and abiraterone acetate plus prednisone. As stated in the Background section, the comparator of interest was continued ADT therapy without an antiandrogen. Our review focused on clinical benefits (i.e., overall survival, health-related quality of life, MFS, and other measures of disease progression), as well as potential harms (drug-related adverse events).

3.2 Methods

Data Sources and Searches

We searched MEDLINE and Cochrane Central Register of Controlled Trials via the Ovid platform and EMBASE via the EMBASE website. All search strategies were generated using the Population, Intervention, Comparator, and Study Design elements described in the scope (Section 1.2). The search strategy included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Appendix Tables A2 and A3. The date of the most recent search was August 20, 2018.

To supplement the database searches, we performed a manual check of the reference lists of included trials. We also invited key stakeholders to share references germane to the scope of the project. We supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Study Selection

After removal of duplicate citations, references went through two levels of screening at both the abstract and full-text levels. Two reviewers independently screened the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada); disagreements were resolved through consensus. Abstracts were screened based on population, intervention, relevant outcomes, and study design.

Citations accepted during abstract-level screening were reviewed as full text. The review followed the same procedures as the title/abstract screening. Reasons for exclusion were categorized according to the PICOTS elements.

Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted studies (See Appendix D). Elements included a description of patient populations, sample size, duration of follow-up, study design features (e.g., double-blind), interventions (agent, dosage, dosing frequency, method of administration), results, and quality assessment for each study. Extracted data were reviewed for logic and were validated by a third investigator for additional quality assurance.

We used criteria employed by the US Preventive Services Task Force ([USPSTF] see Appendix D) to assess the quality of clinical trials, using the categories "good," "fair," or "poor."[49]

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit for each of the antiandrogens relative to ADT alone in the patients with nonmetastatic castration-resistant prostate cancer (See Appendix D and Section 3.4).

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for apalutamide, enzalutamide, and abiraterone acetate using the ClinicalTrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies may indicate whether there is bias in the published literature. For this review, we did not find evidence of any study completed more than two years ago that has not subsequently been published.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Appendix Tables D1 and D2) and are synthesized in the text below. Due to differences in study design, baseline characteristics of study populations, and outcomes assessed, we did not conduct quantitative direct or indirect analyses of the interventions of interest.

3.3 Results

Study Selection

Our literature search identified 2,307 potentially relevant references (see Appendix Figure A1), of which six references (four publications, one conference presentation, and one FDA Multidisciplinary Review packet) relating to four individual studies met our inclusion criteria. The primary reasons for study exclusion included study populations outside of our scope (e.g., patients with metastatic and/or hormone-sensitive prostate cancer), interventions not of interest (e.g., cabazitaxel, bicalutamide), and study designs or publication types outside the scope of our review (e.g., commentaries, preclinical studies).

Two of the four selected studies were Phase III randomized controlled trials (RCTs) of apalutamide and enzalutamide, respectively;[11,20] the remaining two studies were single-arm Phase II clinical studies of apalutamide and abiraterone acetate.[21,22]

Although metastatic castration-resistant prostate cancer was not of focus for this review, there have been several good-quality placebo-controlled trials of enzalutamide and abiraterone acetate conducted in this population (Appendix Table D2).[10,23-25] We report survival and safety data from these trials in order to supplement the sparse evidence identified through our literature search and provide additional efficacy evidence on these agents.

Details of all included studies are summarized in Appendix D and in the sections that follow.

Key Studies

As noted above, we identified two studies of apalutamide, and one each of enzalutamide and abiraterone acetate + prednisone. Key studies are summarized in Table 3.1 and are described in further detail in the sections that follow.

The Phase III trials evaluating apalutamide and enzalutamide in combination with ADT specified similar inclusion criteria.[11,20] Both studies included adult men (≥18 years of age) with adenocarcinoma of the prostate that was castration-resistant. Patients were deemed to be at high risk for developing metastases (i.e., PSA doubling time ≤10 months) despite ongoing ADT with a GnRH analogue or previous orchiectomy. Individuals who had radiographic evidence of distant metastases or symptomatic local or regional disease requiring medical intervention were excluded. Prior cytotoxic chemotherapy was not permitted in the enzalutamide study and was only allowed in the apalutamide study if administered in the adjuvant or neoadjuvant setting. Trial populations appeared similar with respect to baseline characteristics, although patients in the PROSPER trial had

a more rapid PSA doubling time than patients in the SPARTAN trial (median 3.7 months vs. 4.4 months in the PROSPER and SPARTAN trials, respectively).

Both Phase III studies evaluated MFS as the primary endpoint, although the endpoint was defined differently in each study. In the SPARTAN trial of apalutamide, MFS was defined as the time from randomization to the first occurrence of *distant* metastasis (i.e., enlarged lymph nodes outside the pelvis or new bone or soft tissue lesions) or death due to any cause, whichever occurred first.[31] The PROSPER study of enzalutamide defined MFS as the time from randomization to radiographic progression (*distant or loco-regional*), or death without evidence of radiographic progression up to 112 days after discontinuation of the trial regimen, whichever occurred first.[33] In both studies, MFS was assessed by blinded independent central review; imaging and disease assessments occurred every 16 weeks.

Two Phase II studies of apalutamide and abiraterone acetate + prednisone, respectively, also met our inclusion criteria.[21,22] These studies specified similar eligibility criteria as the Phase III studies of enzalutamide and apalutamide (e.g., PSA doubling time ≤10 months) but were single-arm trials. The study of apalutamide assessed the post-treatment percentage change in PSA relative to baseline at 12 weeks; MFS and time to PSA progression were evaluated as secondary endpoints.[21] The IMAAGEN trial of abiraterone acetate + prednisone was statistically powered to measure the proportion of patients achieving at least a 50% reduction in PSA during six cycles of therapy (treatment cycles were 28 days in duration).[22] Although previous trials of abiraterone acetate + prednisone in patients with metastatic castration-resistant prostate cancer administered a 10 mg daily dose of prednisone, the IMAAGEN trial administered just 5 mg of the corticosteroid per day.

Table 3.1. Key Studies

Study	Patient Characteristics	Treatment	Comparator
SPARTAN[11] **Phase III RCT**	Median age: 74yr N0: 84% N1: 17% PSADT≤6m: 72% PSADT>6m: 29% Median time from dx: 7.9yr	**Apalutamide** (n=806)	**Placebo** (n=401)
		Median follow-up: 20.3m	
		OS HR 0.70 (95% CI 0.47-1.04) PFS HR 0.29 (95% CI 0.24-0.36) p<0.001 MFS HR 0.28 (95% CI 0.23-0.35) p<0.001	
		Median PFS: 40.5m Median OS: Not Reached Median MFS: 40.5m D/C due to AEs: 11% SAEs: 25% AEs associated with death: 1%	Median PFS: 14.7m Median OS: 39.0m Median MFS: 16.2m D/C due to AEs: 7% SAEs: 23% AEs associated with death: 0.3%
Smith Eur Urol 2016[21] **Phase I/II Study**	Median age: 71yr N0: NR N1: NR PSADT≤6m: NR PSADT>6m: NR Median time from dx: 119.5m	**Apalutamide** (n=51)	
		Median follow-up: 28m	
		Median time to PSA progression: 24.0m D/C due to TEAE: 18% Serious TEAE: 31% AEs associated with death: NR	
PROSPER[20,29] **Phase III RCT**	Median age: 73.5yr N0: NR N1: NR PSADT<6m: 77% PSADT≥6m: 23% Median time from dx: NR	**Enzalutamide** (n=933)	**Placebo** (n=468)
		Median follow-up: 18.5m	
		OS HR 0.80 (95% CI 0.58-1.09) p=0.1519 MFS HR 0.29 (95% CI 0.24-0.35) p<0.0001	
		Median OS: Not Reached Median MFS: 36.6m • D/C due to AEs: 9% • SAEs: 24% • AEs associated with death: 3%	Median OS: Not Reached Median MFS: 14.7m D/C due to AEs: 6% SAEs: 18% AEs associated with death: 1%
IMAAGEN[22] **Phase II Study**	Median age: 72yr N0: NR N1: NR PSADT≤6m: NR PSADT>6m: NR Median time from dx: 10.2yr	**Abiraterone acetate + prednisone** (n=131)	
		Median follow-up: 40m	
		Median time to PSA progression: 28.7m Median time to radiographic progression: Not Reached (estimated 41.4m [n=15])	

Study	Patient Characteristics	Treatment	Comparator
		D/C due to AEs: 15% SAEs: 44% AEs associated with death: 5%	

OS: overall survival, PFS: progression-free survival, MFS: metastasis-free survival, PSA: prostate-specific antigen, dx: diagnosis, mo: months, HR: hazard ratio, NR: not reported, TEAE: treatment-emergent adverse event, D/C: discontinuation, SAE: serious adverse event, AE: adverse event, PSADT: prostate-specific antigen doubling time, N0: No regional lymph node metastasis, N1: Regional (pelvic) lymph node(s) metastasis

Quality of Individual Studies

Using criteria from the US Preventive Services Task Force (USPSTF [See Appendix D]), we judged the Phase III trials of apalutamide and enzalutamide to be of good quality.[11,20] These studies were well-designed (placebo-controlled, double-blind), had balanced baseline and demographic characteristics between arms, and evaluated both clinically- and patient-relevant outcomes. We did not assign quality ratings to the other included studies due to the single-arm design of the two Phase II studies.

Clinical Benefits

Apalutamide

Mature overall survival data are not yet available; however, available data suggest a trend toward longer survival with apalutamide. Time to symptomatic progression was prolonged by apalutamide, as was the primary outcome of MFS. Clinical benefits were observed across all subgroups of interest. Quality of life scores remained stable during the Phase III SPARTAN trial with no notable differences between treatment groups.

Evidence on apalutamide was primarily derived from the Phase III SPARTAN trial.[11] This study was a multinational trial that randomized 1207 men with nonmetastatic castration-resistant prostate cancer and a prostate-specific doubling time of 10 months or less to apalutamide (n=806) or placebo (n=401); all patients continued to receive background ADT. The study's primary endpoint was MFS.

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.[21]

<u>Overall Survival</u>

The SPARTAN trial evaluated overall survival as a secondary endpoint. At the time of data cut-off, only 24% of the events needed for final analysis had occurred.[31] In an interim analysis, the median overall survival was not reached in the apalutamide group, while the placebo group had a median survival of 39 months. The hazard ratio for overall survival was 0.70 (95% CI 0.47 to 1.04; p=0.07), which did not reach the prespecified statistical significance level of p=0.000012. Apalutamide appeared beneficial in prespecified subgroups, although analyses were based on a small number of events in each group and should be interpreted with caution (see Table 3.2).

Table 3.2. Overall Survival with Apalutamide[11,32]

	Apalutamide+ADT Median (months)	Placebo+ADT Median (months)	Hazard Ratio (95% CI)
All subjects	NE	39	0.70 (0.47 to 1.04)
Loco-regional disease: N0	NE	39	0.72 (0.47 to 1.10)
Loco-regional disease: N1	NE	NE	0.52 (0.19 to 1.42)
PSA doubling time ≤6m	NE	39	0.66 (0.43 to 1.02)
PSA doubling time >6m	NE	NE	0.79 (0.30 to 2.03)

ADT: androgen deprivation therapy, mo: months, CI: confidence interval, N0: no malignant local or regional lymph nodes, N1: malignant regional (pelvic) lymph nodes, PSA: prostate-specific antigen, NE: not estimable

Disease Progression

The primary endpoint of the SPARTAN trial was MFS. At final analysis, the median MFS was 40.5 months in the apalutamide group and 16.2 months in the placebo group (HR 0.28; 95% CI 0.23 to 0.35; p<0.001).[11] An MFS benefit was observed across multiple subgroups of interest, including shorter/longer PSA doubling times and extent of nodal disease (see Table 3.3). Median time to symptomatic progression was also longer with apalutamide (HR 0.45; 95% CI 0.32 to 0.63).

In addition, treatment with apalutamide was associated with improvements in PFS and PSA progression. Results from the SPARTAN trial are presented in Table 3.3 below. In the Phase II study of apalutamide, median time to PSA progression was 24 months and median MFS was not reached.[21]

Table 3.3. Disease Progression in the SPARTAN Trial of Apalutamide[11]

	Apalutamide+ADT Median (months)	Placebo+ADT Median (months)	Hazard Ratio (95% CI)
Metastasis-Free Survival	40.5	16.2	0.28 (0.23 to 0.35)
Time to Metastasis	40.5	16.6	0.27 (0.22 to 0.34)
Progression-Free Survival	40.5	14.7	0.29 (0.24 to 0.36)
Time to PSA Progression	NR	3.7	0.06 (0.05 to 0.08)
Time to Symptomatic Progression	NR	NR	0.45 (0.32 to 0.63)
Subgroup Analyses of Metastasis-Free Survival			
Loco-Regional Disease: N0	40.5	18.3	0.33 (0.26 to 0.41)
Loco-Regional Disease: N1	NR	10.8	0.15 (0.09 to 0.25)
PSA Doubling Time ≤6m	40.5	14.6	0.29 (0.23 to 0.36)
PSA Doubling Time >6m	NR	22.8	0.30 (0.20 to 0.47)

ADT: androgen deprivation therapy, NR: not reached, PSA: prostate-specific antigen, N0: no malignant local or regional lymph nodes, N1: malignant regional (pelvic) lymph nodes

Health-Related Quality of Life

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-3 Levels (EQ-5D-3L) questionnaire. The FACT-P ranges from 0 to 156; higher scores indicate more favorable health-related quality of life. The EQ-5D-3L questionnaire is comprised of the EQ-5D descriptive system and the EQ visual analogue scale; scores range from 0 to 100, with zero indicating the worst possible health and 100 indicating the best possible health. Between baseline and 29 months of follow-up, patients in both treatment groups maintained stable quality of life on both instruments.[11]{Saad, 2018, 862} Mean changes in FACT-P scores were -0.99±0.98 with apalutamide versus -3.29±1.97 in the placebo group; mean EQ-5D-3L scores increased slightly (1.44±0.87 vs. 0.26±1.75).[11] Statistical differences between groups were not reported. The FDA noted 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.[32] Nevertheless, descriptive exploratory analyses of several individual items from the FACT-P led the FDA to further comment that apalutamide appeared to be well-tolerated and did not appear to adversely affect functional outcomes.[32]

Enzalutamide

Mature overall survival data are not yet available; however, available data suggest a trend toward longer survival with enzalutamide. Data on symptomatic progression have not been

reported; the primary outcome of MFS was longer in those taking enzalutamide. Patient-reported outcomes showed no significant differences in quality of life between treatment groups.

Evidence on enzalutamide was primarily derived from the PROSPER trial.[20] This study was a placebo-controlled multinational Phase III trial that randomized 1401 men with nonmetastatic castration-resistant prostate cancer and a rapidly rising PSA to enzalutamide (n=933) or placebo (n=468); all patients continued to receive background ADT. The study's primary endpoint was MFS.

Overall Survival

Median overall survival was not reached in the PROSPER trial's first interim analysis. At the time of data cutoff, the hazard ratio for survival was 0.80 (95% CI 0.58 to 1.09; p=0.1519).[20] Subgroup analyses from this trial are not yet available.

Although not a population of focus for this review, a survival benefit with enzalutamide has been observed in patients with metastatic castration-resistant prostate cancer. In the Phase III placebo-controlled PREVAIL trial, enzalutamide reduced the risk of death by 23% (HR 0.77; 95% CI 0.67 to 0.88; p=0.0002) over 18 months of treatment in chemotherapy-naïve patients.[26] Enzalutamide also significantly prolonged survival in men with metastatic castration-resistant disease after chemotherapy in the Phase III placebo-controlled AFFIRM trial (HR 0.63; 95% CI 0.53 to 0.75; p<0.001).[23]

Disease Progression

Similar to the SPARTAN trial, the PROSPER trial evaluated MFS as a primary endpoint. Final analyses showed a median MFS of 36.6 months (95% CI 33.1 to NR) for the enzalutamide arm versus 14.7 months (95% CI 14.2 to 15.0) for the placebo arm; the difference was statistically significant with a hazard ratio of 0.29 (95% CI 0.24 to 0.35; p<0.0001).[20] An MFS benefit was consistently observed across prespecified subgroups; results stratified by extent of disease were not reported.

Progression events occurred in 219 (23%) of the enzalutamide-treated patients, of which 187 (85%) were due to progression and 32 (15%) were attributed to death without documented radiographic progression. In the placebo arm, progression events occurred in 228 (49%) patients, of which all but 4 (2%) were attributed to radiographic progression. The lower proportion of deaths in the placebo group was likely due to more rapid disease progression.

Enzalutamide also significantly delayed PSA progression. Median time to PSA progression was 37.2 months in the enzalutamide group (95% CI 33.1 to NR) and 3.9 months in the placebo group (95% CI 3.8 to 4.0); enzalutamide lowered the risk of PSA progression by 93% (HR 0.07; 95% CI 0.05 to 0.08; p<0.0001).[20]

We did not identify any data related to symptomatic progression or progression-free survival from the PROSPER trial.

Table 3.4. Disease Progression in the PROSPER Trial of Enzalutamide[29]

	Enzalutamide+ADT Median (months)	Placebo+ADT Median (months)	Hazard Ratio (95% CI)
Metastasis-Free Survival	36.6	14.7	0.29 (0.24 to 0.35)
Time to PSA Progression	37.2	3.9	0.07 (0.05 to 0.08)
Subgroup analyses of Metastasis-Free Survival			
PSA Doubling Time <6m	NR	NR	0.28 (0.23 to 0.35)
PSA Doubling Time ≥6m	NR	NR	0.35 (0.22 to 0.56)

PSA: prostate-specific antigen, ADT: androgen deprivation therapy, mo: month, NR: not reported

Health-Related Quality of Life

The PROSPER trial assessed health-related quality of life and pain using several instruments, including the FACT-P, Quality-of-life Questionnaire-Prostate (QLQ-PR25), European Quality of Life - 5-Dimensions, 5-Level questionnaire (EQ-5D-5L), and Brief Pain Inventory-Short Form (BPI-SF). Results from the FACT-P and BPI-SF were reported in a recent conference abstract and showed no statistically significant or clinically meaningful differences in quality of life or pain scores between treatment arms over 96 weeks of follow-up; at week 97, the least squares mean change from baseline in total FACT-P score was -7.17 (SE 0.92) and -9.20 (SE 1.45) in the enzalutamide and placebo groups, respectively (p=0.184).[27] The median time to degradation in the FACT-P score was the same in both groups (11.1 months; HR 0.92; 95% CI 0.79-1.08).[20]

Abiraterone Acetate

Overall survival with abiraterone acetate + prednisone has not been evaluated in patients with nonmetastatic castration-resistant prostate cancer. 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. We did not identify any quality of life data for abiraterone acetate + prednisone in the population of focus. We are uncertain whether the efficacy of abiraterone acetate in men with nmCRPC is comparable to the efficacy of apalutamide and enzalutamide.

Our review of abiraterone acetate + prednisone was primarily informed by the IMAAGEN trial.[22] This single-arm Phase II study evaluated abiraterone acetate + prednisone in 131 patients with high-risk nonmetastatic prostate cancer. The trial's primary endpoint was the proportion of patients

achieving at least a 50% reduction in PSA during six cycles of therapy (treatment cycles were 28 days in duration).

Overall Survival

Overall survival was not assessed in the Phase II IMAAGEN trial. In the Phase III placebo-controlled COU-AA-302 trial in patients with metastatic disease and no prior chemotherapy, abiraterone acetate reduced the risk of death by 19% (HR 0.81; 95% CI 0.70 to 0.93; p=0.0033).[28] Abiraterone acetate also improved overall survival in a similar trial among patients with metastatic disease and previous chemotherapy (HR 0.65; 95% CI 0.54 to 0.77; p<0.001).[25]

Disease Progression

Thirty-one (23.7%) patients had confirmed radiographic evidence of disease progression in the IMAAGEN study.[22] Median time to radiographic evidence of disease progression was not reached, however a sensitivity analysis that included 15 unconfirmed progressions estimated median time to progression to be 41.4 months (95% CI 27.6 to NE). The median time to PSA progression was 28.7 months (95% CI 21.2 to 38.2).

Health-Related Quality of Life

Health-related quality of life was not evaluated in the IMAAGEN trial.

Comparing abiraterone acetate to apalutamide and enzalutamide

As noted, we have limited evidence on the efficacy of abiraterone acetate in patients with nmCRPC that would allow us to judge the efficacy of this agent relative to apalutamide and enzalutamide, and differences in trial populations and study designs precluded formal quantitative comparisons. The following descriptive results discussed above could help inform any such judgment:

- Abiraterone acetate and enzalutamide have both been evaluated in men with ***mCRPC who had not received prior chemotherapy***. As discussed above, in the Phase III placebo-controlled PREVAIL trial, enzalutamide reduced the risk of death by 23% (HR 0.77; 95% CI 0.67 to 0.88; p=0.0002) over 18 months of treatment in chemotherapy-naïve patients.[26] In the Phase III placebo-controlled COU-AA-302 trial in patients with metastatic disease and no prior chemotherapy, abiraterone acetate performed similarly, reducing the risk of death by 19% (HR 0.81; 95% CI 0.70 to 0.93; p=0.0033).[28]
- Abiraterone acetate and enzalutamide have both been evaluated in men with ***mCRPC who received prior chemotherapy.*** Enzalutamide significantly prolonged survival in men with metastatic castration-resistant disease after chemotherapy in the Phase III placebo-controlled AFFIRM trial (HR 0.63; 95% CI 0.53 to 0.75; p<0.001).[23] Abiraterone acetate

improved overall survival in a trial among patients with metastatic disease and previous chemotherapy (HR 0.65; 95% CI 0.54 to 0.77; p<0.001).[25]

- Abiraterone acetate and apalutamide have both been evaluated in single arm studies in men with ***nmCRPC***. In the Phase II study of apalutamide, median time to PSA progression was 24 months.[21] In the IMAAGEN study of abiraterone acetate, median time to PSA progression was 28.7 months.

These results all suggest that the effects of abiraterone acetate are similar to those of other antiandrogen therapies, both in men with mCRPC and in men with nmCRPC. However, not all data support this hypothesis. In the randomized trials in men with nmCRPC (SPARTAN and PROSPER), the median time to PSA progression with apalutamide was not reached and with enzalutamide was 37.2 months.[11,29] These appear longer than the time discussed above with abiraterone acetate (28.7 months) and could reflect differences in study design, random statistical variation, or true differences in efficacy.[30]

Although we think there is reason to believe that treatment with abiraterone acetate + prednisone in men with nmCRPC achieves similar outcomes to treatment with apalutamide or enzalutamide, the above results create sufficient uncertainty that we chose not to model the use of abiraterone acetate in the economic analyses described in Section 4.

Harms

Despite spending a longer time on study therapy, rates of serious adverse events with apalutamide and enzalutamide + ADT were similar to those reported in patients taking placebo + ADT. Discontinuations due to adverse events were low relative to rates observed with other oncologic therapies, and few deaths have been attributed to antiandrogen-related toxicity. FDA prescribing information for both apalutamide and enzalutamide includes warnings for seizures. Additionally, there may be an increased risk for falls, fractures, and ischemic heart disease with apalutamide and enzalutamide. Patients taking abiraterone acetate should be monitored for mineralocorticoid excess, adrenocortical insufficiency, and hepatoxicity. Fatigue is common with all three agents.

Adverse event (AE) frequencies and rates of Grade 3-4 (severe and life-threatening) events are reported by regimen in Table 3.5.

Table 3.5. Adverse Events of Apalutamide, Enzalutamide, and Abiraterone Acetate

	Apalutamide[11,31,32] (%)		Enzalutamide[10,29,33] (%)		Abiraterone acetate[22,34] (%)	
Median duration of treatment	16.9 months		18.4 months		22.1 months	
Grade ≥3 AEs	45.1		31		57	
SAEs	24.8		24		44	
AEs leading to discontinuation	10.6		9		15	
AEs associated with death	1.2		3		5	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fracture	12	3	10	2	NR	NR
Falls	16	2	11	1	6†	0†
Fatigue	30	1	33	3	40	1
Ischemic heart disease	4	1	3	1	NR	NR
Hypertension	25	14	12	5	42	24
Rash	24	5	NR	NR	8‡	0‡
Hypothyroidism	8	0	NR	0*	NR	NR
Seizure	<1	0	<1	<1	NR	NR
Hypokalemia	NR	NR	NR	NR	34	7
Peripheral edema	11	0	12*	<1*	25	2

NR: not reported, SAE: serious adverse event

*safety data from the PREVAIL trial from Beer et al. (2014). Other enzalutamide data reported from PROSPER trial.

†safety data from the COU-AA-302 trial from Ryan et al. (2013)

Apalutamide

There were ten deaths due to adverse events (AEs) in the Phase III SPARTAN trial, eight of which were potentially due to apalutamide-related toxicity.[32] These deaths included sepsis (n=4), myocardial infarction (n=3), and cerebral hemorrhage (n=1). Rates of non-fatal serious AEs were similar between groups (25% and 23% for the apalutamide and placebo groups, respectively).

Discontinuation of the trial regimen due to AEs was relatively low in the SPARTAN trial. Despite longer exposure to study therapy, just 11% of patients treated with apalutamide discontinued due to AEs, versus 7% of patients treated with placebo. Rash was the most commonly-cited reason for treatment discontinuation.[32]

Ischemic heart disease occurred in more patients treated with apalutamide than placebo in the SPARTAN trial (3.7% vs 2.0%); differences persisted after adjusting for duration of exposure.[32] The rate of Grade ≥3 ischemic heart disease did not differ between treatment arms.

Investigators considered rash, fatigue, hypothyroidism, falls, fractures, and seizures to be potentially related to apalutamide.[32] The FDA prescribing information includes warnings for falls,

fractures, and seizures.[31] In the SPARTAN trial, falls occurred in 16% of apalutamide-treated patients (vs. 9% of placebo-treated patients) and fractures occurred in 12% (vs. 7%).[11] Routine bone density assessments were not performed as part of the trial. Although patients with a history of seizure or conditions that could predispose them to seizure were excluded from the trial, seizures occurred in two (0.2%) apalutamide-treated patients and no placebo-treated patients.[11]

Enzalutamide

In the PROSPER trial, rates of both serious AEs (24%) and discontinuation of enzalutamide due to AEs (9%) were similar to that of apalutamide.[20] Grade ≥3 AEs that occurred with the most frequency included hypertension (5%), fatigue (3%), fractures (2%), and hematuria (2%).[20]

Major cardiovascular events, including acute myocardial infarction, hemorrhagic and ischemic cerebrovascular conditions, and heart failure, occurred in 48 (5%) patients in the enzalutamide arm and 13 (3%) patients in the placebo arm.[20] The incidence of cardiovascular events was higher in patients with predisposing factors, including a history of cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia, or at least 75 years of age. The FDA prescribing information for enzalutamide includes a warning about ischemic heart disease.[33] In a pooled analysis of three RCTs, ischemic heart disease occurred in 2.7% of patients treated with enzalutamide versus 1.2% of patients who received a placebo; Grade 3-4 ischemic events occurred in 1.2% and 0.5% of patients in the enzalutamide and placebo arms, respectively.[33]

To supplement the sparse safety data currently available from the PROSPER trial, we also reviewed evidence from a Phase III placebo-controlled study of 1,717 patients with metastatic castration-resistant prostate cancer who had not received prior cytotoxic chemotherapy.[26] In this trial, patients had a similar exposure to treatment (18.2 months) with enzalutamide as in the PROSPER trial (18.4 months).[26] AEs that led to death occurred in 4% of patients in both the enzalutamide arm and the placebo arm; these were mainly attributed to disease progression and a deterioration in physical health.

Although clinical studies of enzalutamide have excluded individuals with a predisposition to seizure from enrollment, seizures have occurred in approximately 0.5% of patients; 2.2% of individuals with predisposing factors (e.g., history of seizure, history of traumatic brain or head injury, etc.), have reported seizures.[33] The FDA prescribing information for enzalutamide includes a warning for these events.

Abiraterone acetate

Seven (5.3%) patients in the IMAAGEN trial had an AE that led to death; these were due to a motorcycle accident, pneumonia, myocardial infarction, congestive cardiac failure, and coronary artery disease.[22] One patient had sepsis, pneumonia, and acute respiratory failure. Serious AEs occurred in 44% of patients who participated in the trial.[22]

The FDA prescribing information for abiraterone acetate warns that the drug may cause hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess resulting from CYP17 inhibition. Four placebo-controlled trials of abiraterone acetate + prednisone in patients with metastatic disease showed grades 3-4 hypokalemia, hypertension, and fluid retention in 4%, 2%, and 1% of patients, respectively.[34] In the IMAAGEN study, grade 3-4 hypokalemia was observed in 7% of patients, hypertension in 24%, peripheral edema in 2%, and pleural effusion in 1%.[22]

The prescribing information also warns against adrenocortical insufficiency and hepatic toxicity. Adrenal insufficiency occurred in 0.3% of the 2,230 patients with metastatic disease who were treated with abiraterone acetate in five randomized placebo-controlled studies; grade 3-4 elevations in liver enzymes (at least five times the upper limit of normal level of alanine aminotransferase and aspartate aminotransferase) occurred in 6% of patients.[34]

Controversies and Uncertainties

Men with mCRPC are treated with antiandrogen therapy.[6] Although not defined as metastatic disease, rising PSA levels are a marker for disease progression and likely micrometastases. As such, the treatment strategy evaluated in this report essentially involves using the same medications that would be given for mCRPC at an earlier stage of disease progression. Antiandrogen medications have important side effects. Thus, their use earlier in disease management must demonstrate improvements in patient-important outcomes such as survival and quality of life, and not simply an imaging-based surrogate outcome such as MFS. The current trials showed no improvements in quality of life, and survival data are immature such that only trends toward improved survival have been demonstrated to date. However, time to symptomatic progression is a patient-important outcome, and apalutamide showed a clear benefit. Additionally, an analysis presented at the 2018 Annual Meeting of the American Society of Clinical Oncology concluded that MFS is positively correlated with overall survival in patients with high-risk, nonmetastatic castration-resistant prostate cancer.[35]

Conventional imaging modalities (e.g., technetium-99m bone scans, CT scans, MRI scans), which were used in the trials identified for this review, are not as accurate at detecting metastases as newer imaging technologies (e.g., PET scans).[50] Many of the patients who participated in these trials may have already developed distant metastases prior to enrollment that were not detected

through imaging studies. As newer imaging modalities with greater diagnostic accuracy are integrated into care, more patients may be identified with radiographic evidence of metastatic disease.[51] This may create difficulties in comparing trials performed at different points in time, particularly as new antiandrogen therapies are evaluated.

The FDA indications for apalutamide and enzalutamide do not limit their use to high-risk patients alone, although only men with a PSA doubling time of 10 months or less were eligible for the SPARTAN and PROSPER trials. The benefit provided by early treatment with antiandrogens in men with longer PSA doubling times remains uncertain.

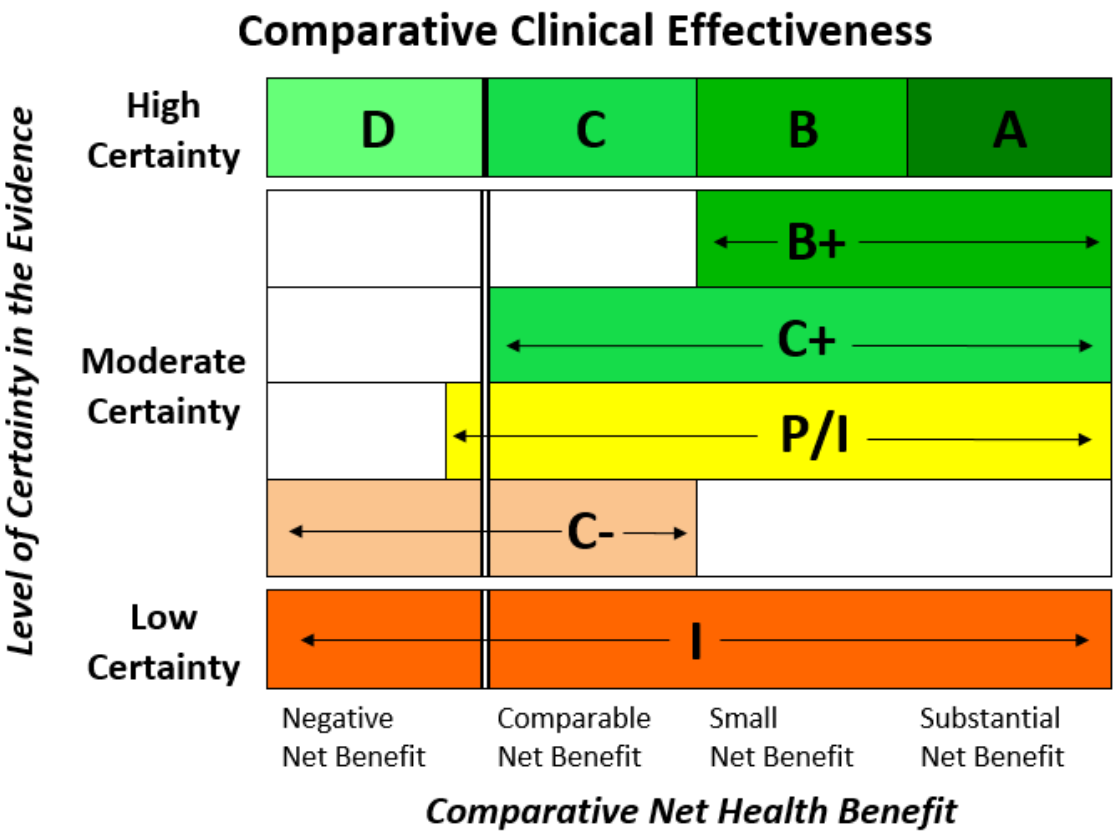
Black men were underrepresented in the SPARTAN trial of apalutamide and PROSPER trial of enzalutamide, accounting for just 6% and 2% of participants, respectively. As noted in Section 1 of this report, African Americans have an incidence of prostate cancer that is 60% higher and a mortality rate that is approximately 110% higher than the overall rates in US men.[2] In the SPARTAN trial, the point estimate for the hazard ratio for MFS among African American men was somewhat higher (0.63 [95% CI 0.23 to 1.72] vs. 0.28 [95% CI 0.23 to 0.35] for the entire group), although given the small sample size and wide confidence interval, we cannot determine whether apalutamide has a differential effect on black men.[11] We did not identify any data related to outcomes in this subgroup from the PROSPER trial. In the single-arm IMAAGEN study of abiraterone acetate, 19 patients (14.5%) were black, and the times to PSA progression and radiographic progression were similar among black and non-black men.[22] Additional data demonstrating the generalizability of the randomized trial results to the subgroup of black men would be helpful.

Finally, head-to-head studies of the therapies of interest have not been performed and there are insufficient data available to indirectly compare these regimens using network meta-analysis. While we heard from clinical experts that abiraterone acetate and enzalutamide have comparable effectiveness in metastatic castration-resistant prostate cancer, it is difficult to determine how these agents compare in the nonmetastatic population without more robust, comparative data. Additionally, even MFS, the primary outcome of SPARTAN and PROSPER, was defined somewhat differently in the two trials. Thus, the comparative effectiveness of the antiandrogens relative to each other cannot be determined at this time.

3.4 Summary and Comment

Using the ICER Evidence Matrix (Figure 3.1), we assigned evidence ratings to each of the antiandrogens relative to ADT alone for nonmetastatic castration-resistant prostate cancer (Table 3.6). As noted previously, the lack of head-to-head data as well as our inability to indirectly compare the regimens through network meta-analysis precluded assessment of the comparative net health benefit of these regimens relative to each other.

Figure 3.1. ICER Evidence Rating Matrix



*A = **"Superior"** - High certainty of a substantial (moderate-large) net health benefit*
*B = **"Incremental"** - High certainty of a small net health benefit*
*C = **"Comparable"**- High certainty of a comparable net health benefit*
*D = **"Negative"**- High certainty of an inferior net health benefit*
*B+ = **"Incremental or Better"** - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
*C+ = **"Comparable or Better"** - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
*P/I = **"Promising but Inconclusive"** - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
*C- = **"Comparable or Inferior"** - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
*I = **"Insufficient"** - Any situation in which the level of certainty in the evidence is low*

Table 3.6. ICER Evidence Ratings

Intervention	Comparator	ICER Evidence Rating
Apalutamide	Placebo + ADT	A
Enzalutamide	Placebo + ADT	A
Abiraterone Acetate + Prednisone	Placebo + ADT	B+

Apalutamide

Compared to ADT alone, apalutamide led to statistically significant delays in disease progression. Although overall survival data are not yet mature, interim analyses indicate a trend toward improved survival. Apalutamide prolonged time to symptomatic progression and improved median MFS by more than two years (24.3 months). The therapy was well-tolerated, and quality of life remained stable for the duration of the SPARTAN trial. In men with nmCRPC and a rapid PSA doubling time (≤10 months), we have high certainty that apalutamide + ADT provides a substantial net health benefit compared with ADT alone ("A").

Enzalutamide

Evidence from the PROSPER trial indicate that enzalutamide delays disease progression. Although overall survival data are preliminary and not yet mature, there was also a trend toward improved survival. Data are not available on symptomatic progression, but median MFS was prolonged substantially. The therapy was well-tolerated, and quality of life remained stable for the duration of the PROSPER trial. Given the evidence that MFS is correlated with overall survival,[35] and the similar results in SPARTAN and PROSPER, in men with nmCRPC and a rapid PSA doubling time (≤10 months), we have high certainty that enzalutamide + ADT provides a substantial net health benefit compared with ADT alone ("A").

Abiraterone Acetate + Prednisone

Due to the lack of direct comparative evidence, we have less certainty of the net health benefit of abiraterone acetate + prednisone. As discussed in detail above, evidence suggests that treatment outcomes with abiraterone acetate and enzalutamide are similar in men with mCRPC, however not all data available are reassuring that abiraterone acetate is non-inferior to apalutamide and enzalutamide in men with nmCRPC. Despite this, mean time to PSA progression in the IMAAGEN trial (28.7 months)[22] was much longer than the times seen for PSA progression in the placebo arms of the SPARTAN and PROSPER trials (3.7 and 3.9 months, respectively).[20,21] As such, in men with nmCRPC and a rapid PSA doubling time (≤10 months), compared with ADT alone, we have moderate certainty that abiraterone acetate + ADT provides a small or substantial net health benefit and high certainty of at least a small net health benefit ("B+").

Comparisons Among the Agents

In the absence of head-to-head comparisons, we have insufficient data ("I") to conclude that the net health benefit of any of the three antiandrogens evaluated in men with nmCRPC is superior/inferior to either of the other two antiandrogens.

4. Long-Term Cost Effectiveness

4.1 Overview

The primary aim of this analysis was to estimate the lifetime cost-effectiveness of antiandrogen therapies as first-line treatment of nmCRPC, from a US health sector perspective. The model includes continued treatment with ADT plus (1) apalutamide (Erleada™; Janssen Biotech, Inc.) or (2) enzalutamide (Xtandi®; Astellas Pharma, Inc. and Pfizer, Inc.). The standard of care comparison was continued ADT alone. Patient survival, quality-adjusted survival, and health care costs were summarized over a lifetime time horizon for each treatment option. In addition, a modified societal perspective was modeled, which included the productivity costs of patients and informal caregivers. All future costs and outcomes were discounted at 3% per year. The analytic framework for this assessment is depicted in Figure 4.1 below. The model was developed in Microsoft Excel (Microsoft Office 365 ProPlus, version 1805; Redmond, WA).

4.2 Methods

Model Structure

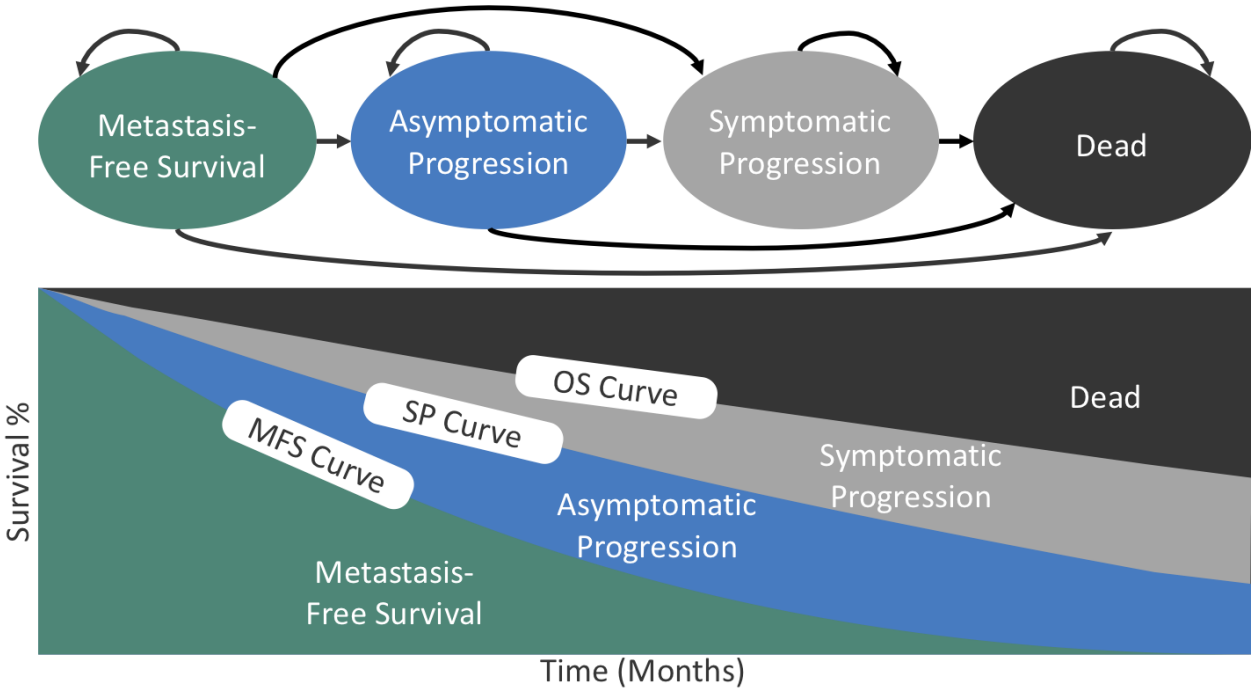
We developed a de novo decision analytic model comprising four health states: MFS, asymptomatic progression, symptomatic progression, and death (Figure 4.1). Health states and transitions among them were modeled using a hybrid approach, combining (a) partitioned survival methods to transition patients among MFS, asymptomatic progression, and symptomatic progression health states, and (b) a Markov approach to model the transition from metastatic CRPC (mCRPC) to death.

The partitioned survival[52] element estimated the proportion of the modeled cohort in each health state for each model cycle based on the difference in parametric survival curves, in this case, those for MFS and time to symptomatic progression; trial-reported overall survival data were used to estimate the proportion of patients who died prior to metastasis. The Markov element utilized real-world, mCRPC survival data to estimate the per cycle proportion of patients who died post-metastasis.[36]

For each treatment regimen, a hypothetical nmCRPC patient population began the model in the MFS health state, where they remained until they either: (a) experienced metastasis/disease progression or (b) died from cancer or other causes. Patients who experienced metastasis/disease progression were either asymptomatic or symptomatic. Asymptomatic patients, defined as patients with a PSA doubling time ≤10 months but not experiencing other symptoms, could

become symptomatic, but symptomatic patients could not return to asymptomatic progression. All patients could transition to death from any of the alive health states.

Figure 4.1. Model Framework



Target Population

Consistent with the populations of the SPARTAN and PROSPER trials, the population of focus for this review was adult men diagnosed with nmCRPC who have a rapidly rising PSA (doubling time of 10 months or less). Note that the "continued ADT" strategy is informed by the average characteristics of the placebo arms of these trials.

Table 4.1. Clinical Trial Population Characteristics

Patient Population	Median Age	Median Weight*	Median Height*	Median Diagnosis to Randomization Time	Median PSA Doubling Time
Apalutamide[11]	74 years	85.0 kg	173 cm	7.95 years	4.4 months
Enzalutamide[20]	74 years	Not reported	Not reported	Not reported	3.8 months
Continued ADT[11,20]	74 years	83.2 kg	172 cm	7.85 years	4.5 months

ADT: androgen deprivation therapy, PSA: prostate specific antigen

*Used to calculate post-metastasis/disease progression treatment cost. The median weight for all patients combined in SPARTAN was 84.4 kg, and the median patient height was 173 cm and 172 cm in the apalutamide and continued ADT trials, respectively.

Treatments

Intervention

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers. The antiandrogen interventions considered for the model were:

- Apalutamide (Erleada™; Janssen Biotech, Inc.)
- Enzalutamide (Xtandi®; Astellas Pharma, Inc. and Pfizer, Inc.)

While we heard from clinical experts that abiraterone acetate and enzalutamide have comparable effectiveness in metastatic castration-resistant prostate cancer, we did not model abiraterone acetate as there are insufficient data available to indirectly compare this regimen in nonmetastatic patients. Abiraterone acetate is thus only included as a treatment option for patients who progress to mCRPC.

Comparator

The universal base-case comparator was continued ADT without antiandrogen therapy.

Key Model Characteristics and Assumptions

The base-case analysis took a health system perspective and focused on direct medical care costs only. Our key model choices included the following.

- Model cycle length was one month (365.25/12 = 30.44 days/month) since each comparator is a daily oral drug, which precludes the need for a shorter cycle length to capture complex/irregular regimen schedules and drug administration fees. Furthermore, monthly model cycles reflect the unit of measurement for nmCRPC survival in clinical trials.[11,15,20]
- Parametric curve functions were fit separately for each survival curve available in the published literature and used to extrapolate the data to a lifetime horizon. Available curves included those for apalutamide (MFS, time to symptomatic progression, and overall survival);[11] enzalutamide (MFS and OS);[20] and continued ADT (MFS [SPARTAN and PROSPER trials], time to symptomatic progression [SPARTAN only], and overall survival [SPARTAN and PROSPER trials]).[11,20]
- Time to symptomatic progression was not a trial outcome in PROSPER.[20] To accommodate the four health state model structure, we estimated an enzalutamide "time to symptomatic progression" hazard ratio versus continued ADT based on PROSPER trial outcomes and the observed differences between apalutamide and continued ADT from the SPARTAN trial.[11] This hazard ratio was then applied to the SPARTAN placebo arm's time to symptomatic progression

curve to derive the missing curve for enzalutamide.

- Survival was weighted by health state utilities to model quality of life. The model includes separate utilities for MFS, asymptomatic progression, and symptomatic progression.[39,53,54]
- The model includes costs for individual grade 3-4 AEs that occur in at least 5% of patients in at least one of the included regimens.[55,56] Grade 2 fractures were also included, as these are considered of specific relevance to patients.
- The model included all treatment costs associated with each individual regimen, including drug acquisition costs,[57] supportive care costs,[58,59] and costs of disease metastasis/disease progression. Disease metastasis/progression costs reflect real-world distributions of subsequent treatments and best supportive care.[37,38,59]

Our key model assumptions are listed in Table 4.2.

Table 4.2. Key Model Assumptions

Assumption	Rationale
Treatment effects as estimated from the parametric survival functions based on available Kaplan-Meier data from SPARTAN[11] and PROSPER[20] are assumed to continue consistently throughout long-term extrapolation.	In the absence of long-term follow-up data, a consistent approach in survival extrapolations is recommended for the base-case analysis.
Trial populations are sufficiently homogeneous to allow for comparisons to a single baseline comparator (continued ADT from the SPARTAN trial[11]) using trial-reported hazard ratios. A scenario analysis using the survival curves from the PROSPER trial[20] is also explored, as is the use of independently fit survival curves instead of hazard ratio-derived curves.	Review of reported 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,[11,20] suggesting that PSA doubling time is not an effect modifier.
Overall survival is modeled using a combination of trial-reported outcomes and real-world 5-year survival data for mCRPC from the Surveillance, Epidemiology, and End Results (SEER) Program.[36]	Trial-reported overall survival data is currently immature and may underestimate real-world survival. We explore the impacts on model results when using extrapolations of the trial-reported overall survival in a scenario analysis.
Time to symptomatic progression is similar between apalutamide and enzalutamide.	This outcome was not reported in PROSPER but is necessary for the chosen model framework. MFS outcomes for apalutamide[11] and enzalutamide[20] are very similar, leading to our assumption that secondary outcomes are also similar. In a scenario analysis, we employed a 3-state partitioned survival model that does not differentiate between asymptomatic and symptomatic progression.

Assumption	Rationale
In the base-case, antiandrogen therapy costs are based on the trial-reported median durations of therapy for apalutamide[11] and enzalutamide.[20] In sensitivity analyses, duration of therapy is varied using the within-model calculated median MFS, multiplied by ratios comparing the trial-reported medians for MFS and duration of therapy.	A notable proportion of nonmetastatic patients discontinue antiandrogen therapy due to AEs or other factors. In the SPARTAN trial, the difference between median duration of therapy and median MFS was 23.6 months;[11] for the PROSPER trial, the difference was 18.2 months.[20] Given the antiandrogens' regimens are treat to progression, we explored the impact of linking treatment duration to total time spent in metastasis-free survival in a scenario analysis.
Instead of modeling trial-reported subsequent therapies, post-progression costs are informed by real-world data on subsequent approved treatments for mCRPC.[37,38,59]	The regimens approved for post-progression therapy within the trials does not reflect the full range of available treatment options for mCRPC.22
Time to subsequent therapy after discontinuation of antiandrogens was based on data from the PROSPER trial.	The PROSPER trial data report that the median interval between the discontinuation of the trial regimen and subsequent antineoplastic therapy was 25 days in the enzalutamide group and 18 days in the placebo group.
Patients on each antiandrogen treatment are assumed to continue to be treated with ADT from model entry until death.	Continued ADT is the standard of care for metastatic CRPC.

Model Inputs

Survival Modeling

Our approach to survival modeling allowed us to model the relative efficacy of the interventions versus a common comparator, model survival beyond available follow-up time, and vary survival curves in sensitivity analysis. Transitions among health states were driven by a combination of (a) trial-based survival curves[11,20] and (b) overall survival data from SEER.[36]

For the partitioned survival element of the model, in the base-case analysis, we utilized Kaplan-Meier curves directly up to month 30, and then parametric "tails" (for placebo/continued ADT) and hazard ratio-derived "tails" (for antiandrogens) were modeled to extrapolate to a lifetime horizon. The 30-month Kaplan-Meier cutoff followed by parametric or hazard ratio-derived tails was common to all modeled curves from both the SPARTAN[11] and PROSPER[20] trials, and was chosen to limit the extrapolation impacts of increased censoring due to limited trial follow-up beyond this time point. In probabilistic sensitivity analysis, the placebo/continued ADT curves defaulted to parametric curves (instead of Kaplan-Meier data) throughout the modeled time horizon, and antiandrogen curves defaulted to hazard ratio-derived curves throughout.

Table 4.3. Survival Parameters

Parameter	Base-case	Lower	Upper	PSA Distribution	Source
Hazard Ratios vs. Continued ADT: Apalutamide					
Metastasis-Free Survival	0.28	0.23	0.35	Log-Normal	SPARTAN[11]
Time to Symptomatic Progression	0.45	0.32	0.63	Log-Normal	SPARTAN[11]
Overall Survival (Pre-Metastasis Only)	0.70	0.47	1.04	Log-Normal	SPARTAN[11]
Hazard Ratios vs. Continued ADT: Enzalutamide					
Metastasis-Free Survival	0.29	0.24	0.35	Log-Normal	PROSPER[20]
Time to Symptomatic Progression	0.47	0.33	0.63	Log-Normal	Derived*
Overall Survival (Pre-Metastasis Only)	0.80	0.58	1.09	Log-Normal	PROSPER[20]
Survival Post-Metastasis (All Comparators)					
mCRPC 5-Year Survival Rate	0.239	0.203	0.277	Log-Normal	SEER[36]

ADT: androgen deprivation therapy; PSA: prostate specific antigen; mCRPC: metastatic castration-resistant prostate cancer

*We estimated an enzalutamide "time to symptomatic progression" hazard ratio versus continued ADT based on PROSPER trial outcomes and the observed differences between apalutamide and continued ADT from the SPARTAN trial.[11] This hazard ratio was then applied to the placebo/continued ADT time to symptomatic progression curve to derive the missing curve for enzalutamide.

We first fit parametric survival tails to the SPARTAN and PROSPER trials' placebo arm Kaplan-Meier data on (1) MFS, (2) time to symptomatic progression (SPARTAN only), and (3) overall survival. We used extracted data points from digitized copies of the trial curves, the number of remaining (non-censored) patients at each time interval, and maximum likelihood functions to estimate curve fits to the underlying individual patient data. The distributional forms considered for each parametric curve were Weibull, exponential, log-normal, and log-logistic. The comparator curve tails for apalutamide and enzalutamide were then derived by applying trial-reported hazard ratios for each outcome to the modeled placebo/continued ADT curves, assuming proportional hazards of the treatment effect over a lifetime horizon. We then selected the best parametric curve fit using Akaike information criterion (AIC) values, visual comparison, and comparison versus the trial-reported medians if available. Further details on our rationales for placebo parametric distribution

selection and use of the proportional hazards assumption to model antiandrogens can be found in Appendix E.

Figure 4.2. Modeled MFS Curves

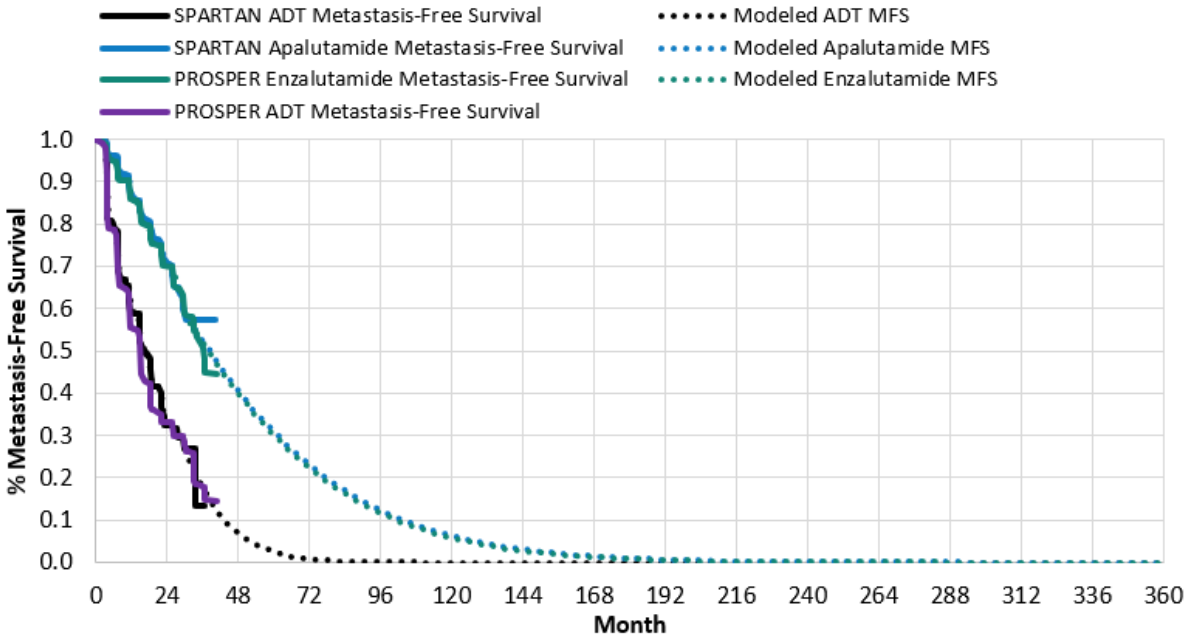
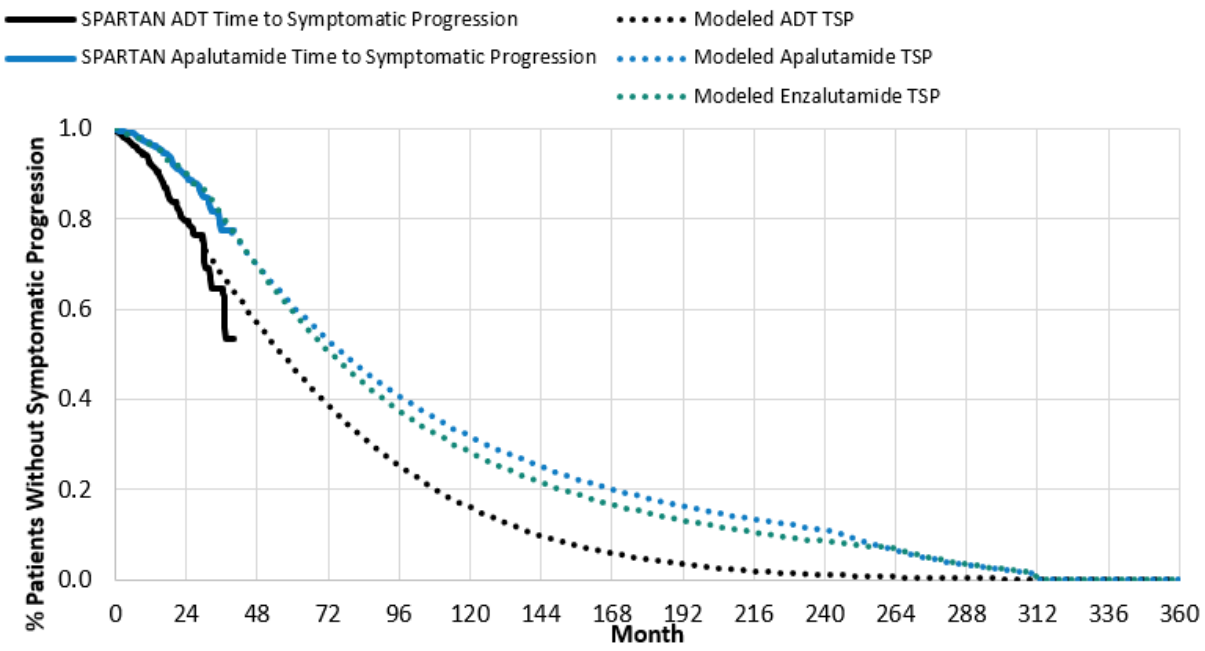
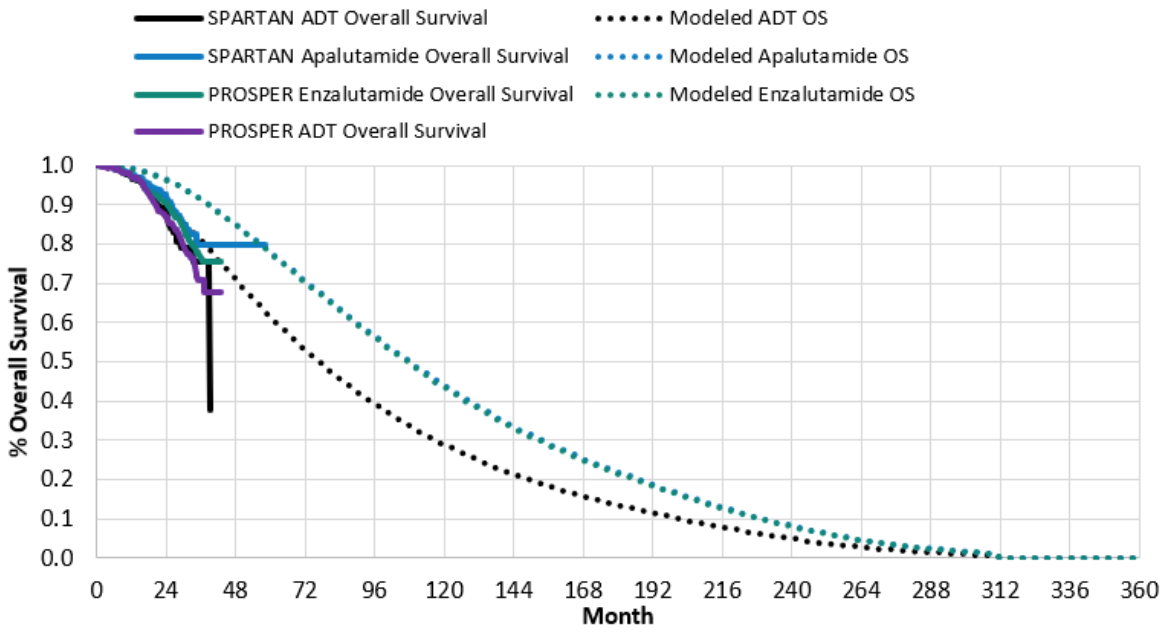


Figure 4.3. Modeled Time to Symptomatic Progression Curves



As stated above, trial-based overall survival curves were used to model death prior to metastasis (a small proportion of patients), and the curves were modeled using the same 30-month cutoff followed by parametric (placebo/continued ADT) or hazard ratio-derived (antiandrogen) tails approach. For post-metastasis overall survival, 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 5-year survival rates for mCRPC from SEER.[36] We present the combined overall survival curves, incorporating both pre- and post-metastasis elements, in Figure 4.4.

Figure 4.4. Modeled Overall Survival Curves (Combined)



Lastly, for each intervention and the common comparator, we took a hierarchical approach to comparing survival data, using the more conservative estimate for each pairwise comparison, in order to prevent curves from "crossing":

1. Overall survival curve: Minimum of US life table[60] survival and overall survival curves derived as described above; then
2. Symptomatic progression curve: Minimum of overall survival and time to symptomatic progression; then
3. MFS curve: Minimum of time to symptomatic progression and MFS.

Drug Utilization

The estimation of drug utilization was derived from the dosing schedule reported in trials (Tables 4.4 and 4.5). Each antiandrogen regimen was administered within the metastasis-free survival health state. Treatment regimen post-progression is based on recently published real world data (Appendix Table E3).[37,38] Drug unit costs (Table 4.8) were applied to the utilization estimates to calculate total estimated treatment costs.

Table 4.4. Treatment Regimen Recommended Dosage, Antiandrogen Therapies

	Apalutamide	Enzalutamide
Brand name	Erleada®	Xtandi®
Manufacturer	Janssen	Astellas & Pfizer
Route of administration	Oral	Oral
Dosage Forms and Strengths*	Tablets: 60 mg	Capsules: 40 mg
Recommended Dosing	240 mg (four 60 mg tablets) administered orally once daily	160 mg (four 40 mg capsules) administered orally once daily†

*Enzalutamide and abiraterone acetate are currently not indicated for nmCRPC. The listed recommended dosing is that for mCRPC.

†For scenario analysis

Table 4.5. Treatment Regimen Recommended Dosage, Continued ADT

	Leuprolide Acetate	Goserelin Acetate	Triptorelin Pamoate	Degarelix Acetate
Brand name	Eligard®	Zoladex®	Trelstar®	Firmagon®
Manufacturer	Tolmar Pharmaceuticals	TerSera Therapeutics	Allergan	Ferring Pharmaceuticals
Route of administration	Subcutaneous injection	Subcutaneous injection	Intramuscular injection in either buttock	Subcutaneous injection
Dosage Forms, Strengths, & Recommended Dosing	• 7.5 mg subcutaneously every month • 22.5 mg subcutaneously every 3 months • 30 mg subcutaneously every 4 months • 45 mg subcutaneously every 6 months	3.6 mg subcutaneously every 28 days	• 3.75 mg every 4 weeks • 11.25 mg every 12 weeks • 22.5 mg every 24 weeks	• Starting dose of 240 mg given as two injections of 120 mg each† • Maintenance doses of 80 mg administered as a single injection every 28 days
Proportion of Patients[11]*	56%	24%	16%	5%

*Used to calculate a weighted continued ADT cost for all comparators

†Starting/loading dose is not included in the model since patients are assumed to enter the model having previously started ADT.

Utilities

Health state utilities as applied to the three alive disease states were derived from published literature. The utility for MFS was sourced from a Canadian cost-effectiveness analysis of prostate-specific antigen-based screening. We used asymptomatic and symptomatic progression utilities from Lloyd et al., who report the five-level EQ-5D-5L and European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) to estimate utilities from a total sample of 163 U.K. men with mCRPC;[39] the EQ-5D-5L utilities stratified by prostate cancer disease states were selected for our model. We also included utilities related to fractures.[53]

Table 4.6. Utility Values for Health States

Parameter	Value	Lower Bound	Upper Bound
Utility: Metastasis-Free Survival[54]	0.900	0.720	0.990
Utility: Metastasis/Progressed Disease: Asymptomatic[39]	0.830	0.795	0.865
Utility: Metastasis/Progressed Disease: Symptomatic[39]	0.692	0.588	0.796
Utility: Fracture Due to Cancer Treatment, First Year[53]	0.83	0.664	0.99
Utility: Fracture Due to Cancer Treatment, Post First Year[53]	0.87	0.69	0.99

Adverse Events

The model included common AEs that occurred in >5% of patients as reported in publicly available sources (e.g., the drug's prescribing information), as well as any serious AEs of interest documented in the trials. For each adverse event we used the associated cost and disutility and applied that to the proportion of patients experiencing that event. Adverse event-related costs (Table 4.7) were obtained from a Truven Health Analytics MarketScan® database study of patients diagnosed with prevalent types of cancer,[56] as well as MS-DRG estimates from Centers for Medicare and Medicaid Services.[55] The cost of each adverse event was multiplied by the proportion of patients who experienced the event, and this cost was applied in the first model cycle for each comparator.

Table 4.7. Adverse Event Inputs

Adverse Events of Interest	Continued ADT[11]	Apalutamide[11]	Enzalutamide[20,33]	Adverse Event Cost
Severe Rash	0.3%	5.2%	Not reported	$3,546[56]
Hypertension	11.8%	14.3%	4.6%	$3,746[56]
Fracture	6.5%	11.7%	9.8%	$4,529[55]
Dizziness	6.3%	9.3%	0.4%	$3,873[55]
Hypothyroidism	2.0%	8.1%	Not reported	$596[56]
Mental Impairment Disorder	3.0%	5.1%	5.2%	$3,000[56]
Cardiovascular-Related Adverse Events*	0.5%	0.5%	1.2%	$9,664[55]

*Continued ADT and enzalutamide estimates are based on grade 3/4 events reported in enzalutamide package insert. The apalutamide estimate assumes grade 3/4 ischemic events for apalutamide and placebo are the same, as reported in the SPARTAN FDA review documentation.[32]

Economic Inputs

Drug Acquisition Costs

For enzalutamide and abiraterone acetate, we obtained net pricing estimates from SSR Health, LLC, which combine data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs, to derive a net price. We estimated net prices by comparing the four-quarter averages (i.e., first quarter of 2017 through fourth quarter of 2017) of both net prices and wholesale acquisition cost (WAC) per unit to arrive at a mean discount from WAC for the drug. Finally, we applied this average discount to the most recently available WAC (May 16, 2018) to arrive at an estimated net price per unit. Because apalutamide was only recently approved by the FDA, we do not have any estimates on its discount from WAC, so we assumed a 29% discount which was in line with the discount from WAC for enzalutamide; we then applied this discount to apalutamide's current WAC to arrive at its assumed net price. For all ADTs except triptorelin pamoate, the net price has been derived using the drug price listed in the May 2018 Federal Supply Schedule, since no SSR price was available for the three out of four ADTs. For prednisone (administered with abiraterone acetate for mCRPC), since multiple inexpensive generic options are available, we used the WAC and not net price in keeping with ICER's drug pricing policy for drugs with generic formulations. Based on the regimen dosage specified above, the model will utilize the lowest cost combination of tablets/vials for each regimen.

Table 4.8. Drug Costs

	WAC Per Dose	Net Price Per Dose	Discount from WAC	Net Price Per Month	Source
Apalutamide (Erleada®) 60mg	$91.00	$64.61	29%*	$7,866.27	Redbook[61]; Assumption
Enzalutamide (Xtandi®) 40mg	$90.88	$64.45	29%	$7,847.62	Redbook[61]; SSR Health[62]
Abiraterone Acetate (Zytiga®) 250mg	$85.27	$58.60	31%	$7,134.79	Redbook[61]; SSR Health[62]
Prednisone 5mg†	$0.52	-	-	$31.66†	Redbook[61]
Leuprolide Acetate (Eligard) - 7.5mg	$451.69	$113.98	75%	$113.98	Redbook[61]; Federal Supply Schedule[63]
Goserelin Acetate (Zoladex) - 3.6mg	$605.00	$276.80	54%	$300.90	Redbook[61]; Federal Supply Schedule[63]
Triptorelin Pamoate (Trelstar) - 3.75mg	$813.24	$434.06	47%	$471.85	Redbook[61]; SSR Health[62]
Degarelix Acetate (Firmagon) - 80mg	$488.45	$199.34	59%	$216.69	Redbook[61]; Federal Supply Schedule[63]
Docetaxel 1mg	$8.07	-	-	$1,977.60†‡ (BSA = 1.98 mg/m^2)	Redbook[61]

BSA: body surface area based on median patient height and weight from SPARTAN, WAC: wholesale acquisition cost

*Discount calculated based on discount for enzalutamide

†Average WAC of generics used in place of net price in accordance with ICER's methods of calculating drug costs when multiple generics are available

‡Includes intravenous administration cost ($163.32), from CPT 96413, average reimbursement, non-facility limiting charge, year 2018: Chemo IV infusion 1 hr.

Duration of Therapy

As noted above, antiandrogen therapy costs are based on the trial-reported median durations of therapy for apalutamide[11] and enzalutamide.[20] We derived monthly transition probabilities from these estimates to model treatment discontinuation, and antiandrogen therapy costs were multiplied by the proportion of patients still on treatment each model cycle. In sensitivity analyses, duration of therapy is varied using the within-model calculated median MFS, multiplied by ratios comparing the trial-reported medians for MFS and duration of therapy. As the median treatment

duration based on trial data in the MFS state is likely an underestimation of real-world treatment duration, and MFS-based treatment duration likely an overestimation of real-world treatment duration, we also calculated the maximum treatment duration at which each comparator would have an ICER just below a WTP of $100,000 or $150,000 respectively.

Table 4.9. Duration of Therapy

	Estimate*^	Derived Discontinuation Monthly TP	Source
Apalutamide	16.9 months	0.040	SPARTAN[11]
Enzalutamide	18.4 months	0.037	PROSPER[20]

TP: transition probability

*In a scenario analysis, uncertainty in duration of therapy is linked to variation of MFS curves;

^In a threshold analysis we estimate the maximum duration of treatment at which the strategy would just remain cost-effective.

Post-Progression Costs

Post-progression costs were informed by real-world data on subsequent approved treatments for mCRPC.[37,38,59], since the regimens approved for post-progression therapy within the trials does not reflect the full range of available treatment options for mCRPC. Time to subsequent therapy was based on the PROSPER trial's reported median interval between the discontinuation of the trial regimen and subsequent antineoplastic therapy of 25 days in the enzalutamide group (applied to both antiandrogens in the model) and 18 days in the placebo group (Table 4.10).[20] These intervals were added to the model-calculated median MFS for each comparator, and from these estimates we derived monthly transition probabilities to calculate the proportion of patients on subsequent therapy during each model cycle.

We based the proportion of patients receiving subsequent treatment post-progression on the SPARTAN trial and the distribution of treatments received on a recent claims data analysis of a national sample of 4,275 mCRPC patients.[11,37] For the apalutamide arm, 314 patients discontinued initial treatment, 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 217 (77.7%) received subsequent treatment for mCRPC and the remainder received no treatment.[11]

Apalutamide and continued ADT patients received a weighted average cost of abiraterone acetate, enzalutamide, docetaxel, sipuleucel, radium-223, cabazitaxel or receive no treatment. Enzalutamide patients received a weighted average cost of abiraterone acetate, docetaxel, sipuleucel, radium-223, cabazitaxel or received no treatment, so that subsequent therapy cost did not include the initial therapy of enzalutamide; for this derivation, the reported proportion of

enzalutamide was added to the proportion of abiraterone acetate. Given that all subsequent treatment regimens are treat to progression, the weighted cost of subsequent treatment was based on the monthly cost of each drug plus monthly administration costs for the intravenously administered treatments.

Table 4.10. Model-Calculated Time to Subsequent Treatment

	Estimate*	Derived Monthly TP	Source
Continued ADT	16.6 months	0.041	PROSPER[20]
Apalutamide	38.8 months	0.018	PROSPER[20]
Enzalutamide	37.8 months	0.018	PROSPER[20]

TP: transition probability

*In sensitivity analyses, uncertainty in time to subsequent treatment calculations is linked to variation of MFS curves

Productivity Costs

Per capita incremental annual costs for unemployment, work-days missed, and absenteeism were previously reported to be $3,601 for patients and $4,013 for caregivers (2010 US dollars) using a sample of 1,313 prostate cancer patients and 874 caregivers from the nationally representative Medical Expenditure Panel Survey.[64] Costs were inflated to April 2018 dollars, using the Bureau of Labor Statistics, Medical Care component of the Consumer Price Index.[65]

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic analyses were also performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. In addition, threshold analyses were done for drug costs across a range of ICERs (from $50,000 to $150,000 per quality-adjusted life year [QALY]).

Scenario Analyses

Multiple scenario analyses were conducted to evaluate the impact of key model choices and assumptions on the robustness of the results and conclusions.

- We used extrapolations of trial-reported overall survival curves instead of the base-case hybrid approach incorporating SEER five-year survival for metastatic CRPC.
- We modeled three health states (MFS, progression, and dead) instead of the base-case four health states (progression split into asymptomatic and symptomatic progression) in recognition that PROSPER did not examine time to symptomatic progression.

- We explored the impacts of using independently fit antiandrogen curve extrapolations versus the base-case approach of using hazard ratio-derived curves.
- We estimated the impacts of using the currently available metastasis-free and overall survival curves for the placebo control in the PROSPER trial as the universal comparator.
- We explored the impact of modeling specific sub-populations, using subgroup-specific MFS hazard ratios, from the clinical trials.
- We explored the impact of linking treatment duration to total time spent in metastasis-free survival, instead of the trial-reported median durations of therapy.
- We included a modified societal perspective, accounting for productivity loss costs to patients and their informal care givers.

Model Validation

Model validation followed standard practices in the field. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. We then tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). Independent modelers also tested the mathematical functions in the model as well as the therapy-specific inputs and corresponding outputs. We also conducted sensitivity analyses with null input values to ensure the model produced findings consistent with expectations. Finally, we compared the ICER model to previously published models. We searched the literature to identify models that were similar to our own, with comparable populations, settings, perspective, and treatments.

4.3 Results

Base-Case Results

Apalutamide and enzalutamide resulted in increased life years, increased QALYs, increased time in MFS and asymptomatic progression, and increased costs compared to continued ADT. The gain in QALYs for antiandrogens was approximately 1.5 years, driven primarily by gains in time spent in MFS compared to continued ADT. Although antiandrogens increased treatment costs prior to metastasis, the delay of metastasis compared to continued ADT alone resulted in a savings in post-progression treatment costs.

The base-case ICERs for both antiandrogens versus continued ADT alone were below a threshold of $100,000 per QALY, with apalutamide having a slightly lower ICER ($68,000) than enzalutamide ($84,000).

Table 4.11. Base-case Results for Antiandrogen Therapies Compared to ADT

Treatment	Drug Cost (nmCRPC)	Post-Progression Treatment Costs	Total Cost	Life Years	QALYs	ICER vs. continued ADT
Continued ADT	$4,500	$427,000	$475,000	6.77	5.51	
Apalutamide + ADT	$195,000	$342,000	$583,000	8.45	7.10	$68,000
Enzalutamide + ADT	$209,000	$345,000	$601,000	8.40	7.01	$84,000

QALYs: quality-adjusted life years, ICER: incremental cost-effectiveness ratio
Costs are rounded to the nearest $1,000; total costs include drug costs.

Societal Perspective Results

Including patient and caregiver productivity costs in the analysis increases the total expected costs in all strategies and does not have an important impact on ICERs.

Table 4.12. Societal Perspective Results for Antiandrogen Therapies Compared to ADT

Treatment	Total Cost	Life Years	QALYs	ICER vs. continued ADT*
Continued ADT	$476,000	6.77	5.51	
Apalutamide + ADT	$584,000	8.45	7.10	$68,000
Enzalutamide + ADT	$601,000	8.40	7.01	$84,000

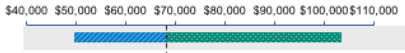
*Changes in the ICER compared to the base-case are smaller than $1,000.
Costs are rounded to the nearest $1,000; total costs include drug costs.

Sensitivity Analysis Results

We performed one-way sensitivity analysis to evaluate the impact of single parameter uncertainty on ICERs versus continued ADT. For the comparison of apalutamide to continued ADT, the parameters with the greatest impacts on the ICER were duration of therapy, the cost of apalutamide, time to subsequent therapy parameters, the utility for MFS, and apalutamide hazard ratios versus continued ADT. For the comparison of enzalutamide to continued ADT, the parameters with the greatest impacts on the ICER were very similar to those driving the apalutamide comparison, although variation of three parameters resulted in ICERs greater than $100,000: duration of enzalutamide therapy, the cost of enzalutamide, and the utility for MFS. For antiandrogen treatment duration, we note that these parameters were a function of the calculated median MFS in the model.

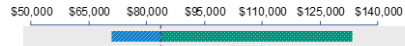
Figure 4.5. Tornado Diagram(s) for One-Way Sensitivity Analyses of ICERs for Antiandrogen Therapies versus ADT

Apalutamide vs. Continued ADT



Parameter	Low Value	High Value	Low Result	High Result	Spread
Apalutamide Duration of Therapy	14.0 m	22.5 m	$49,681	$103,410	$53,729
Apalutamide Cost: 60 mg tablet	$52	$78	$44,898	$91,492	$46,594
Apalutamide Time to Subsequent Therapy	34.8 m	54.8 m	$76,286	$39,837	$36,449
Utility: Metastasis-Free Survival	0.72	0.99	$89,659	$60,905	$28,754
Apalutamide Hazard Ratio: MFS	0.23	0.35	$58,477	$82,132	$23,655
Apalutamide Hazard Ratio: OS	0.47	1.04	$61,686	$78,806	$17,120
ADT Time to Subsequent Therapy	14.6 m	17.6 m	$61,415	$71,543	$10,127
Cost/Month: Sipuleucel	$57,315	$85,973	$72,848	$63,542	$9,307
Abiraterone Cost: 250 mg tablet	$47	$70	$70,697	$65,693	$5,005
Enzalutamide Cost: 40 mg capsule	$52	$77	$70,285	$66,106	$4,179
ADT Proportion Subsequent Therapy	0.75	0.81	$70,122	$66,269	$3,853
SEER mCRPC 5-year Survival Rate	0.20	0.28	$69,954	$66,158	$3,795
Utility: Symptomatic Progression	0.59	0.80	$66,556	$69,917	$3,361
Apalutamide Hazard Ratio: TSP	0.32	0.63	$68,195	$70,175	$1,980
Cost/Month: MFS Supportive Care	$2,197	$3,295	$67,465	$68,926	$1,461

Enzalutamide vs. Continued ADT



Parameter	Low Value	High Value	Low Result	High Result	Spread
Enzalutamide Duration of Therapy	16.5 m	26.1 m	$70,861	$133,416	$62,555
Enzalutamide Cost: 40 mg capsule	$52	$77	$59,230	$108,115	$48,885
Utility: Metastasis-Free Survival	0.72	0.99	$110,799	$74,547	$36,252
Enzalutamide Time to Subsequent Therapy	33.8 m	51.8 m	$92,383	$56,584	$35,799
Enzalutamide Hazard Ratio: MFS	0.24	0.35	$70,573	$95,832	$25,259
Enzalutamide Hazard Ratio: OS	0.58	1.09	$75,320	$94,094	$18,774
ADT Time to Subsequent Therapy	14.6 m	17.6 m	$76,507	$87,211	$10,704
Cost/Month: Sipuleucel	$57,315	$85,973	$88,399	$78,947	$9,452
Abiraterone Cost: 250 mg tablet	$47	$70	$86,214	$81,131	$5,083
ADT Proportion Subsequent Therapy	0.75	0.81	$85,629	$81,716	$3,913
SEER mCRPC 5-year Survival Rate	0.20	0.28	$85,280	$81,814	$3,466
Enzalutamide Hazard Ratio: TSP	0.33	0.63	$83,540	$85,133	$1,593
Cost/Month: MFS Supportive Care	$2,197	$3,295	$82,926	$84,420	$1,494
Utility: Asymptomatic Progression	0.80	0.87	$83,041	$84,314	$1,273
Utility: Symptomatic Progression	0.59	0.80	$83,129	$84,223	$1,094

We performed probabilistic sensitivity analysis to evaluate the impacts of joint parameter uncertainty over 5,000 model simulations, then calculated the probability of each antiandrogen being cost-effective versus continued ADT at different willingness to pay per QALY thresholds. For both antiandrogens, only a small percentage of all 5,000 simulations fell below the $50,000 per QALY cost-effectiveness threshold. Approximately 80% of simulations for enzalutamide and nearly 100% of simulations for apalutamide fell below the $100,000 per QALY cost-effectiveness threshold. Almost all 5,000 simulations fell below a $150,000 per QALY threshold for both antiandrogens. Additional details on the results of probabilistic sensitivity analysis can be found in Appendix E.

Table 4.13. Probabilistic Sensitivity Analysis Results: Antiandrogen Therapies versus ADT

Comparator vs. Continued ADT	Probability ICER < $50,000 per QALY	Probability ICER < $100,000 per QALY	Probability ICER < $150,000 per QALY
Apalutamide + ADT	33%	99%	100%
Enzalutamide + ADT	3%	82%	99%

ADT: androgen deprivation therapy, ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year

Scenario Analyses Results

We performed various scenario analyses to test the degree to which alternative model structure and parameter decisions resulted in different conclusions compared to our base-case model, and to test whether results differed for trial patient sub-populations stratified by PSA doubling times.

Using the overall survival curves to model all transitions to death, versus the base-case hybrid approach, resulted in decreased survival and decreased cost (due to less time spent in progression) for all comparators, with a slight increase in the ICERs.

Table 4.14. Long-Term Extrapolations of Trial-Reported Overall Survival Curves Instead of the Base-case Hybrid Approach Incorporating SEER Five-Year Survival for mCRPC

Treatment	Drug Cost (nmCRPC)	Post-Progression Treatment Costs	Total Cost	Life Years	QALYs	ICER vs. Continued ADT
Continued ADT	$4,500	$332,000	$370,000	5.74	4.80	
Apalutamide + ADT	$195,000	$253,000	$482,000	7.20	6.23	$78,000
Enzalutamide + ADT	$209,000	$230,000	$471,000	6.85	5.95	$88,000

ADT: androgen deprivation therapy, ICER: incremental cost-effectiveness ratio, nmCRPC: nonmetastatic castration-resistant prostate cancer, QALYs: quality-adjusted life years
Costs are rounded to the nearest $1,000; total costs include drug costs

The PROSPER trial did not report time to symptomatic progression, thus it could be argued that the 4-state model employed in the base-case is inappropriate to model enzalutamide. When we converted the model to three health states instead of the base-case model's four health states, we used the average of the utilities for asymptomatic progression and symptomatic progression (average = 0.76) as the utility applied to the single progression health state; this was a simplifying assumption in recognition that each comparator had different time spent in each health state, making a weighted average of utilities based on time spent in asymptomatic versus symptomatic progression problematic given the constraint of employing consistent utilities across comparators.

In this scenario, total life years remained the same as expected, however QALYs were decreased for each comparator since the modeled time to symptomatic progression curves, which divide asymptomatic and symptomatic progression health states in the base-case model, were generally closer to overall survival curves than the MFS curves, resulting in more time spent in asymptomatic progression (utility = 0.83) than in symptomatic progression (utility = 0.69) in the four-state model. Thus, ignoring the difference between asymptomatic and symptomatic progression may slightly

underestimate post-metastasis quality of life in mCRPC patients. Nevertheless, these differences were minor, and the ICERs were mostly unchanged.

Table 4.15. Three Health States (MFS, Progression, and Dead) Instead of the Base-case Four Health States (Progression Split into Asymptomatic and Symptomatic Progression)

Treatment	Drug Cost (nmCRPC)	Post-Progression Treatment Costs	Total Cost	Life Years	QALYs	ICER vs. continued ADT
Continued ADT	$4,500	$427,000	$475,000	6.77	5.39	
Apalutamide + ADT	$195,000	$342,000	$583,000	8.45	6.95	$69,000
Enzalutamide + ADT	$209,000	$345,000	$601,000	8.40	6.91	$83,000

ICER: incremental cost-effectiveness ratio, QALYs: quality-adjusted life years
Costs are rounded to the nearest $1,000. Total costs include drug costs.

The subgroup hazard ratios for MFS, stratified by PSA doubling time in both trials were not notably different than the total population hazard ratios for apalutamide and enzalutamide for doubling times less than six months; therefore, there was little difference in results compared to the base-case. For patients with a doubling time greater than six months, the hazard ratio for enzalutamide had the largest impact.

Table 4.16. Subgroup-Specific MFS Hazard Ratios

	MFS Hazard Ratio	
PSA Doubling Time	Apalutamide	Enzalutamide
<6 months*	0.29	0.28
>6 months*	0.30	0.35

MFS: metastasis-free survival, PSA: prostate specific antigen
*In SPARTAN, PSA doubling times were stratified as ≤6 months and >6 months; in PROSPER, PSA doubling times were stratified as <6 months and ≥6 months.

Table 4.17. Subgroup Specific Results for Antiandrogen Therapies Compared to ADT

Treatment	Drug Cost (nmCRPC)	Post-Progression Treatment Costs	Total Cost	Life Years	QALYs	ICER vs. continued ADT
PSA Doubling Time <6 months						
Apalutamide + ADT	$195,000	$345,000	$587,000	8.41	7.07	$72,000
Enzalutamide + ADT	$209,000	$341,000	$597,000	8.43	7.04	$80,000
PSA Doubling Time >6 months						
Apalutamide + ADT	$195,000	$346,000	$587,000	8.37	7.04	$73,000
Enzalutamide + ADT	$208,000	$350,000	$605,000	8.21	6.87	$96,000

ADT: androgen deprivation therapy, ICER: incremental cost-effectiveness ratio, nmCRPC: nonmetastatic castration-resistant prostate cancer, QALYs: quality-adjusted life years

Costs are rounded to the nearest $1,000. Total costs include drug costs.

Note that for apalutamide the reported MFS hazard ratios for the subgroups are based on unstratified analyses and are both higher than the base-case MFS hazard ratio of 0.28 that resulted from the main stratified analysis. Hence, the ICERs for both apalutamide subgroups are slightly higher than the base-case ICER.

Duration of Therapy

We explored the impact of linking treatment duration to total time spent in MFS in a scenario analysis. This notably increased time on treatment compared to the base-case, with apalutamide and enzalutamide treatment durations increasing to 4.2 and 4.1 years, respectively. When considering the increased drug cost due to longer therapy duration and assuming that efficacy would be unchanged, each drug would exceed the $150,000 per QALY threshold. For further details on this scenario see Appendix Table E8. As real-world duration of therapy will be influenced by the occurrence of severe AEs and other factors, yet data to quantify this accurately are lacking, we present the maximum duration of therapy at which the incremental cost-effectiveness ratio for the specific drug would fall at the $100,000 and $150,000 per QALY thresholds (Table 4.18).

Table 4.18. Maximum Duration of Therapy at which the Incremental Cost-Effectiveness Ratio Would Fall at the Threshold

Duration of Therapy (months)	Threshold of $100,000 per QALY Gained	Threshold of $150,000 per QALY Gained
Apalutamide	21.9	30.3
Enzalutamide	20.8	28.7

QALY: Quality-adjusted life year

Threshold Analysis Results

The unit prices at which antiandrogens would reach cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained are presented below.

Table 4.19. Threshold Analysis Results

	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY
Apalutamide + ADT	$11,079	$7,866	$6,638	$10,014	$13,391
Enzalutamide + ADT	$11,065	$7,847	$5,685	$8,895	$12,105

ADT: androgen deprivation therapy, QALY: quality-adjusted life year

*WAC prices for the two investigational drugs were not available as of the date of this report.

Model Validation

All mathematical functions in the model were consistent with the report (and supplemental Appendix materials). The model produced findings consistent with expectations when testing individual functions. Sensitivity analyses with null input values ensured the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model, as well as specific inputs and corresponding outputs.

In our review of the published literature, we found no economic models evaluating the cost-effectiveness of apalutamide or enzalutamide compared to each other or to the existing standard of care in patients with nmCRPC. Hence our review of other relevant models, from a setting and population perspective, is limited to a comparison of methodologies used, and not results. Additionally, we have included in our review only models published in the last 10 years.

A cost-effectiveness model by Pollard et al., 2017 reviewed several treatment sequence options versus standard of care in patients with mCRPC.[38] All treatment sequences included initiation with Sipuleucel-T, with additional treatment upon disease progression, that included enzalutamide, abiraterone, docetaxel, radium 223 and cabazitaxel, in increasing order of drugs per sequence. Additionally, they also developed a second cost-effectiveness model comparing treatment

sequences that excluded sipuleucel-T and began with enzalutamide. Both models were built from a societal perspective and calculated cost per life year gained at a threshold of $100,000. Unlike the ICER model which derived cost inputs using the SSR and FSS database, Pollard et al.'s model derives these estimates from the authors' institution's pharmaceutical drug supplier, Besse Medical. These costs are specific to New York City and do not represent a national-average cost, which the ICER model attempts to represent. Treatment duration was dependent on data pertaining to standard dosing schedules or RCT-derived survival data, like in the ICER model. Survival duration in the mCRPC phase in Pollard et al.'s model was 41 months, while in the ICER model, it was 39 months for apalutamide and 36 months for enzalutamide. Unlike the ICER model, Pollard et al.'s model does not include non-drug costs such as those related to skeletal events, palliative care, and pain.

A cost-effectiveness model submitted to NICE by the manufacturers of degarelix was reviewed by Uttley et al., 2017, the Evidence Review Group sponsored by NICE.[66] The model compared degarelix, a luteinizing hormone releasing hormone (LHRH) antagonist, to goserelin (Zoladex®), an LHRH agonist in patients with advanced hormone-dependent prostate cancer, from a UK National Health Service. In the model submitted to NICE, subsequent therapies following degarelix included antiandrogen addition or withdrawal, chemotherapy, abiraterone, and supportive and palliative care, while in the ICER model, subsequent therapies after either apalutamide or enzalutamide aligned with those seen in the SPARTAN trial. The manufacturer model employed a 30-year time horizon, while the ICER model employed a 50-year lifetime time horizon. In both models, transition to subsequent therapies were dependent on disease progression. The manufacturer-submitted model employs health state utilities based on trial data, while the ICER model uses utilities recorded in a Canadian and UK perspective since none from a US setting are currently available.

Among other economic models reviewed, one by Pilon et al., 2016 compared the cost-effectiveness in terms of cost per median overall survival month for treatment with abiraterone acetate plus prednisolone or enzalutamide in chemotherapy naïve asymptomatic/mildly symptomatic mCRPC patients.[67] Survival data for this model were obtained from the drugs' respective trials, namely, COU-AA-302 for abiraterone acetate plus prednisolone and PREVAIL for enzalutamide. Like the ICER model, Pilon et al. model assessed cost-effectiveness using a survival modeling approach and trial-reported median treatment duration. Unlike the ICER model, which used a partitioned-survival modeling approach to account for costs and outcomes pertaining to MFS, asymptomatic progression, and symptomatic progression, Pilon et al. model costs are based only on overall survival curves presented in the trials. Also, unlike the ICER model, Pilon et al. used the WAC instead of an estimated net price for the assessed therapies, which may overestimate drug costs.

4.4 Summary and Comment

Our analysis indicates that the long-term cost-effectiveness of apalutamide and enzalutamide, compared to continued ADT without antiandrogen therapy, in patients with nmCRPC fell below $100,000 per QALY gained.

Both therapies were estimated to be more effective and to generate more life years and QALYs at higher total cost, both from a health sector and societal perspective, compared to continued ADT treatment (assuming a 29% discount on list prices of enzalutamide and apalutamide). This finding remained robust in most sensitivity analyses and in all scenario analyses[a] except the analysis linking duration of therapy to total time spent in MFS, which resulted in incremental cost-effectiveness ratios greater than $150,000 per QALY gained. Due to lack of published data, this scenario analysis neither considers drug discontinuation or dose reduction/interruption in case of ≥3 grade AEs, nor considers the potential increase in efficacy due to longer exposure to therapy, and therefore likely overestimates the incremental cost-effectiveness ratios for both drugs. Longer term data on duration of treatment should clarify the true cost-effectiveness of these therapies.

Based on one-way sensitivity analysis, the parameters with the greatest impacts on the ICER were the antiandrogen drug costs, time to subsequent therapy, utility for MFS, duration of antiandrogen therapy, and antiandrogen hazard ratios versus continued ADT. For the comparison of apalutamide to continued ADT, only the duration on therapy resulted in an ICER versus continued ADT greater than $100,000 per QALY. For the comparison of enzalutamide to continued ADT, variation of the cost of enzalutamide, the duration of antiandrogen therapy, and the utility for MFS resulted in incremental cost-effectiveness ratios greater than $100,000.

Of note, these results reflect the existing costs of antiandrogen treatments which are already used for mCRPC and are generally similarly priced. For example, enzalutamide is already used for treatment of mCRPC and thus the cost-effectiveness of earlier treatment with enzalutamide reflects that existing price (as well as the similar price of abiraterone acetate). This evaluation did not look at the long-term value of antiandrogen therapy for mCRPC, and so the results should be interpreted as reflecting the value of early treatment with antiandrogens in nmCRPC compared with treating when metastatic disease develops given the existing costs of antiandrogen therapy.

[a]The latter included extrapolation of trial-reported overall survival curves instead of using long term SEER survival data; modelling three health states (MFS, progression, and dead) instead of the base-case four health states (progression split into asymptomatic and symptomatic progression); and subgroup analyses for patients with a PSA doubling time either smaller or greater than six months.

Limitations

The modeled lifetime outcomes are highly dependent on extrapolations of the short-term outcomes observed in the SPARTAN[11] and PROSPER[20] trials. In particular, long term extrapolations of overall survival and time to symptomatic progression are based on limited follow-up data. For overall survival, we employed long-term survival estimates for mCRPC from SEER,[36] however it is uncertain whether survival after mCRPC in patients who are naïve to antiandrogen therapy is similar to survival after progression on antiandrogen therapy. The model was most sensitive to our modeling of treatment duration, which was based on the trial-reported medians. Our scenario analysis linking therapy duration to time spent in MFS was limited by the availability of data to account for drug discontinuation, dose reductions or interruptions, as well as the potential impact of longer therapy duration on long-term drug efficacy.

Conclusions

In conclusion, the findings of our analysis suggest that apalutamide and enzalutamide provide gains in life years and QALYs at higher costs compared to continued ADT over a lifetime horizon. Based on the current data and model assumptions, the incremental cost-effectiveness of these antiandrogen therapies versus continued ADT is expected to fall within commonly cited thresholds of $50,000 to $150,000 per QALY gained. Longer term data on duration of treatment and overall survival should clarify the true cost-effectiveness of these therapies.

5. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the review of apalutamide, enzalutamide, and abiraterone acetate.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

5.1 Potential Other Benefits

Given the disproportionate impact of prostate cancer on black men, improved therapy for nmCRPC has the potential to reduce health disparities across racial and socio-economic categories in the US.

Although we have no evidence from clinical trials, we heard from patient groups and clinical experts that there may be psychological benefits to having a therapy available for men who are experiencing rising PSA test results.

5.2 Contextual Considerations

In the absence of more mature survival data, there is significant uncertainty about the survival benefit, if any, of treating men with nmCRPC with antiandrogen therapy.

6. Value-Based Price Benchmarks

ICER's value-based price benchmarks are meant to showcase drug prices that are required to align with value, defined as a willingness-to-pay (WTP) price range of between $100,000 to $150,000 per QALY. In cases where prices fall outside the upper bound and sometimes within this range, we present value-based prices.

For the antiandrogens, we did not estimate value-based prices that would meet WTP thresholds because the analysis in this report effectively compares earlier use of these agents (i.e., in nmCRPC) to later use of these and other drugs (in mCRPC), making problematic any attempt to understand the effects of price premiums.

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of apalutamide and enzalutamide in the nmCRPC population. We used the WAC, an estimate of discounted WAC, and the three threshold prices for each drug in our estimates of budget impact.

7.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug and non-drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included the candidate populations eligible for treatment: adult males diagnosed with nmCRPC eligible for first-line therapy with antiandrogens. Scher et al. estimated the incidence of nmCRPC using a dynamic transition model that used prostate-cancer-specific risk of disease progression and mortality.[68] The progression and mortality estimates were sourced from published trials, meta-analyses, and observational study data, and incidence and prevalence estimates across eight prostate cancer health states were simulated between 2009 and 2020. nmCRPC was defined as localized prostate cancer with biochemical failure after hormonal therapy with a projected incidence of approximately 59,000 cases in 2020. Applying this incidence to the projected 2020 US adult male population resulted in an incidence estimate of 0.05%. We then applied this estimate to the five-year estimated and projected US adult male population between 2018 and 2022, which resulted in an annual incident population of approximately 59,000 patients eligible for treatment with either antiandrogen therapy. This reflects the labeled indication for Apalutamide and enzalutamide, although the clinical trials enrolled a higher risk population with more rapid PSA doubling times. At least initially, it is likely that not all patients with nmCRPC would be treated with antiandrogen therapy.

ICER's methods for estimating potential budget impact are described in detail elsewhere{Pearson, 2018, 10001} and have been recently updated. The intent of our revised approach to budgetary impact is to document the percentage of patients who could be treated at selected prices without

crossing a budget impact threshold that is aligned with overall growth in the US economy. For 2018-19, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $991 million per year for new drugs.

Briefly, we evaluated a new drug that would take market share from one or more drugs and calculated the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that either apalutamide or enzalutamide would replace existing standard of care: ADT without antiandrogen therapy.

7.3 Results

Apalutamide

Table 7.2 illustrates the per-patient budget impact calculations in more detail, based on WAC ($133,000 per year), discounted WAC ($94,400 per year), and the price to reach $50,000 per QALY for apalutamide ($79,700 per year) compared to ADT alone. We did not estimate potential budgetary impact at the prices that would meet thresholds of $100,000 and $150,000 per QALY. While theoretically the current price of apalutamide could increase and meet these thresholds, this analysis effectively compares earlier use of the drug (i.e., in nmCRPC) to later use of this and other drugs (in mCRPC), making problematic any attempt to understand the budgetary effects of price premiums.

Table 7.1. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Apalutamide

	Average Annual Per Patient Budget Impact		
	WAC	Discounted WAC	$50,000/QALY
Apalutamide	$91,058	$68,201	$59,297
ADT		$29,073	
Difference	$61,985	$39,128	$30,224

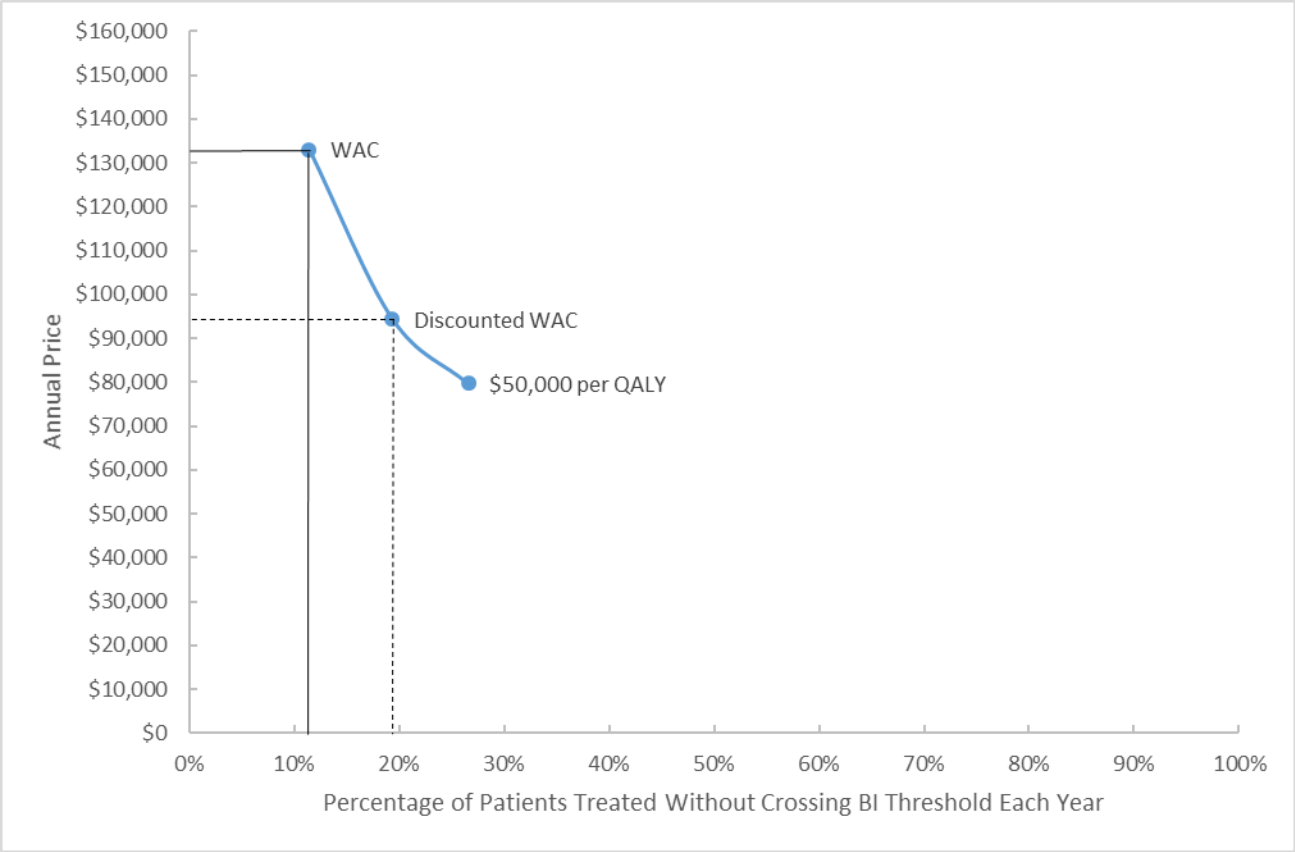
ADT: androgen deprivation therapy, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

The average potential budgetary impact when using the WAC was an additional per-patient cost of approximately $62,000, and approximately $39,100 using the discounted WAC. Average potential budgetary impact at the $50,000 per QALY cost-effectiveness threshold prices was approximately $30,200 per patient.

As shown in Figure 7.1, approximately 11% of eligible patients could be treated in a given year without crossing the ICER annual budget impact threshold of $991 million at apalutamide's WAC and approximately 19% of patients at the discounted WAC. Approximately 27% of the eligible

population could be treated before exceeding the $991 million threshold at the $50,000 per QALY threshold price.

Figure 7.1. Potential Budget Impact Scenarios at Different Prices of Apalutamide to Treat Adult Males with nmCRPC



Enzalutamide

Table 7.3 illustrates the per-patient budget impact calculations in more detail, based on WAC ($132,800 per year), discounted WAC ($94,200 per year), and the price to reach $50,000 per QALY for enzalutamide ($68,200 per year) compared to ADT. As stated earlier, we did not estimate potential budgetary impact at the prices that would meet thresholds of $100,000 and $150,000 per QALY. While theoretically the current price of enzalutamide could increase and meet these thresholds, this analysis effectively compares earlier use of the drug (i.e., in nmCRPC) to later use of this and other drugs (in mCRPC), making problematic any attempt to understand the budgetary effects of price premiums.

Table 7.2. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Enzalutamide

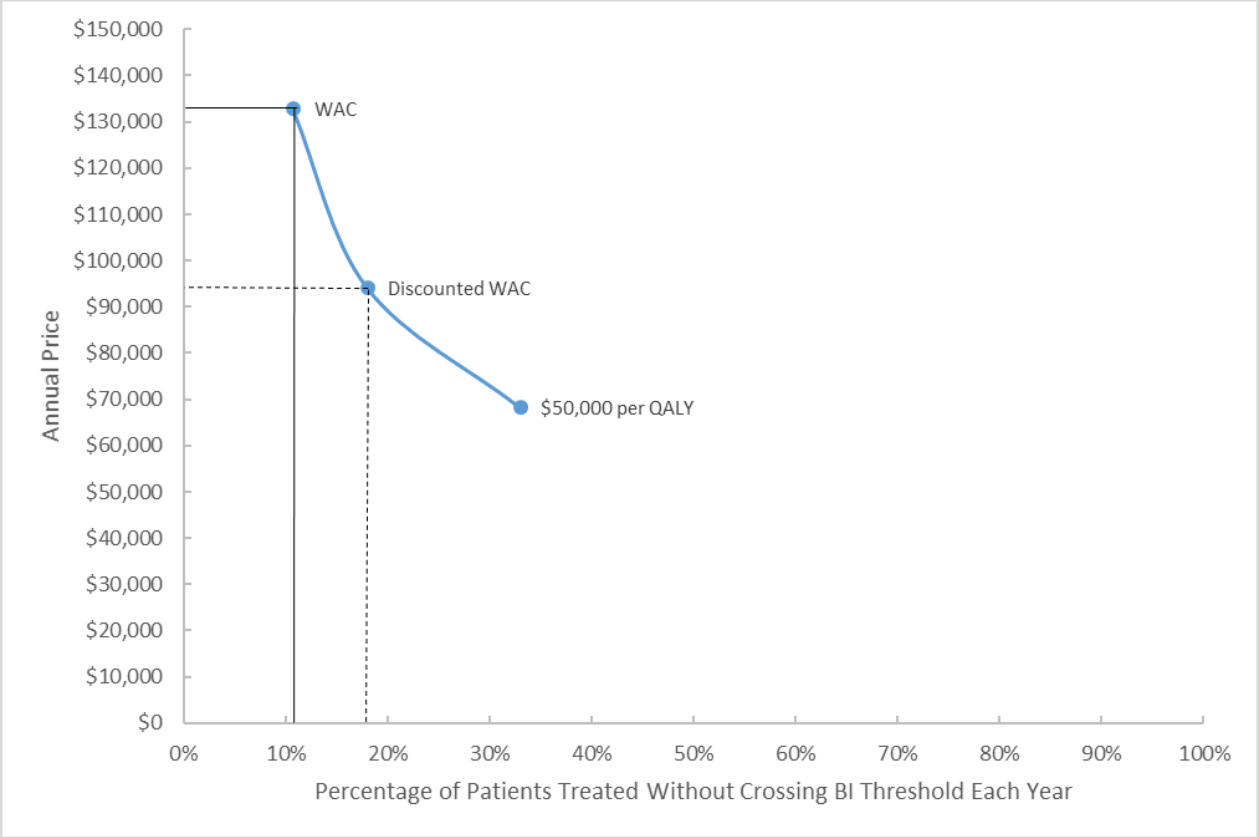
	Average Annual Per Patient Budget Impact		
	WAC	Discounted WAC	$50,000/QALY
Enzalutamide	$93,824	$70,033	$54,048
ADT		$29,073	
Difference	$64,751	$40,959	$24,975

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

The average potential budgetary impact when using the WAC was an additional per-patient cost of approximately $64,800, and approximately $41,000 using the discounted WAC. Average potential budgetary impact per patient at the $50,000 per QALY cost-effectiveness threshold price was approximately $25,000 annually.

As shown in Figure 7.2, approximately 11% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $991 million at enzalutamide's WAC and approximately 18% of patients at the discounted WAC. Approximately one-third of the entire eligible patient population could be treated in a given year without crossing the $991 million threshold at the $50,000 per QALY threshold price.

Figure 7.2. Potential Budget Impact Scenarios at Different Prices of Enzalutamide to Treat Adult Males with nmCRPC



As illustrated in the above analysis, treating the entire eligible nmCRPC eligible population with either antiandrogen therapy would result in a substantial budget impact. However, at the September 13th, 2018 Midwest CEPAC meeting, clinical experts indicated that these antiandrogen therapies will initially likely be prescribed only in an nmCRPC sub-population with rapid PSA doubling times, and not the larger nmCRPC population indicated by the drugs' FDA labels. ICER is therefore not issuing an access and affordability alert at this time, but recommends that health systems likely to be covering large numbers of affected patients, such as the Veterans' Administration, pay close attention to actual use and costs of antiandrogen treatment.

8. Summary of the Votes and Considerations for Policy

8.1 About the Midwest CEPAC Process

During the Midwest CEPAC public meetings, the Midwest CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to the Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

At the September 13th meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of antiandrogen therapies, and treatment for non-metastatic castrate resistant prostate cancer (nmCRPC). Following the evidence presentation and public comments (public comments from the meeting can be accessed https://www.youtube.com/watch?v=2WUkEJCGg4A, starting at minute 1:22:08) the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to antiandrogen therapies. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 8.1 below):

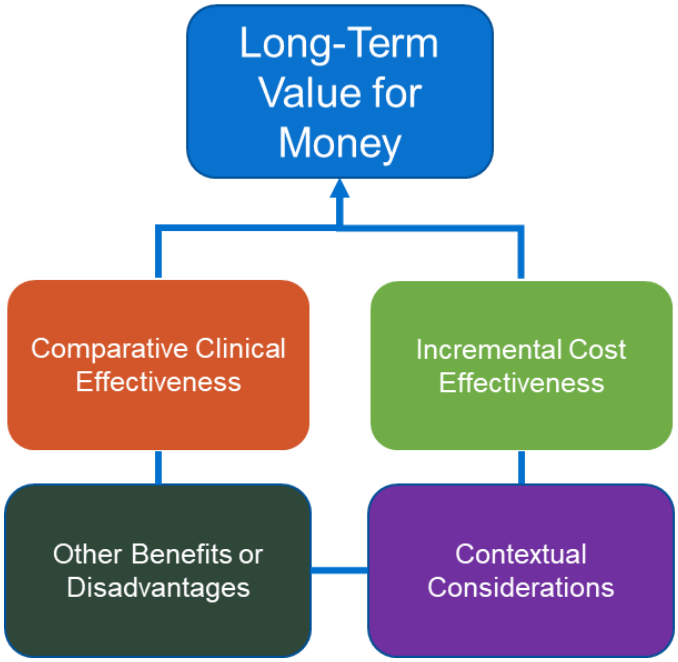
1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the Midwest CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base-case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

3. Potential other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 8.1. Conceptual Structure of Long-term Value for Money



8.2 Voting Results

All voting questions pertain to the following patient population: For each question, we are considering men with high risk (PSA doubling time ≤10 months) nonmetastatic castration-resistant prostate cancer being treated with androgen deprivation therapy. The comparator is waiting to add antiandrogen therapy with either abiraterone acetate or enzalutamide until the development of detectable metastatic disease.

Clinical Effectiveness

1) **Is the evidence adequate to demonstrate a net health benefit of treating with apalutamide?**

Yes: 10 votes	No: 1 vote

Comments: After clarifying that voting yes on this question does not mean that further evidence is not needed, nor does it mean the panel endorses an "A" rating for the evidence, the panel voted overwhelmingly that the evidence was adequate to demonstrate a net

health benefit. Some panelists noted, however, that they felt the net health benefit was smaller than ICER's "A" rating suggested and should have been a "B+."

2) **Is the evidence adequate to demonstrate a net health benefit of treating with enzalutamide?**

Yes: 8 votes	No: 3 votes

Comments: One of the panel members who voted yes on question one, but no on question two, commented that the lack of evidence on time to symptomatic progression for patients on enzalutamide was concerning and factored in to her "no" vote. Some panelists who voted yes felt that the net health benefit was smaller than ICER's "A" rating suggested and the rating should have been a "B+" for enzalutamide as well.

3) **Is the evidence adequate to demonstrate a net health benefit of treating with abiraterone acetate?**

Yes: 2 votes	***No: 10 votes***

Comments: The panel discussed the promising nature of the data around abiraterone acetate, but some expressed reservations about the risk of the drug due to the necessary concomitant steroid use. The panel also remarked that direct trials comparing abiraterone acetate to enzalutamide and apalutamide would be most useful. Given the risks and lack of evidence, the panel voted that there was not enough evidence to demonstrate a net health benefit at this time.

4) **Is the evidence adequate to distinguish the net health benefits of apalutamide and enzalutamide?**

Yes: 0 votes	***No: 11 votes***

Comments: No discussion followed this vote since the lack of comparable evidence for both treatments had already been thoroughly discussed.

5) **Is the evidence adequate to demonstrate that abiraterone acetate has comparable efficacy to apalutamide and enzalutamide?**

Yes: 0 votes	***No: 11 votes***

Comments: No discussion followed this vote since the lack of comparable evidence for all treatments had already been thoroughly discussed.

Potential Other Benefits

6) **Does treating patients with antiandrogen therapies offer one or more of the following "potential other benefits?" (select all that apply)**

Potential Other Benefits	Number of Votes
This intervention offers reduced complexity that will significantly improve patient outcomes.	0 / 11
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	0 / 11
This intervention will significantly reduce caregiver or broader family burden.	0 / 11
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.	2 / 11
This intervention will have a significant impact on improving the patient's ability to return to work or school and/or their overall productivity.	0 / 11
There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention	3 / 11

Comment: The panel discussed how these treatments fail to reduce health disparities across any category and may in fact exacerbate disparities due to systemic inequities in access to the health care system. Two panel members voted that these treatments offered a novel mechanism of action, but both hoped for more robust evidence in the future. Three panel members voted that these treatments had important other potential benefits or disadvantages that should be considered, including the option for men to begin treatment sooner given that many men find it difficult to take a "wait and see" approach.

7) **Are any of the following contextual considerations important in assessing antiandrogen therapies' long-term value for money? (select all that apply)**

Potential Other Contextual Considerations	Number of Votes
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	3 / 11
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	4 / 11
This intervention is the first to offer any improvement for patients with this condition.	0 / 11
There is significant uncertainty about the long-term risk of serious side effects of this intervention.	3 / 11
There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	8 / 11
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	3 / 11

Comment: The panel again commented on the need for robust head-to-head trials of these treatments. The lack of evidence led a majority of panel members to vote that significant uncertainty remains regarding the long-term benefits of these treatments. A few members who voted for potential additional contextual considerations expressed concern that this treatment would be used outside the high-risk subgroup, which would subject a larger pool of patients to unknown risks.

Long-Term Value for Money

Comments: A thorough discussion about treatment duration accompanied both long-term value for money votes. Panel members expressed concern that the median treatment duration in the clinical trials was shorter than is typical in clinical practice, and thus the cost of treatment would be higher than the ICER model reflects. This influenced the majority votes for "intermediate value". To respond to these concerns, ICER conducted an additional scenario analysis with treatment duration being tied to metastasis-free-survival. This can be found in section 4.3 and is reflected in the Summary and Comment section above.

8) **In men with high risk (PSA doubling time ≤10 months) non-metastatic castration resistant prostate cancer being treated with androgen deprivation therapy, given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering potential other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with apalutamide compared with waiting to add antiandrogen therapy with either abiraterone acetate or enzalutamide until the development of detectable metastatic disease?**

Low: 2 votes	***Intermediate: 7 votes***	High: 2 votes

9) **In men with high risk (PSA doubling time ≤10 months) non-metastatic castration resistant prostate cancer being treated with androgen deprivation therapy, given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering potential other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with enzalutamide compared with waiting to add antiandrogen therapy with either abiraterone acetate or enzalutamide until the development of detectable metastatic disease?**

Low: 2 votes	***Intermediate: 8 votes***	High: 1 vote

8.3 Key Policy Recommendations

During its deliberation of evidence, the Midwest CEPAC Panel was joined by a clinical expert, Dr. Russell Szmulewitz from the University of Chicago, and patient representative, Joel Nowak, a prostate cancer patient and advocate (Conflict of interest disclosures found in Appendix G). The evidence presentation and subsequent discussion between Midwest CEPAC panel members and the clinical and patient representatives was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. Given this discussion and previous research, ICER generated the following policy recommendations:

Payers and Clinicians

- The FDA approved indications for apalutamide and enzalutamide are broad and do not include limitations related to the rapid PSA doubling times that were part of the eligibility criteria for pivotal studies. Since benefits for patients have not been directly demonstrated among patients with slower PSA doubling times, payers may therefore consider limiting coverage to patients similar to those in the clinical trials. One clinical expert expressed that such an approach would not be viewed as clinically inappropriate by some clinicians but that many would consider intrusion into their clinical decision-making offensive.
- If apalutamide and enzalutamide are considered for treatment of men with nmCRPC and longer PSA doubling times, clinicians should practice shared decision-making with their patients and make them aware that the clinical trials only examined men with doubling times ≤10 months.

Payers

- The evidence base is not adequate to distinguish the clinical benefits or risks of apalutamide and enzalutamide in treating nmCRPC. Since lower prices benefit patients as well, payers may consider negotiating preferential price discounts linked to formulary tiering or step therapy favoring the less expensive option.
- Since price appears to be aligned with the added benefits from early treatment, payers should work to design and implement benefit designs that would cover antiandrogen therapy in a way that reduces financial toxicity for patients.

Federal Government

- There are no financial incentives for the manufacturer of abiraterone acetate, which is going off patent soon, to perform trials of abiraterone acetate that might undermine interest in newer agents. If clinical equivalence could be demonstrated, however, there could potentially be substantial savings for both payers and patients. The Japanese government is sponsoring a trial of abiraterone acetate among men with CRPC. Funding for a similar trial

in the US should actively be considered by the Patient-Centered Outcomes Research Institute (PCORI) or the NIH.

Manufacturers and Researchers

- Manufacturers and researchers should collaborate to ensure that future clinical trials of treatments for men with nmCRPC or mCRPC use identical endpoints to allow for clear comparison of drug effectiveness. All trials in nmCRPC should also include patient-important endpoints such as time to symptomatic progression and should be powered to measure changes in overall survival.
- Data from the large trials of apalutamide and enzalutamide should be analyzed jointly to better inform the understanding of whether metastasis-free survival is a valid surrogate for overall survival in men receiving antiandrogen therapy for nmCRPC.

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This is the first ICER review of antiandrogens for nonmetastatic castration-resistant prostate cancer.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.

	#	Checklist item
Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A2. Search Strategy of Medline and Cochrane Central Register of Controlled Trials (via Ovid)

1	Prostatic Neoplasms, Castration-Resistant/
2	(prostat* and (cancer* or carcinoma* or tumo* or malignan* or adeno* or neoplas*)).ti,ab.
3	(androgen* or hormon* or castrat*).ti,ab.
4	(independent or insensitive or refractory or resistant).ti,ab.
5	3 and 4
6	2 and 5
7	1 or 6
8	exp Androgen Antagonists/
9	Steroid Synthesis Inhibitors/
10	Abiraterone acetate/
11	(Abiraterone adj1 acetate).ti,ab.
12	(zytiga or 'CB 7630' or 'CB-7630' or 'CB7630').ti,ab.
13	(Enzalutamide or xtandi or MDV3100 or 'MDV-3100').ti,ab.
14	(apalutamide or erleada or arn509 or arn?509).ti,ab.
15	Or/8-14
16	7 and 15
17	(animals not (humans and animals)).sh.
18	16 not 17
19	Limit 18 to English language
20	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase i or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.
21	cohort studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or comparative study.pt.
22	control groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or (random?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab.
23	21 or 22
24	19 not 20
25	23 and 24

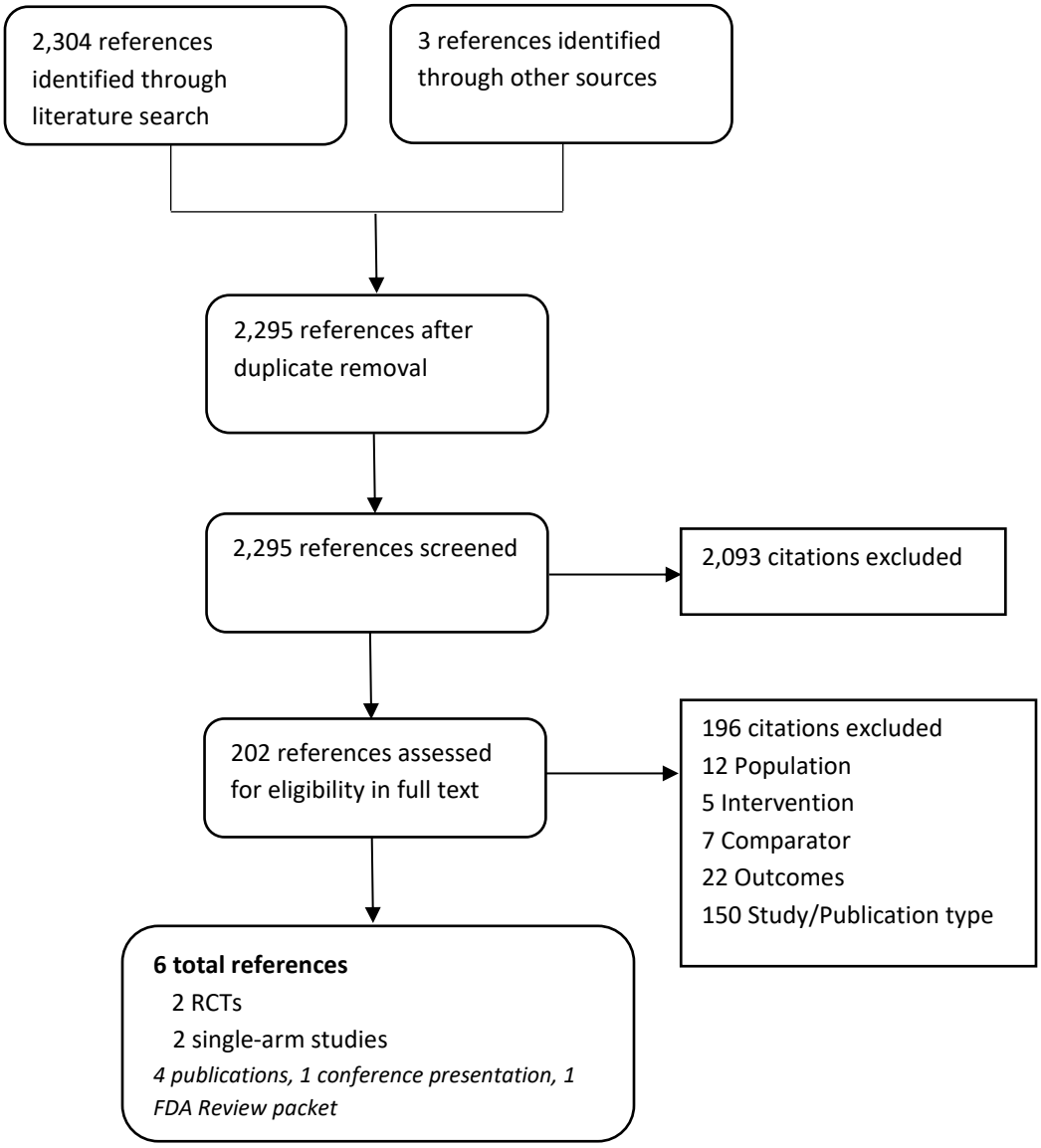
Date of search: August 20, 2018

Table A3. Search Strategy of EMBASE

#1	'castration resistant prostate cancer'/exp
#2	prostat*:ti,ab AND (cancer*:ti,ab OR carcinoma*:ti,ab OR tumo*:ti,ab OR malignan*:ti,ab OR adeno*:ti,ab OR neoplas*:ti,ab)
#3	androgen*:ti,ab OR hormon*:ti,ab OR castrat*:ti,ab
#4	independent:ti,ab OR insensitive:ti,ab OR refractory:ti,ab OR resistant:ti,ab
#5	#3 AND #4
#6	#2 AND #5
#7	#1 OR #6
#8	'abiraterone acetate'/exp
#9	(abiraterone NEXT/1 acetate):ti,ab
#10	zytiga:ti,ab OR 'cb 7630':ti,ab OR 'cb-7630':ti,ab OR 'cb7630':ti,ab
#11	‘enzalutamide’/exp
#12	enzalutamide:ti,ab OR xtandi:ti,ab OR mdv3100:ti,ab OR 'mdv-3100':ti,ab
#13	'apalutamide'/exp
#14	apalutamide:ti,ab OR erleada:ti,ab OR arn509:ti,ab OR arn*509:ti,ab
#15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	#7 AND #15
#17	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#18	'human'/exp
#19	#17 AND #18
#20	#17 NOT #19
#21	#16 NOT #20
#22	#21 AND [english]/lim
#23	#22 AND [medline]/lim
#24	#22 NOT #23
#25	#24 AND ('chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#26	#24 NOT #25

Date of search: August 20, 2018

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Antiandrogen Therapies for nmCRPC



Appendix B. Previous Systematic Reviews and Technology Assessments

We did not identify any completed health technology assesments or peer-reviewed systematic reviews in the nonmetastatic castration-resistant prostate cancer population. However, there are four ongoing technology assesments in this population that are cited below.

NICE: Enzalutamide for treating nonmetastatic hormone-relapsed prostate cancer [ID1359]

https://www.nice.org.uk/guidance/indevelopment/gid-ta10300

NICE is currently appraising the clinical and cost effectiveness of enzalutamide for treating nonmetastatic hormone-relapsed prostate cancer.

NICE: Apalutamid for treating localised hormone-relapsed prostate cancer (ID1174)

https://www.nice.org.uk/guidance/indevelopment/gid-ta10377

NICE is currently appraising the clinical and cost effectiveness of apalutamide for treating localized hormone-relapsed prostate cancer.

CADTH: Erleada for Castrate Resistant Prostate Cancer

https://www.cadth.ca/apalutamide-castrate-resistant-prostate-cancer-details

The Pan-Canadian Oncology Drug Review is currently reviweing apalutamide for the treatment of nonmetastatic castrate resistant prostate cancer.

CADTH: Xtandi for non-metastatic Castration-Resistant Prostate Cancer

https://www.cadth.ca/xtandi-non-metastatic-castration-resistant-prostate-cancer-details

The Pan-Canadian Oncology Drug Review is currently reviweing enzalutamide for the treatment of nonmetastatic castrate resistant prostate cancer.

Appendix C. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Enzalutamide					
Japanese Research for Patients with Non-metastatic Castration Resistant Prostate Cancer – Enzalutamide Translational Research Center for Medical Innovation, Kobe, Hyogo, Japan NCT02588001	Open label study Estimated enrollment: 60 Patients will be followed up at 2 and 3 years after enrollment.	1. Enzalutamide - 160 mg (four 40 mg capsules) orally once daily. 12-week cycle visit until patients meet withdrawal criteria	**Inclusion Criteria** •Patients with histologically or cytologically confirmed prostate cancer •History of radical prostatectomy or radiation therapy for radical treatment •Patients who receive continuous ADT using both GnRH agonist and antagonist, or using surgical castration •History of bicalutamide or flutamide at any time after first recurrence confirmed since radical treatment completed •3 increased PSA test results **Exclusion Criteria** •Patients with history of steroid usage as treatment for prostate cancer •History of 5-alpha-reductase inhibitor, estrogen or steroidal antiandrogen within past 4 weeks prior to initial administration of enzalutamide •History of malignant tumor other than prostate cancer within past 3 years •History of seizure or predisposing disease of seizure •Severe liver dysfunction	**Primary Outcome Measure** •PSA-progression-free survival [Time Frame: 6 years] **Secondary Outcome Measures** •Overall survival OS •Progression-free survival •MFS •Time-to-PSA-progression •PSA response rate •Time to first use of chemotherapy •QOL assessment using Japanese version of the FACT-P scales •Medication adherence •Safety assessment on the incidence and severity of adverse events using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0	September 30, 2021

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Apalutamide					
An Open-Label Expanded Access Protocol for Apalutamide Treatment of Subjects with Non-Metastatic Castration-Resistant Prostate Cancer Aragon Pharmaceuticals, Inc. NCT03523338	Phase III, open-label study Estimated enrollment: 500	1. Apalutamide - 240 mg orally once daily 2. ADT (Standard of Care) - Participants who did not undergo surgical castration, should receive and remain on a stable regimen of ADT.	**Inclusion Criteria** •Participants with confirmed prostate cancer, with evidence of castration resistance, with a rising PSA while on ADT. •Willingness to continue GnRHa throughout study if the participant is medically castrated •Must sign an informed consent form •Participants must use a condom during sexual activity while on study drug and for 3 months following the last dose of study drug. Donation of sperm is not allowed while on study drug and for 3 months following the last dose. **Exclusion Criteria** •Enrolled in another interventional clinical study of antineoplastic agents •Ongoing grade greater than (>) 1 acute toxicity due to prior therapy or surgical procedure •Concurrent therapy with medications known to lower the seizure threshold must have been discontinued or substituted at least 4 weeks prior to study entry • History of seizure or condition that may predispose to seizure.	**Primary Outcome Measures** •Number of Participants Reporting Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs) [Time Frame: Up to 30 days after last dose of study drug (approximately 1 year)]	September 28, 2018

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Darolutamide					
A Multinational, Randomized, Double-blind, Placebo-controlled, Phase III Efficacy and Safety Study of Darolutamide (ODM-201) in Men With High-risk Non-metastatic Castration-resistant Prostate Cancer Bayer NCT02200614	Phase III randomized double-blind, placebo-controlled study Actual enrollment: 1502	1. Darolutamide-600 mg (2 tablets of 300 mg) twice daily with food, total daily dose of 1200 mg. 2. Placebo- 2 tablets twice daily with food.	**Inclusion Criteria** •Histologically or cytologically confirmed adenocarcinoma of prostate without neuroendocrine differentiation or small cell features. •PSA doubling time of ≤ 10 months and PSA > 2ng/ml. •ECOG PS of 0-1. •Blood counts at screening: hemoglobin ≥ 9.0 g/dl, absolute neutrophil count ≥ 1500/µl, platelet count ≥ 100,000/µl. •Sexually active patients must agree to use condoms as an effective barrier method and refrain from sperm donation during the study treatment and for 3 months after the end of the study treatment. **Exclusion Criteria** •Active viral hepatitis, active human immunodeficiency virus (HIV) or chronic liver disease •Any of the following within 6 months before randomization: stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure New York Heart Association (NYHA) Class III or IV. •Prior chemotherapy or immunotherapy for prostate cancer	**Primary Outcome Measure** •MFS (Time from randomization to evidence of metastasis or death from any cause) **Secondary Outcome Measures** •Overall Survival •Time to first symptomatic skeletal event •Time to initiation of first cytotoxic chemotherapy for prostate cancer •Time to pain progression •Safety and tolerability of ODM-201	September 14, 2018

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Two investigators reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to apalutamide. These included internal FDA review documents and the sponsor clinical study report from the SPARTAN trial.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix D)[49] Guidance for quality ratings using these criteria is presented below.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

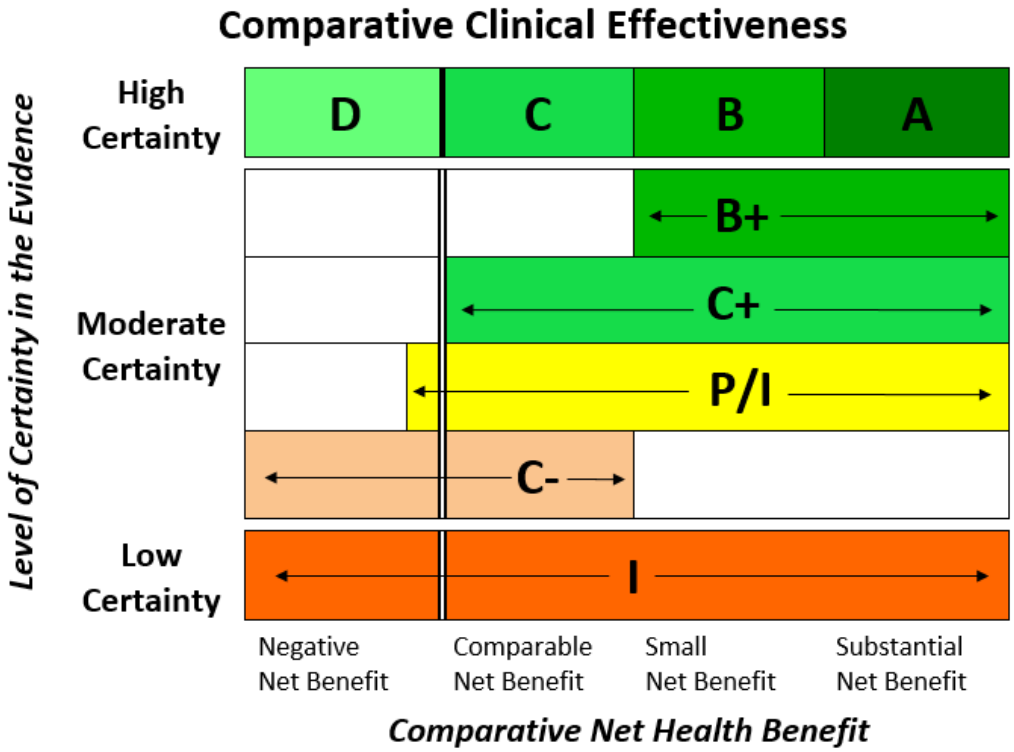
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[70]

Figure D1. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Table D1. Evidence Table: Nonmetastatic Castration-Resistant Prostate Cancer

Trial Author & Year of Publication Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
SPARTAN **Smith N Engl J Med 2018**[11] **Good quality**	Double-blind Phase III RCT Median follow-up at clinical cutoff date for primary analysis: 20.3 months	N=1207 1) Apalutamide (240 mg QD PO), (n=806) 2) Placebo (QD PO), (n=401) ADT continued throughout trial Apalutamide and placebo were administered orally according to a continuous daily dosing regimen until protocol-defined progression, adverse events, or withdrawal of consent. After first detection of distant metastasis, patients eligible to receive sponsor-provided abiraterone acetate + prednisone	**Inclusion criteria** Age ≥18 yrs; histologically or cytologically confirmed adenocarcinoma of the prostate; castration-resistant; high-risk for the development of metastasis (PSA doubling time of 10 months or less during continuous ADT: bilateral orchiectomy or treatment with GnRH agonists or antagonists); no local or regional nodal disease or malignant pelvic lymph nodes measuring <2 cm in short axis and located below aortic bifurcation	**Median age, yr (range)** 1) 74 (48-94) 2) 74 (52-97) **Median PSADT (mo)** 1) 4.40 2) 4.50 **PSADT ≤6mo/>6mo, n (%)** 1) 576 (71.5)/230 (28.5) 2) 284 (70.8)/117 (29.2) **Prostatectomy or radiation** 1) 76.6 2) 76.6 **Previous 1st gen antiandrogen** 1) 73.4 2) 72.3 **Median time since dx (yr)** 1) 7.95 2) 7.85 **N0, n (%)** 1) 673 (83.5) 2) 336 (83.8) **N1, n (%)** 1) 133 (16.5) 2) 65 (16.2)	**Median MFS (months)** 1) 40.5 2) 16.2 HR 0.28 (95% CI 0.23-0.35) p<0.001 **Median PFS (months)** 1) 40.5 2) 14.7 HR 0.29 (95% CI 0.24-0.36) p<0.001 **Median overall survival (months)** 1) NR 2) 39.0 HR 0.70 (95% CI 0.47-1.04) **Median time to symptomatic progression (months)** 1) NR 2) NR HR 0.45 (95% CI 0.32-0.63) p<0.001 **Median time to PSA progression (months)** 1) NR 2) 3.7	*n (%)* **Discontinuation due to AEs** 1) 85 (10.6) 2) 28 (7.0) **Serious AEs** 1) 199 (24.8) 2) 92 (23.1) **AE associated with death** 1) 10 (1.2) 2) 1 (0.3) *Grade 3 or 4 AEs, n (%)* **Fatigue** 1) 7 (0.9) 2) 1 (0.3) **Hypertension** 1) 115 (14.3) 2) 47 (11.8) **Rash** 1) 42 (5.2) 2) 1 (0.3) **Fracture** 1) 22 (2.7) 2) 3 (0.8) **Falls** 1) 14 (1.7) 2) 3 (0.8) **Seizures**: 0

Trial Author & Year of Publication Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					HR 0.06 (95% CI 0.05-0.08) **Change in FACT-P/EQ VAS baseline-29 months (SD)** 1) -0.99 (0.98)/1.44 (0.87) 2) -3.29 (1.97)/0.26 (1.75)	
Smith Eur Urol 2016[21] **Quality not rated**	Open-label Phase I/II Clinical study with three cohorts (nonmetastatic, chemotherapy/ abiraterone-acetate-naïve metastatic, post-abiraterone acetate metastatic) *Nonmetastatic cohort summarized here* Median follow-up: 28 mo	N=51 Apalutamide (240 mg QD PO) Ongoing hormonal therapy Treatment until disease progression (PSA or radiographic progression) or clinical progression (skeletal-related event or pain progression requiring intervention)	Histologically or cytologically confirmed prostate cancer; received ongoing ADT with GnRH analogue or inhibitor or orchiectomy; no radiographic evidence of distant metastases as determined by central review (pelvic lymph nodes <3 cm below the iliac bifurcation were allowed; castrate levels of serum testosterone ≤50 ng/dL within 4 wk of study enrollment; ECOG PS 0-1; life expectancy ≥3 mo; corrected QT interval ≤450 ms; adequate cardiac, renal, hepatic, and bone marrow function; high-risk for developing metastases (either PSA ≥8 ng/ml or PSADT ≤10 mo	**Median age, yr (range):** 71 (51-88) **ECOG PS=0, n (%):** 39 (76) **ECOG PS=1, n (%):** 12 (24) **Median time since initial diagnosis, months (range)**: 119.5 (20-238) **Median PSA, ng/mL (range):** 10.7 (0.5-201.7) **Median PSA ≥8, ng/ml (range):** 21 (41) **PSADT ≤10 months**: 23 (45) *Prior Therapy, n (%)* **LHRH**: 46 (90) **Antiandrogen**: 41 (80)	**Median MFS, mo (95% CI):** NR (33.4-NR) **Median time to PSA progression, mo (95% CI):** 24.0 (16.3-NR)	*Treatment-emergent Adverse Events*, n (%) **Discontinuation due to TEAE**: 9 (18) **Serious TEAE**: 16 (31) *Grade 3 or 4 AEs* **Fatigue**: 2 (4) **Arthralgia**: 1 (2) **Hypothyroidism**: 0 **Hypertension**: 2 (4) **Seizure**: 0 *Any grade AEs* **Falls**: 5 (10)

Trial Author & Year of Publication Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
			Excluded: previous enzalutamide, abiraterone acetate, ketoconazole; potential for seizures			
PROSPER **Hussain N Engl J Med 2018**[20,27] **Good quality**	Double-blind Phase III RCT Median follow-up Enzalutamide: 18.5 mo Placebo: 15.1 mo	N=1401 1) Enzalutamide (160 mg QD PO), n=933 2) Placebo (QD PO), n=468 ADT continued throughout trial	Histologically or cytologically confirmed adenocarcinoma of the prostate; ongoing ADT with GnRH agonist or antagonist or prior bilateral orchiectomy; testosterone <=50 ng/dL (≤1.73 nmol/L); progressive disease on ADT; PSA ≥2 mcg/L; PSADT ≤10 mo; no prior or present evidence of metastatic disease; asymptomatic cancer; ECOG PS 0 or 1; estimated life expectancy ≥12 mo Excluded: prior cytotoxic chemo; prior hormonal or biologic tx for prostate cancer (other than bone targeting agents and GnRH agonist/antagonist); history of seizure; CVD; other invasive cancer	**Median age, yr** 1) 74 2) 73 **PSADT <6 mo, n (%)** 1) 715 (77) 2) 361 (77) **Median serum PSA** 1) 11.1 2) 10.2 **ECOG PS 0/1, n (%)** 1) 747 (80)/185 (20) 2) 382 (82)/85 (18) **Median PSA doubling time (range), mo** 1) 3.8 (0.4-37.4) 2) 3.6 (0.5-71.8) **PSA doubling time, n (%)** **<6 mo** 1) 715 (77) 2) 361 (77) **≥6 mo** 1) 217 (23) 2) 107 (23)	**Median MFS, mo (95% CI)** 1) 36.6 (33.1-NR) 2) 14.7 (14.2-15.0) HR 0.29 (0.24-0.35) p<0.0001 **Median overall survival, mo (95% CI)** 1) NR 2) NR HR 0.80 (0.58-1.09) p=0.1519 **Median time to PSA progression, mo (95% CI)** 1) 37.2 (33.1-NR) 2) 3.9 (3.8-4.0) HR 0.07 (0.05-0.08) p<0.0001 **FACT-P Score Degradation, n (%)** 1) 506 (54) 2) 239 (51) no statistically significant nor clinically meaningful difference in effect on	**Discontinuation due to AEs, (%)** 1) 9 2) 6 **Serious AEs, (%)** 1) 24 2) 18 **Grade 3 or 4 AEs n, (%)** **Fatigue** 1) 27 (3) 2) 3 (1) **Hypertension** 1) 43 (5) 2) 10 (2) **Hematuria** 1) 16 (2) 2) 13 (3) **Fall** 1) 12 (1) 2) 3 (1) **Asthenia** 1) 11 (1) 2) 1 (<1)

Trial Author & Year of Publication Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					HRQoL or pain between ENZA and PBO	
IMAAGEN **Ryan (2018)[22]**	Phase II, open-label, single-arm Enrollment: April 2011-July 2013 Median duration of follow-up: 40 months Median duration of treatment: 22.14 months (0.1, 52.0)	N=131 AA 1000 mg + prednisone (5 mg) + ADT oral, daily 28-day cycles Median number of cycles at data cutoff: 25 cycles (range 1-57)	Inclusion: Men age ≥ 18 Confirmed nmCRPC Serum testosterone < 50 mg/dL or < 2.0 nM Rising PSA: (PSADT<=10 months or absolute PSA >=10 ng/mL) Exclusion: Metastatic disease Chemotherapy Prior use of aminoglutethimide or ketoconazole Current antiandrogen	**Median age, yr (range):** 72 (48-90) **Median screening PSA (range):** 11.9 ng/dL (1.3, 167.8) **Median time since initial dx to first AA dose** (range): 10.2 years (1.5, 26) **Primary tumor stage at dx, n (%):** 1: 39 (32.8) 2: 44 (37.0) 3: 36 (30.3) 4: 0 **ECOG PS, n (%)** 0: 112 (85.5) 1: 18 (13.7) 2: 1 (0.8)	*Primary outcome:* proportion patients achieving PSA50 by end cycle 6, n (%) 106 (86.9) (95% CI, 80.9%, 92.9%) *Secondary outcomes:* **Median time to PSA progression, mo**: 28.7 (95% CI, 21.2, 38.2) **Median time to radiographic evidence of progression, months** (estimated by sensitivity analysis) 41.1 (95% CI, 27.6, not estimable) **Proportion of patients achieving PSA50 by end cycle 3, n (%)** 104 (85) (95% CI, 86%, 96%) **Confirmed radiographic diagnosis based on investigator assessment**: 31 (23.7%) **Overall survival**: NR	n (%) **AE total**: 126 (96.2) **Grade 1 or 2 (%)**: 35 **Grade 3 or 4 (%)**: 57 **SAE total**: 57 (43.5) **Drug-related SAE**: 29 (22.1) **Discontinuation due to AEs**: 20 (15.3) **AE resulting in death**: 7 (5.3) Common AEs Grade ≥3 (>15% of population): Hypertension: 31 (23.7) Hypokalemia: 9 (6.9)

Table D2. Evidence Table: Metastatic Castration-Resistant Prostate Cancer

Trial Author & Year of Publication Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
COU-AA-302 **Ryan NEJM 2013[24,28]** **Good**	Double-blind Phase III RCT Median follow-up: 49.2 months for overall survival and safety data Median follow-up: 22.2 months for PFS and PSA progression data	N=1088 1) AA (1000mg) + prednisone (5mg BID) (N=546) 2) PBO + prednisone (N=542)	**Inclusion Criteria** Age >= 18; metastatic adenocarcinoma of the prostate; PSA progression according to PCWG2 criteria2 or radiographic progression in soft tissue or bone with or without PSA progression; ongoing androgen deprivation with serum testosterone level <50 ng per deciliter (1.7 nmol per liter); ECOG grade 0 or; no symptoms or mild symptoms; previous antiandrogen Excluded: visceral metastases, prior ketoconazole >7days	**Median age, yr (range)** 1) 71 (44-95) 2) 70 (44-90) **Previous Surgery, n (%)** 1) 256 (47) 2) 244 (45) **Previous Radiotherapy, n (%)** 1) 283 (52) 2) 303 (56) **Previous Hormonal Therapy, n (%)** 1) 544 (100) 2) 542 (100) **Median PSA, ng/ml (range)** 1) 42.0 (0.0-3927.4) 2) 37.7 (0.7-6606.4) **Bone only metastasis, n (%)** 1) 274 (51) 2) 267 (49) **Soft tissue or node metastasis, n (%)** 1) 267 (49) 2) 271 (50) **Median time from initial diagnosis to first dose, yr** 1) 5.5 2) 5.1	*Primary endpoints* **Median Radiographic PFS (BICR), mo** 1) 16.5 2) 8.3 HR 0.53 (95% CI 0.45-0.62) p<0.001 **Median overall survival, mo (95% CI)** 1) 34.7 (32.7-36.8) 2) 30.3 (28.7-33.3) HR 0.81 (95% CI 0.70-0.93) p=0.0033 *Secondary endpoints* **Median time to PSA progression, mo** 1) 11.1 2) 5.6 HR 0.49 (95% CI: 0.42-0.57) p<0.001	**Any SAE, n (%)** 1) 208 (38) 2) 148 (27) **Discontinuation d/t AE, n (%)** 1) 69 (13) 2) 52 (10) **Deaths d/t AE, n (%)** 1) 24 (4) 2) 15 (3) *Grade3/4 AEs, n (%)* **Hypertension** 1) 25 (5)/0 2) 17 (3)/0 **Cardiac disorders** 1) 35 (6)/6 (1) 2) 17 (3)/3 (<1) **ALT Increased** 1) 28 (5)/4 (<1) 2)3 (<1)/1 (<1)

COU-AA-301 **Fizazi Lancet Oncology 2012**[71] **Good**	Double-blind Phase III RCT Median follow-up:20.2 months	N=1195 1) AA (1000 mg) + prednisone (5 mg BID) (n=797) 2) PBO + prednisone (5 mg BID) (n=398)	**Inclusion Criteria** Confirmed prostate cancer previously treated with docetaxel; Disease progression according to the criteria of the PCWG (2 consecutive increases in PSA concentration over a reference value); Radiographic evidence of disease progression in soft tissue or bone with or without disease progression on the basis of the PSA value; Ongoing androgen deprivation, with a serum testosterone level of 50 ng per deciliter or less (≤2.0 nmol per liter); ECOG≤2	**Median age, yr (range)** 1) 69 (42-95) 2) 69 (39-90) **Previous surgery n, (%)** 1) 429 (54) 2) 193 (49) **Previous radiotherapy, n (%)** 1) 570 (72) 2) 285 (72) **Previous hormonal therapy, n (%)** 1) 796 (100) 2) 396 (100) **Median PSA, ng/mL (range)** 1) 128.8 (0.4-9253.0) 2) 137.7 (0.6-10114.0) **Bone metastasis. n (%)** 1) 709 (89) 2) 357 (90) **Node metastasis, n (%)** 1) 361 (45) 2) 164 (41) **ECOG PS, n (%)** 0 or 1: 1) 715 (90) 2) 353 (89)	**Median Radiographic PFS (BICR), months (95% CI)** 1) 5.6 (5.6-6.5) 2) 3.6 (2.9-5.5) HR 0.66 (95% CI 0.58-0.76) p<0.0001 **Median overall survival, months (95% CI)** 1) 15.8 (14.8-17) 2) 11.2 (10.4-13.1) HR 0.74 (95% CI 0.64-0.86) p<0.0001 **Median time to PSA progression, months (95% CI)** 1) 8.5 (8.3-11.1) 2) 6.6 (5.6-8.3) HR 0.63 (95% CI 0.52-0.78) p<0.0001	*Grade 3/4 AEs, n (%)* **Anemia** 1) 53 (7)/9 (1) 2) 26 (7)/6 (2) **Fatigue** 1) 70 (9)/2 (<1) 2) 38 (10)/3 (<1) **Back pain** 1) 53 (7)/ 3 (<1) 2) 39 (10)/1 (<1) **Arthralgia** 1) 40 (5)/0 2) 17 (4)/0 **Bone pain** 1) 49 (6)/2 (<1) 2) 27 (7)/4 (1) **Hypertension** 1) 10 (1)/0 2) 1 (<1)/0 **Deaths d/t AEs, n (%)** 1) 105 (13) 2) 61 (16) **Discontinuation d/t AEs, n (%)** 1) 105 (13) 2) 71 (18) **SAE or Admission to hospital, n (%)** 1) 73 (9) 2) 28 (7)
PREVAIL **Beer NEJM 2014**[10] **Good**	Randomized, placebo-controlled trial Median duration of follow-up to ascertain survival status: 22 months	N=1717 1) Enzalutamide (160 mg QD PO), (n=872) 2) Placebo (QD PO), (n=845)	**Inclusion Criteria** Adenocarcinoma of the prostate with documented metastases and PSA progression, radiographic progression, or both in bone or soft tissue, despite LHRH analogue	**Median age, yr (range)** 1) 72.0 (43.0-93.0) 2) 71.0 (42.0-93.0) **Previous antiandrogen therapy, n (%)** 1) 760 (87.2) 2) 730 (86.4)	**Median radiographic PFS, months (95% CI)** 1) 20.0 (18.9-22.1) 2) 5.4 (4.0-5.6) HR 0.32 (95% CI 0.28-0.36) **Median overall survival, months (95% CI)**	**Any AE, n (%)** 1) 844 (97) 2) 787 (93) **Any grade ≥3 AE, n (%)** 1) 374 (43) 2) 313 (37) **SAE, n (%)**

			therapy or orchiectomy, with serum testosterone level of 1.73 nmol per liter (50 ng per deciliter) or less. Continued ADT required. Previous antiandrogen therapy and concurrent use of glucocorticoids permitted but not required; no prior cytotoxic chemotherapy, ketoconazole, or abiraterone acetate, ECOG grade 0 or 1; asymptomatic or mildly symptomatic. visceral disease, including lung or liver metastases, were eligible	**Median serum PSA µg/L (range)** 1) 54.1 (0.1-3182.0) 2) 44.2 (0.3-3637.0) **Bone only metastasis, n (%)** 1) 348 (39.9) 2) 335 (39.6) **Soft tissue or node, n (%)** 1) 124 (14.2) 2) 149 (17.6) **Both bone and soft tissue, n (%)** 1) 393 (45.1) 2) 355 (42.0)	1) 35.3 (32.2-not reached) 2) 31.3 (28.8-34.2) HR 0.77 (95% CI 0.67-0.88) **Median time to PSA progression, months** 1) 11.2 2) 2.8 HR 0.17 (95% CI 0.15-0.20)	1) 279 (32) 2) 226 (27) **AE leading to tx discontinuation, n (%)** 1) 49 (6) 2) 51 (6) **AE leading to death, n (%)** 1) 37 (4) 2) 32 (4) *Most common grade ≥3 AEs, n (%)* **Fatigue** 1) 16 (2) 2) 16 (2) **Back pain** 1) 22 (3) 2) 25 (3) **Hypertension** 1) 59 (7) 2) 19 (2)
AFFIRM **Scher N Engl J 2012**[23] **Good**	Double-blind Phase III RCT Median duration of follow-up to ascertain survival status: 14.4 mo	N=1199 1) Enzalutamide (160 mg QD PO), (n=800) 2) Placebo (QD PO), (n=399) Study therapy continued until radiographically confirmed disease progression, unacceptable toxicity, death, or withdrawal Prednisone/ glucocorticoids	**Inclusion criteria** Histologically or cytologically confirmed diagnosis of prostate cancer, castrate levels of testosterone (<50 ng/dL [1.7 nmol per liter]), previous treatment with docetaxel, and progressive disease defined according to PCWG2 criteria, including three increasing values for PSA or radiographically confirmed progression	**Median age, yr (range)** 1) 69 (41-92) 2) 69 (49-89) **Median years since dx** 1) 5.9 2) 6.0 **1/2/≥3 prior chemos (%)** 1) 72.4/24.5/3.1 2) 74.2/23.8/2.0 **Previous surgery, n (%)** 1) 531 (66.4) 2) 243 (60.9)	**Median radiographic PFS, months (95% CI)** 1) 8.3 (8.2-9.4) 2) 2.9 (2.8-3.4) HR 0.40 (95% CI 0.35-0.47) p<0.001 **Median overall survival, months (95% CI)** 1) 18.4 (17.3-NR) 2) 13.6 (11.3-15.8) HR 0.63 (95% CI 0.53-0.75) p<0.001	*n (%)* **Discontinuation due to AEs** 1) 61 (8) 2) 39 (10) **AE leading to death** 1) 23 (3) 2) 14 (4) **Serious AE** 1) 268 (34) 2) 154 (39) *Grade 3 or 4 AEs, n (%)* **Fatigue** 1) 50 (6)

		permitted but not required	with or without a rise in the PSA level	**Previous radiation therapy, n (%)** 1) 571 (71.4) 2) 287 (71.9) **Median PSA (range)** 1) 107.7 (0.2-11794.1) 2) 128.3 (0.0-19000.0) **Bone metastasis, n (%)** 1) 745 (92.2) 2) 364 (91.5) **Soft tissue, n (%)** 1) 567 (70.9) 2) 275 (68.9)	**Median time to PSA progression, months (95% CI)** 1) 8.3 (5.8-8.3) 2) 3.0 (2.9-3.7) HR 0.25 (95% CI 0.20-0.30) p<0.001	2) 29 (7) **Seizure** 1) 5 (<1) 2) 0 **Hypertension (any grade)** 1) 53 (6.6) 2) 13 (3.3)

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, As Relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al.[72]

Health Care Utilization and Cost Inputs

The interventions of interest are orally administered, so administration costs are not considered in the model. Other health care costs were derived from the published literature. We based costs of supportive care for MFS and metastatic disease on a published analysis of SEER-Medicare data in 7,482 patients diagnosed with subsequent metastases 12 months or more after the initial prostate cancer diagnosis.[59] Costs of prostate cancer death were based on a previous cost-effectiveness analysis of localized prostate cancer by Cooperberg et al.[58] All costs were inflated to April 2018 dollars, using the Bureau of Labor Statistics, Medical Care component of the Consumer Price Index.[65]

Table E2. Health Care Utilization and Cost Inputs

	Estimate	Source
Annual MFS Supportive Care	$2,746	Li et al.[59] Bureau of Labor Statistics[65]
Annual Metastasis Supportive Care	$6,500	Li et al.[59] Bureau of Labor Statistics[65]
Prostate Cancer Death (Last Year)	$52,262	Cooperberg et al.[58] Bureau of Labor Statistics[65]

Table E3. Post-Progression Treatment Inputs

Subsequent Treatment	Cost/Month	Apalutamide[11]	Enzalutamide*	Continued ADT[11]
No Treatment (continued ADT only)	$220.67‡	47.5%	47.5%	22.2%
Abiraterone Acetate + Prednisone	$7,134.79	17.9%[37]	31.66%[37]	26.6%[37]
Enzalutamide	$7,847.62	13.7%[37]	--	20.3%[37]
Docetaxel	$1,977.60	15.2%[37]	15.2%[37]	22.6%[37]
Sipuleucel	$71,644[38]	3.3%[37]	3.3%[37]	4.9%[37]
Radium-223	$13,353[38]	1.9%[37]	1.9%[37]	3.0%[37]
Cabazitaxel	$12,088[38]	0.3%[37]	0.3%[37]	0.5%[37]

*The proportion of enzalutamide reported for apalutamide patients was added to the proportion of abiraterone acetate.

Table E4. Results of Probabilistic Sensitivity Analysis, By Comparator

Detailed results of the probabilistic sensitivity analyses are shown for each comparator in the tables below. The Cost-Effectiveness Acceptability Curve (CEAC) shows that 3% and 33% of the model simulations for enzalutamide and apalutamide respectively fall below the $50,000 per QALY threshold. At a threshold of $100,000 per QALY gained, 82% of model simulations for enzalutamide

and 99% of simulations for apalutamide fall below that threshold. Both antiandrogens most certainly have an ICER that falls below a willingness to pay threshold of $150,000 per QALY (99% for enzalutamide and 100% for apalutamide).

By Comparator	ADT (baseline)		Apalutamide		Enzalutamide	
	Base-case	Credible Range	Base-case	Credible Range	Base-case	Credible Range
Total Costs	$475,000	($393,000 - $578,000)	$583,000	($499,000 - $667,000)	$601,000	($525,000 - $711,000)
Antiandrogen Cost			$185,000	($139,000 - $255,000)	$199,000	($166,000 - $297,000)
ADT Cost	$4,500	($3,500 - $5,000)	$10,000	($8,200 - $13,800)	$10,000	($8,100 - $13,400)
Adverse Event Cost	$1,100	($900 - $1,300)	$2,000	($1,600 - $2,100)	$1,000	($700 - $1,100)
Supportive Care Cost	$37,700	($30,800 - $44,400)	$41,000	($34,400 - $47,500)	$41,000	($34,300 - $47,800)
Progression Tx Cost	$427,000	($344,000 - $529,000)	$342,000	($257,000 - $410,000)	$345,000	($264,000 - $412,000)
Cancer Death Cost	$4,900	($1,900 - $9,600)	$4,000	(-$300 - $10,700)	$5,000	($1,000 - $11,500)
Total QALYs	5.51	(4.99 - 5.79)	7.10	(6.34 - 8.05)	7.01	(6.24 - 7.92)
MFS QALYs	1.52	(1.13 - 1.68)	3.42	(2.67 - 4.65)	3.35	(2.63 - 4.56)
Asymptomatic Prog. QALYs	2.85	(1.73 - 3.89)	2.80	(0.58 - 4.13)	2.58	(0.40 - 3.79)
Symptomatic Prog. QALYs	1.14	(0.31 - 2.13)	0.88	(-0.21 - 2.68)	1.08	(0.10 - 2.81)
Total Life Years (OS)	6.77	(6.47 - 6.94)	8.45	(7.95 - 9.35)	8.40	(7.94 - 9.29)
MFS LYs	1.69	(1.42 - 1.78)	3.80	(3.19 - 4.98)	3.73	(3.18 - 4.90)
Asymptomatic Prog. LYs	3.43	(2.07 - 4.67)	3.37	(0.70 - 4.98)	3.11	(0.49 - 4.57)
Symptomatic Prog. LYs	1.65	(0.44 - 3.02)	1.28	(-0.29 - 3.81)	1.56	(0.15 - 4.01)

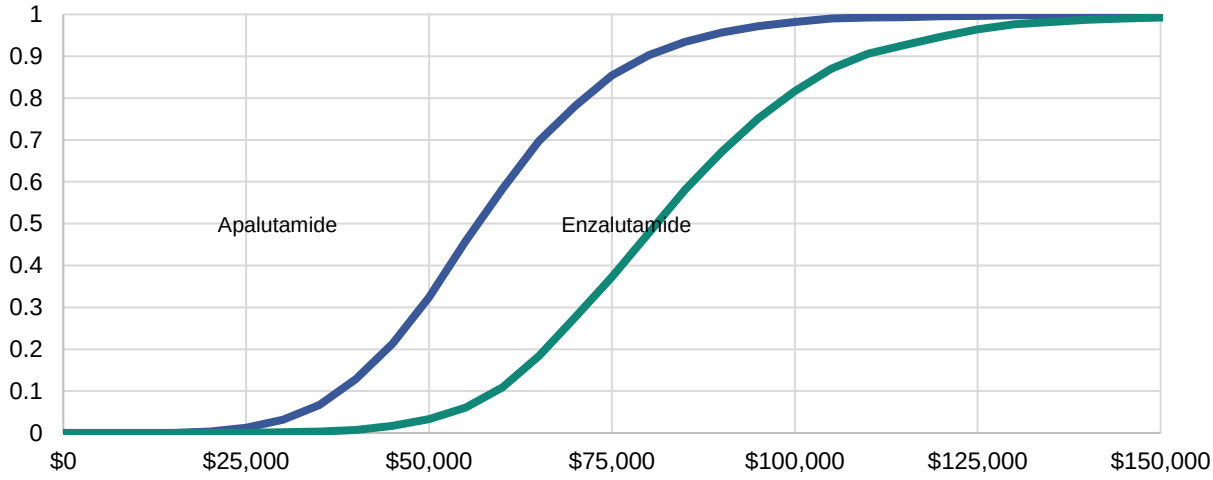
ADT: Androgen deprivation therapy, LYs: life years, QALYS: quality-adjusted life years

Table E5. Results of Probabilistic Sensitivity Analysis, Incremental

Incremental	Apalutamide		Enzalutamide	
	Base-case	Credible Range	Base-case	Credible Range
ICER (QALYs)	68,000	($28,000 - $92,000)	84,000	($48,000 - $129,000)
ICER (LYs)	65,000	($27,000 - $82,000)	77,000	($46,000 - $103,000)
Incremental Total Costs	108,000	($52,000 - $152,000)	126,000	($84,000 - $192,000)
Antiandrogen Cost	185,000	($139,000 - $255,000)	199,000	($166,000 - $297,000)
ADT Cost	5,600	($4,500 - $9,000)	5,400	($4,300 - $8,600)
Adverse Event Cost	700	($400 - $1,000)	-200	(-$500 - $0)
Supportive Care Cost	2,900	($1,800 - $5,300)	2,900	($1,700 - $5,200)
Progression Tx Cost	-85,200	(-$144,800 - - $70,900)	-81,800	(-$137,500 - - $69,000)
Cancer Death Cost	-800	(-$4,700 - $4,000)	0	(-$3,900 - $4,800)
Incremental QALYs	1.59	(1.19 - 2.43)	1.50	(1.10 - 2.30)
MFS QALYs	1.90	(1.47 - 3.02)	1.84	(1.43 - 2.95)
Asymptomatic Prog. QALYs	-0.05	(-1.80 - 1.04)	-0.27	(-2.04 - 0.76)
Symptomatic Prog. QALYs	-0.26	(-1.17 - 1.11)	-0.07	(-0.94 - 1.29)
Incremental Life Years (OS)	1.67	(1.36 - 2.58)	1.62	(1.34 - 2.47)
MFS LYs	2.11	(1.70 - 3.29)	2.04	(1.68 - 3.17)
Asymptomatic Prog. LYs	-0.06	(-2.17 - 1.24)	-0.33	(-2.45 - 0.92)
Symptomatic Prog. LYs	-0.38	(-1.65 - 1.60)	-0.09	(-1.37 - 1.86)

ADT: androgen deprivation therapy, MFS: metastasis free survival, LYs: life years, QALYS: quality-adjusted life years

Figure E1. Results of Probabilistic Sensitivity Analysis: Cost-Effectiveness Acceptability Curves



Survival Modeling Approach

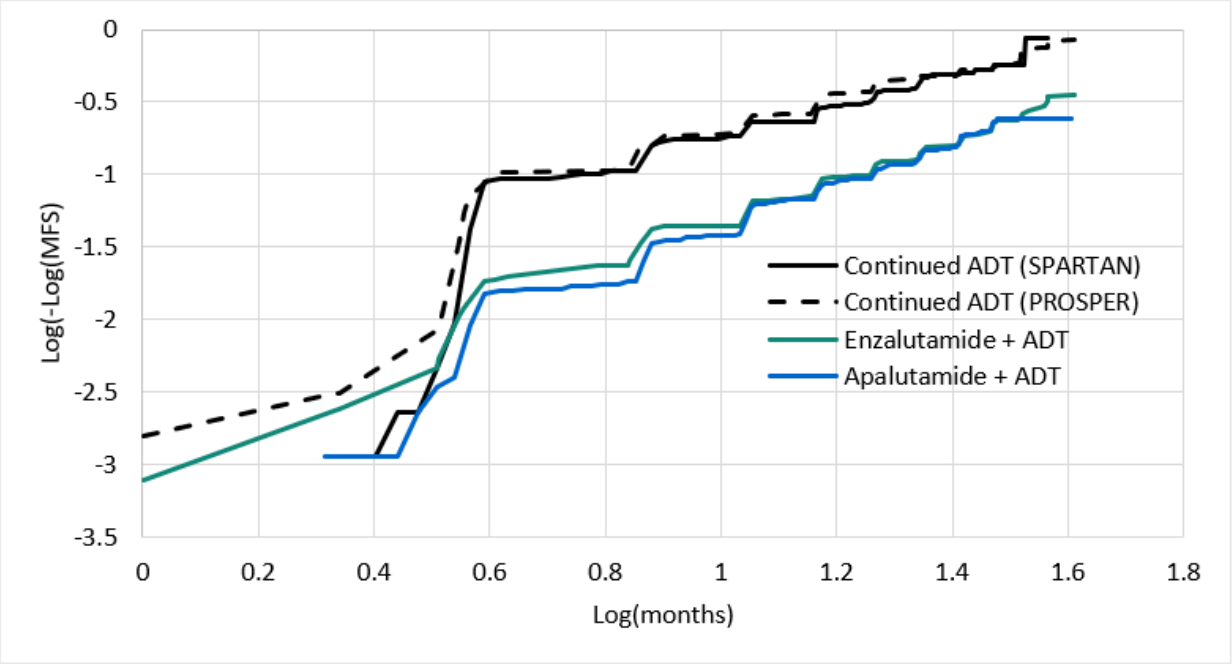
Proportional Hazard Assumption Testing

The first assumption to check when choosing an extrapolation model is whether the proportional hazard assumption holds. The proportional hazard assumption states that the hazard in one group (arm A) is a constant proportion of the hazard in the other group (arm B). This proportion is the hazard ratio. That is, although the hazard may vary with time, the ratio of the hazard rates is constant.

One way to test for the PH assumption is a graphical method by observing the log-cumulative hazards plots, which plots the log(time) versus log(–log(S(time)). If the curves are parallel, i.e. they do not move further apart over time or closer together then the PH assumption is reasonable. As shown in the figure below, the two curves are relatively parallel which signals that the PH assumption holds.

We concluded that using proportional hazards to model antiandrogens, wherein we applied the trial-reported hazard ratios to continued ADT curves to derive antiandrogen curves, was a reasonable approach.

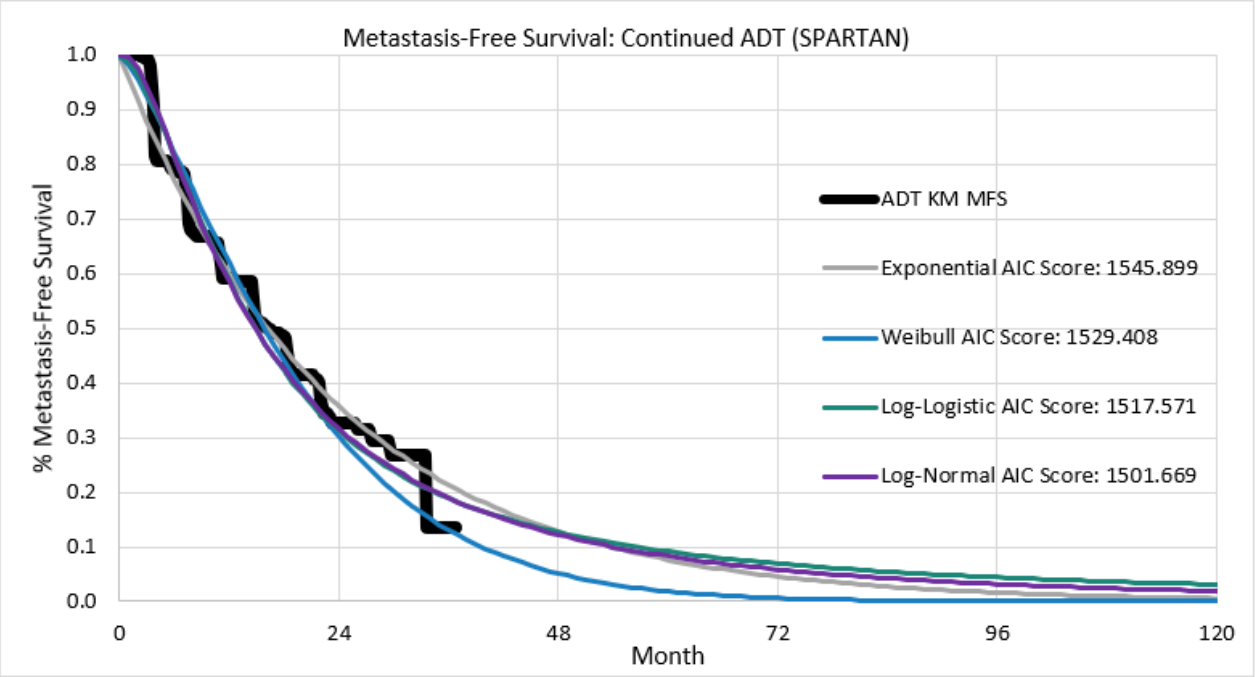
Figure E2. Log-cumulative Hazards Plots of Kaplan-Meier Curves for MFS

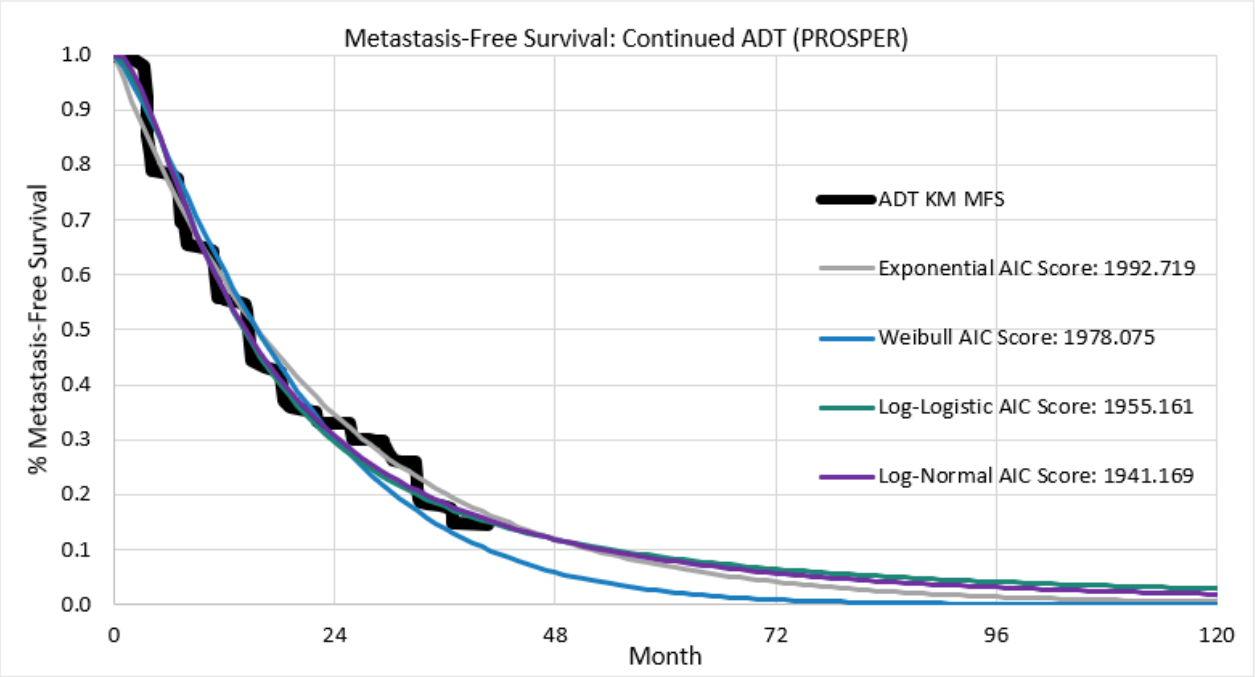


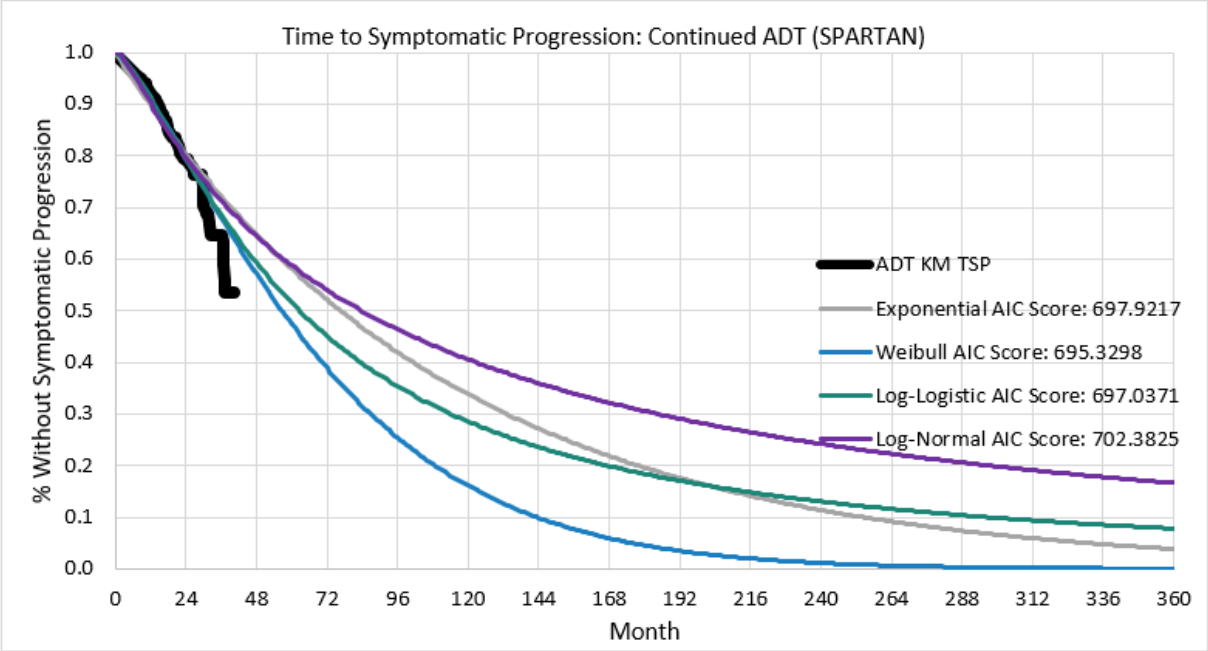
Fitted Parametric Curves: Continued ADT

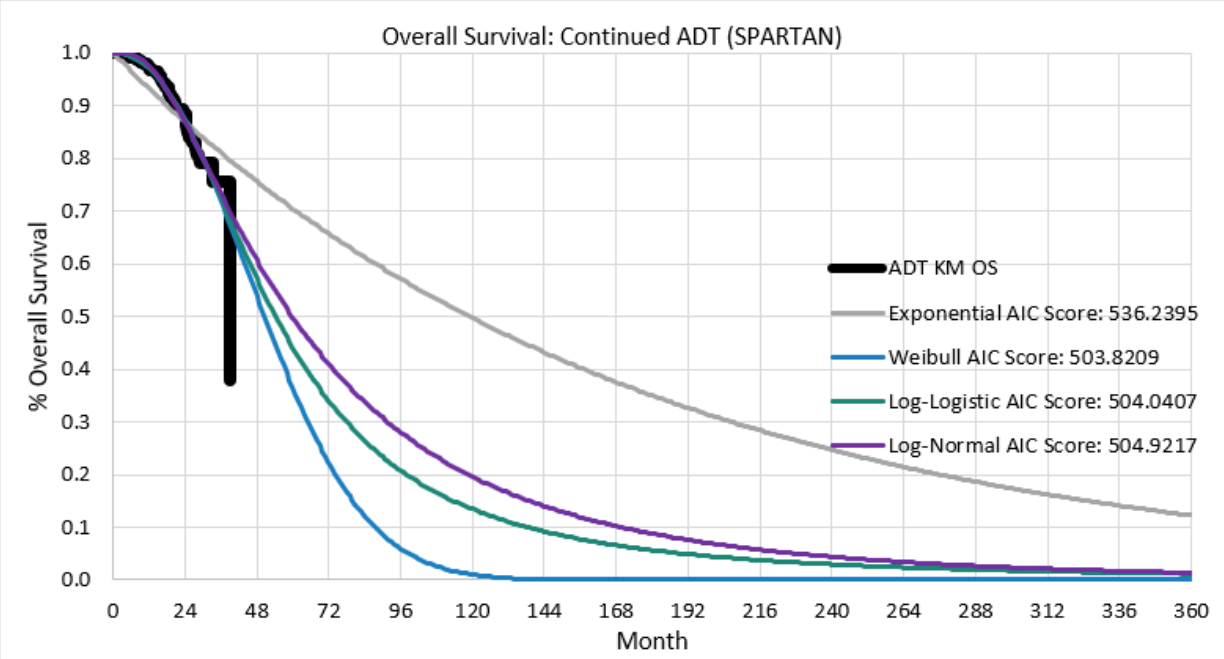
We fit the following parametric curves to Kaplan-Meier data for the continued ADT arm of the SPARTAN and PROSPER trials: exponential, Weibull, log-logistic, and log-normal. Curve fits to MFS were perceived as having good face validity by visual inspection; although the Weibull curves were the third best fits for MFS, it was chosen to model the tails of continued ADT in the model because it led to the best model fits for antiandrogens after applying modeled hazard ratios.

For time to symptomatic progression (SPARTAN trial only) and overall survival (used to model the transition from MFS to death only; see main text), except for the exponential curves, parametric fits were generally well fit to the available data. However, the high degree of patient data censoring beyond the first few years of follow-up led to high uncertainty in the tails of the parametric curve fits. Ultimately, we chose the Weibull to model time to symptomatic progression, and the log-normal to model overall survival, based on visual inspection.


Metastasis-Free Survival: Continued ADT (SPARTAN)
% Metastasis-Free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
24
48
72
96
120
Month
ADT KM MFS
Exponential AIC Score: 1545.899
Weibull AIC Score: 1529.408
Log-Logistic AIC Score: 1517.571
Log-Normal AIC Score: 1501.669


Metastasis-Free Survival: Continued ADT (PROSPER)
% Metastasis-Free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
24
48
72
96
120
Month
ADT KM MFS
Exponential AIC Score: 1992.719
Weibull AIC Score: 1978.075
Log-Logistic AIC Score: 1955.161
Log-Normal AIC Score: 1941.169


Time to Symptomatic Progression: Continued ADT (SPARTAN)
% Without Symptomatic Progression
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
24
48
72
96
120
144
168
192
216
240
264
288
312
336
360
Month
ADT KM TSP
Exponential AIC Score: 697.9217
Weibull AIC Score: 695.3298
Log-Logistic AIC Score: 697.0371
Log-Normal AIC Score: 702.3825


Overall Survival: Continued ADT (SPARTAN)
% Overall Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
24
48
72
96
120
144
168
192
216
240
264
288
312
336
360
Month
ADT KM OS
Exponential AIC Score: 536.2395
Weibull AIC Score: 503.8209
Log-Logistic AIC Score: 504.0407
Log-Normal AIC Score: 504.9217

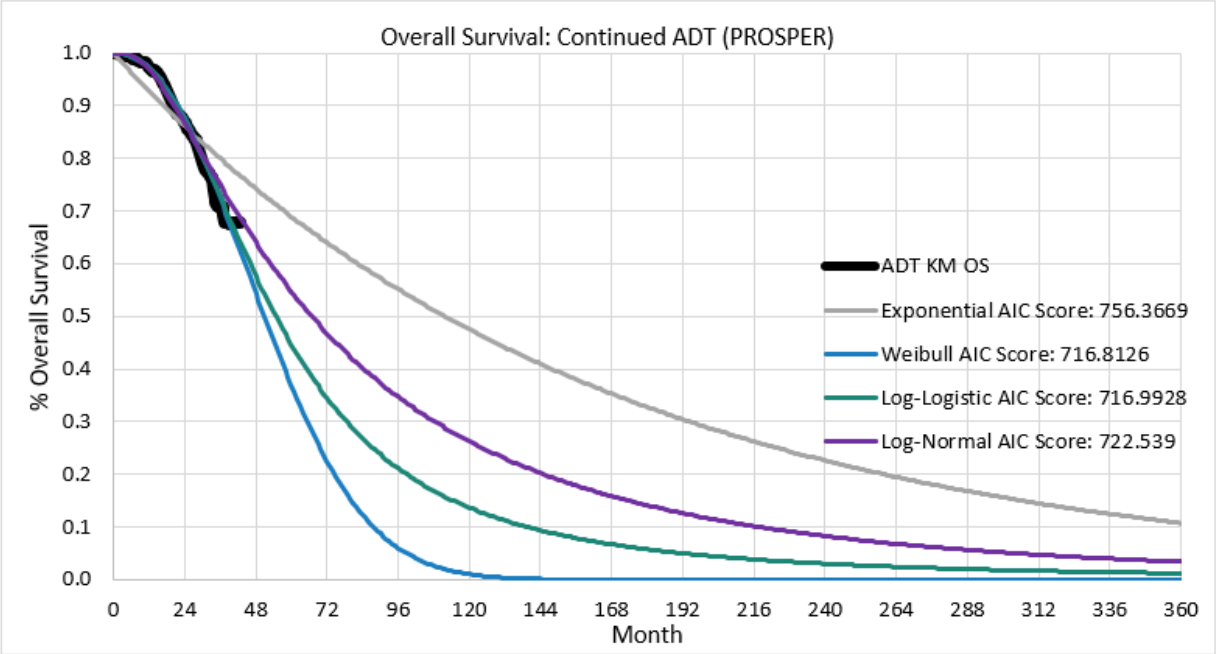


Table E6. Independently Fit Antiandrogen Curve Extrapolations versus the Base-Case Approach of Using Hazard Ratio-Derived Curves

For both antiandrogens, this scenario results in slightly higher expected incremental costs and lower expected LYs and QALY. Hence, the resulting ICERs are higher compared to the base-case analysis yet remain within the $50,000-$150,000 per QALY range.

Treatment	Drug Cost (nmCRPC)	Post-Progression Treatment Costs	Total Cost	Life Years	QALYs	ICER vs. continued ADT
Continued ADT	$4,500	$427,000	$475,000	6.77	5.51	
Apalutamide + ADT	$194,000	$352,000	$594,000	8.06	6.63	$106,000
Enzaluatamide + ADT	$208,000	$351,000	$606,000	8.09	6.69	$111,000

ADT: androgen deprivation therapy, ICER: incremental cost effectiveness ratio, nmCRPC: nonmetastatic castration-resistant prostate cancer, QALYs: quality-adjusted life years

Table E7. Metastasis-Free and Overall Survival Curves for the Placebo/Continued ADT Based on PROSPER Trial Instead of the Base-Case Approach Using Curves from the SPARTAN Trial

The parametric tails for the survival curves based on the PROSPER trial indicate slightly better survival compared to the curves based on the SPARTAN trial, and therefore lower ICERs for both antiandrogens versus the base-case scenario. Again, the estimates remain within the $50,000-$150,000 per QALY range.

Treatment	Drug Cost (nmCRPC)	Post-Progression Treatment Costs	Total Cost	Life Years	QALYs	ICER vs. continued ADT
Continued ADT	$4,400	$437,000	$485,000	6.77	5.50	
Apalutamide + ADT	$195,000	$340,000	$581,000	8.57	7.28	$54,000
Enzaluatamide + ADT	$209,000	$340,000	$595,000	8.51	7.20	$65,000

ADT: androgen deprivation therapy, ICER: incremental cost effectiveness ratio, nmCRPC: nonmetastatic castration-resistant prostate cancer, QALYs: quality-adjusted life years

Table E8. Treatment Duration Linked to Total Time Spent in Metastasis-Free Survival

A notable proportion of non-metastatic patients discontinue antiandrogen therapy due to AEs or other factors. In the SPARTAN trial, the difference between median duration of therapy and median MFS was 23.6 months; for the PROSPER trial, the difference was 18.2 months. We explored the impact of linking treatment duration to total time spent in metastasis-free survival in a scenario analysis. This notably increased time on treatment compared to the base-case with apalutamide and enzalutamide treatment durations increasing to 4.2 and 4.1 years, respectively, which increased drug cost. Importantly, we note that this scenario only increased drug cost, and assumed that efficacy was unchanged; in a real-world setting, an increase in treatment duration and/or adherence would likely lead to increased metastasis-free survival, and a lower ICER compared to the below result. The current base-case incremental cost-effectiveness ratios are tied to median treatment duration seen in the trials, but if as seen in this scenario analysis the MFS is closely tied to the time on treatment, these drugs' incremental cost-effectiveness ratios would exceed the $150,000 per QALY thresholds. We need to see longer term follow-up results from the trial to understand efficacy improvement (MFS) and associated treatment costs.

Treatment	Drug Cost (nmCRPC)	Post-Progression Treatment Costs	Total Cost	Life Years	QALYs	ICER vs. Continued ADT
Continued ADT	$4,500	$427,000	$475,000	6.77	5.51	
Apalutamide + ADT	$368,000	$342,000	$757,000	8.45	7.10	$178,000
Enzaluatamide + ADT	$361,000	$345,000	$752,000	8.40	7.01	$185,000

ADT: androgen deprivation therapy, ICER: incremental cost-effectiveness ratio, nmCRPC: nonmetastatic castration-resistant prostate cancer, QALYs: quality-adjusted life years

Table E9. Modified Societal Perspective

Per capita incremental annual costs for unemployment, days missed, and job absenteeism were previously reported to be $3,601 (2010 US dollars) by Rizzo et al. 2016, using a sample of 1,313 prostate cancer patients from the nationally representative Medical Expenditure Panel Survey. Including these costs in the analyses does not have an important impact on the base-case ICERs (changes in the ICER are smaller than $1000).

Treatment	ICER (cost per QALY gained) Comparator: Continued ADT
Apalutamide	$68,000
Enzalutamide	$84,000

ADT: androgen deprivation therapy, ICER: incremental cost effectiveness ratio, QALY: quality-adjusted life year

Appendix F. Public Comments

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on September 13, 2018 in Chicago, IL.

A video recording of all comments can be found here beginning at minute 1:22:08. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Neil M. Schultz, PharmD, MS
Associate Director, Health Economics & Outcomes Research, Oncology
Astellas Pharma

On behalf of Astellas Pharma US, Inc. (Astellas) and Pfizer Inc. (Pfizer), we are responding to the Institute for Clinical and Economic Review's (ICER) review of antiandrogen therapies for non-metastatic castration-resistant prostate cancer (nmCRPC).

While Astellas and Pfizer note that ICER's analysis supports enzalutamide's cost effectiveness in this patient population, we continue to have concerns regarding the methodology utilized.

- There remains no clear evidence that substantive learnings from patient engagement or clinical experts, such as the American Urological Association (AUA), were incorporated into ICER's process and findings.
- We, and other stakeholders, previously noted abiraterone acetate is not approved by the FDA for use in nmCRPC, and there is inadequate data to support an evidence grade of B+ for its use in the nmCRPC population.
- Wording within ICER's report suggests differences between apalutamide and enzalutamide despite no direct comparison between these two agents. This is compounded by a lack of transparency regarding the high degree of uncertainty around the point estimates used within the model.

As scientific leaders with an ongoing commitment to patients, Astellas and Pfizer appreciate the opportunity to make these comments to ICER. Our clinical scientists and outcomes researchers welcome an opportunity to understand ICER's feedback in more detail.

Appendix G. Conflict of Interest Disclosure

Tables G1 through G3 contain conflict of interest (COI) disclosures for all participants at the September 13, 2018 Public meeting of the Midwest CEPAC.

Table G1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosures
Ellie Adair, MPA	ICER	None
Laura Cianciolo, BA	ICER	None
Greg Guzauskas, MSPH, PhD	University of Washington	None
Dan Ollendorf, PhD	ICER	None
Steve Pearson, MD, MSc	ICER	None
David Rind, MD, MSc	ICER	None
Matthew Seidner, BS	ICER	None
Patty Synnott, MALD, MS	ICER	None

Table G2. Midwest CEPAC Panel Member COI Disclosures

Name	Organization	Disclosures
Eric Armbrecht, PhD	St. Louis University	*
Ryan Barket, MSW, MPPA	Missouri Foundation for Health	*
Aaron Carroll, MD, MS	Indiana University School of Medicine	*
Rena Conti, PhD	University of Chicago	*
Gregory Curfman, MD	Journal of the American Medical Association (JAMA)	*
Jill Johnson, PharmD	University of Arkansas	*
Timothy McBride, PhD	Washington University in St. Louis	*
Reem Mustafa, MD, MPH, PhD	University of Kansas	*
Harold Pollack, PhD	University of Chicago	*
Timothy Wilt, MD, MPH	Minneapolis VA Center for Chronic Disease Outcomes Research	*
Stuart Winston, DO	St. Joseph Mercy Health System	*

* No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table G3. Clinical and Patient Expert COI Disclosures

Name	Organization	Disclosures
Joel Nowak, MA MSW	Co-founder, Cancer ABC's; Prostate Cancer patient and advocate	None declared.
Russell Szmulewitz, MD	Program Leader, Genitourinary Oncology, Assistant Professor of Medicine Hematology/Oncology, University of Chicago	Served on advisory boards for Astellas, Pfizer, Janssen Pharmaceutical companies, but any compensation received was under $5,000.