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

Research Protocol

April 24, 2018

Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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Background, Objectives, and Research Questions

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]

Objectives

The scope of this project was previously available for public comment and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project will assess both the comparative clinical effectiveness and economic impacts of the antiandrogen therapies, apalutamide, enzalutamide, and abiraterone acetate for the treatment of non-metastatic castration-resistant prostate cancer. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). See the model analysis plan for details on the proposed methodology and model structure that will be used for the economic evaluation (expected publication May 31, 2018).

Research Questions

To inform our review of the clinical evidence, we have developed the following research questions with input from clinical experts, patients and patient groups:

- In patients with non-metastatic castration-resistant prostate cancer, what is the comparative efficacy, safety, and effectiveness of enzalutamide, apalutamide, and abiraterone acetate versus each other on outcomes such as overall survival, metastasis-free survival, and quality of life?
- In patients with non-metastatic castration-resistant prostate cancer, what is the comparative efficacy, safety, and effectiveness of enzalutamide, apalutamide, and abiraterone acetate versus androgen deprivation therapy on outcomes such as overall survival, metastasis-free survival, and quality of life?

PICOTS Criteria

In line with the above research questions, the following criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Population

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 include:

- Overall survival
- Metastasis-free survival
- Progression-free survival
- Symptomatic progression
- PSA progression
- Health-related quality of life
- Grade 3 or 4 adverse events
- Adverse events leading to discontinuation
- Adverse events leading to death
- Other Adverse events (e.g., fracture, falls, rash, fatigue, seizure, hypothyroidism)

Timing

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

Setting

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

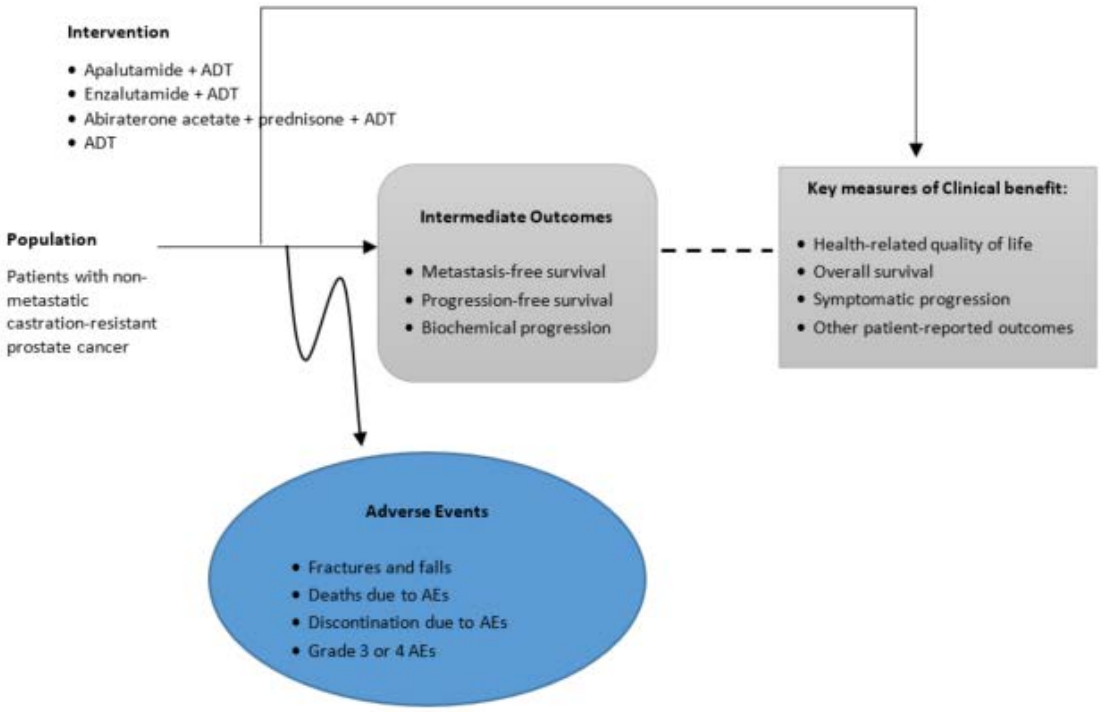
Study Eligibility Criteria

All eligible randomized controlled trials (RCTs) will be included regardless of sample size. Single-arm and non-randomized comparative studies will be included based on criteria that will be finalized after the eligible RCTs have been assessed and the gaps in the evidence base are known. We will also include all observational, open-label extensions of included RCTs, regardless of sample size or follow-up duration. We will also review RCTs of these agents in metastatic CRCP (mCRPC) to attempt to assess whether there is heterogeneity of effect in nmCRPC and mCRPC. All eligible studies will be included regardless of publication type or status, including peer-reviewed articles, conference abstracts or presentations, and registry entries (e.g., completed study data from https://clinicaltrials.gov/). In vitro, in silico, animal, and non-English language studies will be excluded.

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 clinical or 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 clinical benefit (e.g., health-related quality of life). The key measures of clinical 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 an action (typically treatment), which are listed within the blue ellipsis.

Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on enzalutamide, apalutamide, and abiraterone acetate for non-metastatic castration-resistant prostate cancer will follow established best methods.[13,14] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings identified from the systematic literature search. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Eligibility criteria described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-2 below.

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

Table 1: 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

Table 2. 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

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all publications using DistillerSR (Evidence Partners, Ottawa, Canada) and will work to resolve any issues of disagreement through consensus. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

Data will be extracted into evidence tables. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations, sample size, duration of follow-up, study design features, interventions (agent, dosage, frequency, schedules), outcome assessments, results, and quality assessment for each study.

Data extraction will be performed in the following steps:

1. Two reviewers will extract information from the full articles.
2. Extracted data will be reviewed for logic, and data will be validated by a third investigator for additional quality assurance.

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories “good,” “fair,” or “poor.”[16]

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 paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: 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: 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 or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include "enzalutamide", "apalutamide", and "abiraterone acetate". We will select studies which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: (1) a summary of the evidence base and (2) a synthesis of outcome results.

Summary of Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. An evidence table shell is presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

The results of the studies will be synthesized for each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base (see below). Key considerations for interpreting the results will be specified and described in the Evidence Report.

If studies are sufficiently similar in terms of patient populations, outcomes assessed, interventions, and comparators, we will conduct random effect pairwise meta-analyses and network meta-analyses where feasible. A pairwise meta-analysis quantitatively synthesizes results from multiple studies that assessed the same intervention and comparator.[17] A network meta-analysis extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator(s)). [18,19] The specific approach for any (network) meta-analysis will depend on the available evidence and will be detailed in the report. Whether or not formal quantitative comparisons are found to be feasible, descriptive comparisons will be reported.

To explore heterogeneity across studies, we will examine if there are differences in the distribution of key characteristics across studies. For this project, key characteristics include PSA doubling time, local disease, regional nodal disease, or metastatic disease, and previous prostate-cancer treatment. If studies differ with respect to these characteristics, subgroup analyses or meta-regressions may be performed where sufficient data exist.

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[15] Additional explanation of each item can be found in Liberati et al. 2009.[21]

Section/Topic	#	Checklist Item	Reported on Page #
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.	
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 and (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.	

doi:10.1371/journal.pmed.1000097.t001

Appendix B. Data Extraction Summary Table Shell

Author & Year of Publication (Trial)	Study Design	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes