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

Final Background and Scope

April 9, 2018

Background

Prostate cancer is the second most common cause of cancer death in American men (after lung cancer), and the most common cancer in men other than non-melanoma skin cancers.[1] It is estimated that in 2018 in the US there will be approximately 165,000 new cases of prostate cancer and 30,000 prostate cancer deaths.[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 androgen, 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 who progress on ADT or who develop metastatic disease on ADT benefit from treatment with antiandrogen therapies.[3] Antiandrogens include abiraterone acetate (Zytiga®; Janssen Biotech, 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).[3,7] Enzalutamide and apalutamide are androgen receptor inhibitors that bind to the ligand-binding domain of the androgen receptor.[8,9]

The management of patients without metastatic disease who progress on ADT (non-metastatic 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. Apalutamide and enzalutamide were evaluated in placebo-controlled randomized trials in patients with high-risk (as defined by rate of increase in PSA) nmCRPC. Apalutamide was approved in February 2018 by the US FDA for treatment of nmCRPC.[10] Enzalutamide is expected to be reviewed for this same indication in July of 2018.[11] Abiraterone acetate has not been studied in this specific population in a randomized trial, but we have received expert input that it may have efficacy in patients with nmCRPC and a phase 2 trial suggested efficacy in this population.[12]

Stakeholder Input

This document was developed with input from diverse stakeholders, including patients and patient groups, clinicians, researchers, and manufacturers of the agents of focus in this review. Stakeholders stressed the serious risks of morbidity and mortality in patients with CRPC and how this affects patients 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. Patient groups stressed the important financial toxicities of therapies for prostate cancer and reported that some patients choose to forgo such therapies because of this. 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 may also have disproportionate effects in terms of financial toxicities and choices about undergoing and adhering to therapies.

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.

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

Report Aim

This project will evaluate the health and economic outcomes of antiandrogen therapies for non-metastatic castration-resistant prostate cancer. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

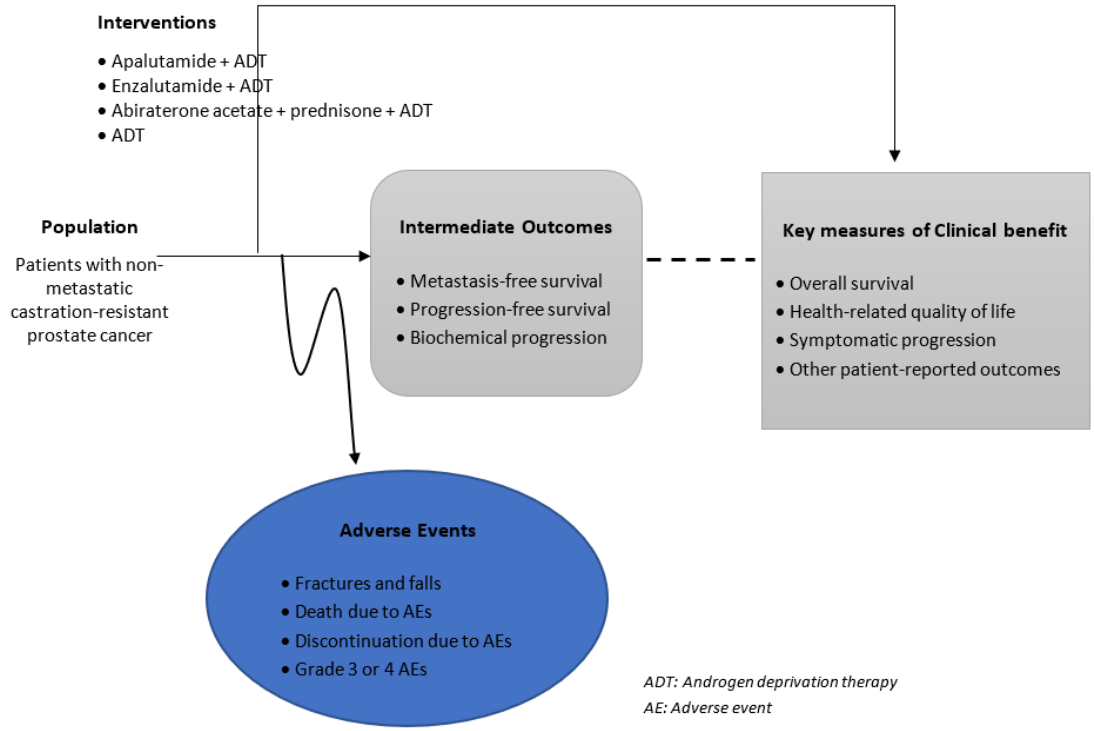
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence will be synthesized qualitatively. Wherever possible, we will seek head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of antiandrogen therapies for non-metastatic castration-resistant prostate cancer is depicted in Figure 1.1 below.

Figure 1.1. Analytic Framework: Antiandrogen Therapies for Non-Metastatic Castration-Resistant Prostate Cancer



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., progression-free survival), and those within the squared-off boxes are key measures of benefit (e.g., overall survival). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.[13]

Populations

The population of focus for this review is men with non-metastatic castration-resistant prostate cancer. If data permit, we will examine subgroups 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 list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

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

Patients will continue to be treated with ADT therapy.

Comparators

Data permitting, we intend to compare apalutamide, enzalutamide, and abiraterone acetate to each other and to continued ADT therapy without antiandrogen therapy

Outcomes

The outcomes of interest are described in the table below.

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

Timing

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

Settings

All relevant settings will be considered, including inpatient, clinic, and outpatient settings.

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 elements (not specific to this topic) are listed in the table below.

Table 1.2. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.
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.
Potential Other 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.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a simulation model to assess the lifetime cost-effectiveness of apalutamide, enzalutamide, and, data permitting, abiraterone. The model structure will be based in part on a literature review of published prostate cancer decision models.[14-21] The base case analysis will take a health-system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity losses will be considered in a separate societal perspective analysis. The target population will consist of men with nmCRPC. We will likely employ a three-state partitioned survival modeling approach, common in cancer modeling, consisting of the following health states: (1) metastasis/failure-free survival, (2) metastasis/progression, and (3) death. A cohort of patients will transition between states during likely monthly cycles over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness may be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ between treatment options to reflect real-world variation among interventions. Treatment effectiveness will be estimated based on available clinical trial data.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of metastases avoided, and life-years and quality-adjusted life years (QALYs) gained. Quality of life weights will be applied to each health state and (if available) to serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug acquisition, condition-related care, and serious adverse events. In addition, productivity losses will be included in a separate societal perspective analysis if available data allow. All outcomes and costs will be discounted at a rate of 3% annually. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained and cost per life-year gained.

In separate analyses, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by antiandrogens (e.g., apalutamide), as such services will be captured in the economic model. Rather, we are seeking services used in the current management of prostate cancer beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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