Summary

CASTRATION-RESISTANT PROSTATE CANCER

Prostate cancer is the second most common cause of cancer death in men.

Prostate cancer that has not metastasized—or spread to other parts of the body—is frequently treated with androgen deprivation therapy (ADT). Men who have never previously been treated with ADT or whose disease responds to ADT treatment are said to have "castration-sensitive" disease. When cancer progresses despite this treatment, the disease is considered "castration-resistant."

Patients with disease that has not metastasized, as identified by conventional imaging, who progress on ADT are said to have nonmetastatic castration-resistant prostate cancer (nmCRPC). Patients with nmCRPC typically have increases in prostate specific antigen (PSA), a biochemical marker for disease progression that may indicate metastases that have not yet appeared on conventional imaging. Changes in PSA are measured by doubling time, with a rapid doubling time indicating higher risk.

KEY REPORT FINDINGS

ICER's report found that both apalutamide and enzalutamide provide a substantial net health benefit when compared to ADT alone, and that both therapies are cost-effective in the long-term when treating nonmetastatic disease. There's currently only moderate certainty that abiraterone acetate, used in combination with prednisone, achieves a net health benefit over ADT alone. The report was the subject of a public meeting of the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC).

TREATMENT OPTIONS

Previously, patients with nmCRPC were treated with continued ADT and surveillance for signs of metastases; however, a class of therapies called antiandrogens, which have shown benefit in CRPC with metastases, have recently been evaluated for use in nmCRPC. These include:

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

Abiraterone acetate does not currently have an FDA indication in patients with nmCRPC.

KEY POLICY RECOMMENDATIONS

- 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.
- 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.
- 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.

Clinical Analyses

ICER EVIDENCE RATINGS

How strong is the evidence that antiandrogens improve outcomes in patients with nmCRPC?

In men with nmCRPC and a rapid PSA doubling time, compared to ADT alone:

- High certainty that **apalutamide + ADT** provides a substantial net health benefit
- High certainty that **enzalutamide + ADT** provides a substantial net health benefit
- 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

Evidence was insufficient to distinguish the net health benefit of the antiandrogens compared to one another.

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

ENZALUTAMIDE AND APALUTAMIDE	**Overall Survival**	Mature overall survival data are not yet available; however, available data suggest a trend toward longer survival with both apalutamide and enzalutamide compared to ADT alone.
	Time to Disease Progression	In trials, apalutamide and enzalutamide prolonged metastasis-free survival (i.e., time from randomization to the first detection of metastasis on imaging or death from any cause) from 22 to 24 months.
	Quality of Life	Available data from trials of apalutamide and enzalutamide indicate that quality of life remained stable while on therapy.
ABIRATERONE ACETATE	Overall survival was not assessed in a Phase II trial of patients with high-risk nmCRPC; however in a trial of patients with metastatic disease, abiraterone acetate appeared to improve overall survival at rates similar to those observed in trials of enzalutamide in patients with metastatic disease. Further, median time to progression for patients with metastatic disease was similar in single-armed studies of abiraterone acetate and apalutamide. These results 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.	

Clinical Analyses (continued)

HARMS

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.

Patients taking abiraterone acetate should be monitored for mineralocorticoid excess, adrenocortical insufficiency, and hepatoxicity.

Fatigue is common with all three agents.

SOURCES OF UNCERTAINTY

- **Patient Population:** Enzalutamide and apalutamide were studied only in patients with rapid increases in PSA, but the FDA labels are for all patients with nmCRPC.
- **Patient-Important Outcomes:** Because these agents can have significant side effects, 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 outcomes such as MFS.
- **Generalizability:** Black men were underrepresented in trials of apalutamide and enzalutamide, yet 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.
- **Antiandrogen Comparisons:** More robust data are needed to determine how the antiandrogens compare to each other.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

Do these treatments meet established thresholds for long-term cost-effectiveness?

Cost effectiveness analyses compared early treatment with apalutamide and enzalutamide with later treatment (i.e., after progression to metastatic prostate cancer).

At the assumed net prices* both therapies **fall within commonly accepted thresholds for cost-effectiveness** of $50,000-$150,000 per quality-adjusted life year (QALY) when compared to taking ADT alone until progression to mCRPC.

Apalutamide + ADT	Enzalutamide + ADT
$68,000 per QALY gained	$84,000 per QALY gained

**Net prices used were $7,866 for apalutamide and $7,848 for enzalutamide. These prices account for typically observed rebates and discounts*

We did not model abiraterone acetate as there are insufficient data available in nonmetastatic patients.

VALUE-BASED PRICE BENCHMARKS

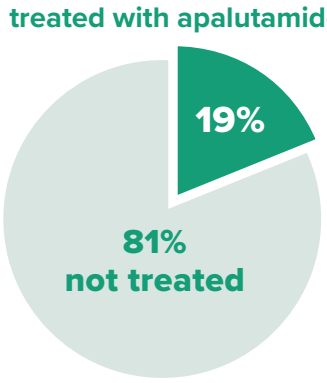
What is a fair price for these treatment based on their value to patients and the health care system?

ICER did not estimate value-based prices for the antiandrogens 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.

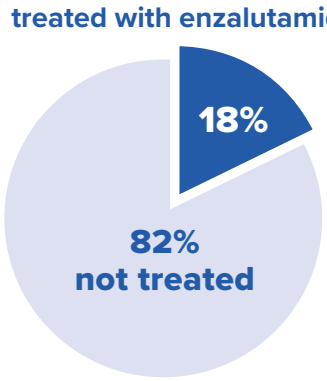
POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients can be treated with apalutamide or enzalutamide before crossing ICER's $991 million budget impact threshold?

At apalutamide's discounted WAC price, approximately 19% of the eligible population cohort could be treated each year before the budget exceeded the ICER annual budget impact threshold of $991 million.



Approximately 18% of the eligible population could be treated annually with enzalutamide before crossing the threshold.



Voting Summary

The Midwest CEPAC deliberated on key questions raised by ICER's report at a public meeting on September 13, 2018. The results of the votes are presented below. More detail on the voting results is provided in the full report.

CLINICAL EVIDENCE

The panel found evidence sufficient to show a net health benefit of treating nmCRPC with apalutamide and enzalumatide, compared to ADT alone. However, evidence was insufficient to distinguish between apalutamide and enzalumatide.

The panel found evidence insufficient to show a net health benefit for treating with abiraterone acetate.

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

Before voting on value, panel members weighed the therapies' other benefits and contextual considerations. Commenting on the need for robust head-to-head trials of these treatments, the majority of panel members voted that significant uncertainty remains regarding the long-term benefits of the treatments. Some panel members also noted the particularly high burden of illness for men with prostate cancer.

LONG-TERM VALUE FOR MONEY

A majority of the panel voted that both apalutamide and enzalumatide represent an intermediate long-term value for money. There was no vote on the long-term cost-effectiveness of abiraterone acetate because the panel found the evidence insufficient to show a net health benefit.

Policy Recommendations

Throughout the Midwest CEPAC public meeting, participants discussed the implications of the evidence for policy and practice. None of the resulting policy statements should be taken as a consensus view held by all participants. For a more detailed discussion, please see the full report.

FOR 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.

FOR 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.

Policy Recommendations (continued)

FOR THE 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.

FOR 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.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER's website (www.icer-review.org).