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CADTH Reimbursement Review

Niraparib and Abiraterone Acetate (Akeega)

Sponsor: Janssen Inc.
Therapeutic area: Metastatic castration-resistant prostate cancer

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Abbreviations

AE	adverse event
AR	androgen receptor
ARPi	androgen receptor pathway inhibitor
BICR	blinded independent central review
CCS	Canadian Cancer Society
CCSN	Canadian Cancer Survivor Network
CI	confidence interval
EBRT	external beam radiotherapy
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FACT-P	Functional Assessment of Cancer Therapy–Prostate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
HRQoL	health-related quality of life
HRR	homologous recombination repair
IPD	individual participant data
ITC	indirect treatment comparison
MAIC	matching-adjusted indirect comparison
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MID	minimal important difference
nmCRPC	nonmetastatic castration-resistant prostate cancer
OH-CCO	Ontario Health (Cancer Care Ontario)
OS	overall survival
PARP	poly-(ADP [adenosine diphosphate]-ribose) polymerase
PCWG	Prostate Cancer Clinical Trials Working Group
PSA	prostate-specific antigen
RCT	randomized controlled trial
RECIST 1.1	Response Evaluation Criteria in Solid Tumours Version 1.1
rPFS	radiographic progression-free survival
SAE	serious adverse event
SMD	standardized mean difference
SOC	standard of care
TCC	time to initiation of cytotoxic chemotherapy

TEAE	treatment-emergent adverse event
TPP	time to pain progression
TSP	time to symptomatic progression
ULN	upper limit normal
WDAE	withdrawal due to adverse event

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Background Information on Application Submitted for Review

Item	Description
Drug product	Niraparib and abiraterone acetate (Akeega), 100 mg/500 mg, 50 mg/500 mg, film-coated tablets administered orally
Sponsor	Janssen Inc.
Indication	For the treatment of adult patients with deleterious or suspected deleterious *BRCA* mutated (germline and/or somatic) mCRPC who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated
Reimbursement request	As per indication
Health Canada approval status	Approved
Health Canada review pathway	NOC/c
NOC date	June 12, 2023
Recommended dose	200 mg niraparib and 1,000 mg abiraterone acetate (two 100 mg/500 mg tablets) as a single daily dose; used with 10 mg prednisone or prednisolone daily

mCRPC = metastatic castration-resistant prostate cancer; NOC = Notice of Compliance; NOC/c = Notice of Compliance with conditions.

Introduction

Prostate cancer is the most common cancer among Canadian males, affecting 1 in 8 males during their lifetime.[1] A patient may progress to metastatic castration-resistant prostate cancer (mCRPC) from metastatic castration-sensitive prostate cancer (mCSPC) based on biochemical recurrence (characterized by rising prostate-specific antigen [PSA] levels despite medical or surgical castration) or from nonmetastatic castration-resistant prostate cancer (nmCRPC) based on presentation of metastases (assessed radiographically).[2,3] This condition is characterized by increased symptomatic burden and reduced health-related quality of life (HRQoL),[4-6] and goals of treatment include delaying progression and improving HRQoL.[5] Approximately 10% of all patients with mCRPC harbour *BRCA* gene alterations.[7] When the disease progresses to the mCRPC stage, the 5-year survival rate reduces to approximately 26% to 28%.[8,9] Patients with *BRCA* gene–mutated mCRPC are more likely to present with advanced disease, nodal involvement, and distant metastases at diagnosis.[10]

Clinical experts consulted by CADTH indicated that there are several systemic therapies that are approved for the treatment of patients with mCRPC, and the sequencing of these treatments depends on patient and disease factors, and prior treatments used in the mCSPC setting. The clinical experts noted that docetaxel, cabazitaxel, abiraterone acetate, enzalutamide, olaparib (for *BRCA1* and *BRCA2*, the *ATM* gene), radium-223 (for patients with bone-predominant disease and no visceral metastasis), and lutetium vipivotide tetraxetan are all Health Canada–approved and, with the exception of lutetium vipivotide tetraxetan, are widely available in all provinces across Canada. The clinical experts highlighted that chemotherapy is the most commonly

used first-line treatment since most patients have already received an androgen receptor pathway inhibitor (ARPi) in the mCSPC setting.

The objective of CADTH's Clinical Review Report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of niraparib (200 mg) and abiraterone acetate (1,000 mg) with prednisone (10 mg) for the treatment of adult patients with deleterious or suspected deleterious *BRCA* gene–mutated (germline [inherited] and/or somatic [acquired in tumour cells during tumourigenesis]) mCRPC who are asymptomatic or mildly symptomatic, and in whom chemotherapy is not clinically indicated.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups that responded to CADTH's call for input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Two patient groups, the Canadian Cancer Society (CCS) and the Canadian Cancer Survivor Network (CCSN), provided input for this review. In total, 24 responses were gathered by CCS (from 21 patients and 3 caregivers), and 8 responses (from 8 patients) were gathered by CCSN. Overall, 97% of respondents in a CCS survey and 6 of the patients in a CCSN survey lived in Canada. Patients reported that the following symptoms affected their quality of life and day-to-day living: changes in libido, sexual function or fertility, hot flushes, fatigue, low energy, difficulties with urination, loss of appetite, bone or skeletal pain, indigestion, bowel problems, peripheral neuropathy, dizziness, and muscle loss. From the patients' perspective, the prospect of cure, the avoidance of metabolic syndrome, the avoidance of metastases progressing to other body locations, and the prevention or mitigation of the spread of cancer in the bones are the most important aspects of their disease to control. One patient from the CCSN survey who had taken niraparib reported constipation and decreased appetite as adverse effects. When asked about their experience with niraparib in comparison to other therapies, the respondent noted that there was little or no difference in symptom management, side effects, and ease of use. The patients also noted that the experience regarding disease progression was much better compared to that of other therapies.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical specialists with expertise in the diagnosis and management of mCRPC reported that since mCRPC is a terminal phase of prostate cancer, the unmet needs of patients would be prolonged overall survival (OS), improved HRQoL, and reduced toxicity. Both clinical experts highlighted that the balance between treatment efficacy and HRQoL would be important. They highlighted a need for new treatments since these patients have primary or acquired resistance to offered treatments in the mCRPC setting. Clinical experts agreed that it remains unclear whether niraparib and abiraterone acetate would lead to a shift in the current treatment paradigm due to the increased use of ARPi in the mCSPC setting. They believe many medical oncologists would favour a change to chemotherapy in patients progressing on an ARPi, although the CADTH review team noted this could vary across clinicians and treatment centres in Canada.

In their opinion, niraparib and abiraterone acetate will be positioned as a second-line treatment for mCRPC due to the decreasing number of patients who are ARPi-naive. The clinical experts agreed that niraparib and abiraterone acetate would be for the *BRCA* gene–mutated mCRPC population. It was noted that most patients with mCRPC — especially those who are otherwise well — would be considered for treatment with cytotoxic chemotherapy. However, the clinical experts reported that it is rare for patients to have an absolute contraindication to chemotherapy. According to the clinical experts, clinicians may consider alternatives to chemotherapy in patients whose disease is asymptomatic or minimally symptomatic and palliative to minimize the toxic effects of treatments. Furthermore, the clinical experts noted that some patients may not want to receive chemotherapy due to adverse effects. In terms of assessing the response treatment, they noted that a combination of radiographic, biochemical, and clinical parameters are used to determine whether a patient with mCRPC is responding to treatment. The clinical experts indicated that treatment should be discontinued if it is intolerable, if the disease progresses, or if it's the patient's preference to stop the treatment. Clinical experts noted that poly-(ADP [adenosine diphosphate]-ribose) polymerase (PARP) inhibitors have the potential to be toxic. Therefore, they noted that patients receiving niraparib and abiraterone acetate must be under the care of a medical oncologist to manage toxicity.

Clinician Group Input

Clinician group input was received from the Ontario Health (Cancer Care Ontario) (OH-CCO) Genitourinary Cancer Drug Advisory Committee. A total of 8 clinicians provided input on behalf of OH-CCO. OH-CCO highlighted the need to have therapies in the first-line mCRPC setting that can prolong life, considering there is currently no cure and no targeted treatments are currently available at this setting. They also mentioned the need for treatments that can maximize quality of life. The group noted that niraparib and abiraterone acetate with prednisone would become a standard of care (SOC) in treatment-naive patients with mCRPC with homologous recombination repair (HRR) mutation, although the CADTH review team noted that the Health Canada–approved indication is for patients with *BRCA* mutations only. The group indicated that while PSA would be used to determine the burden of disease and to monitor response to therapy, serial radiographic imaging would also be used to monitor response and to determine progression as per SOC. They also noted that they would discontinue treatment in cases of significant side effects or disease progression.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following items were identified as key factors that could potentially impact the implementation of a CADTH recommendation for niraparib and abiraterone acetate:

- relevant comparators
- consideration for the initiation of therapy
- consideration for the continuation of therapy
- generalizability
- care provision issues
- funding algorithm.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs (Table 4).

Clinical Evidence

Systematic Review

Description of Studies

One phase III, double-blind, placebo-controlled, randomized controlled trial (RCT) (MAGNITUDE study, N = 423) met the inclusion criteria for the systematic review conducted by the sponsor. A subgroup of the population accounted for patients with *BRCA1* and *BRCA2* gene alterations (N = 225) as per the Health Canada–approved indication and requested reimbursement population. In the *BRCA* subgroup, 113 patients were randomized to receive niraparib 200 mg and abiraterone acetate 1,000 mg with prednisone 10 mg once daily and 112 patients were randomized to receive placebo and abiraterone acetate 1,000 mg with prednisone 10 mg once daily. The objective of the MAGNITUDE trial was to evaluate the efficacy and safety of niraparib and abiraterone acetate with prednisone versus placebo and abiraterone acetate with prednisone in adult patients with mCRPC. The study is ongoing, and patients will be followed up every 3 months to 60 months (5 years) or until death, loss to follow-up, withdrawal of consent, or study termination. The primary outcome was radiographic progression-free survival (rPFS) assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1), and secondary outcomes were OS and time to symptomatic progression (TSP). Time to pain progression (TPP) and HRQoL measured by the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire were included as exploratory outcomes in the trial. These outcomes from the trial — OS, rPFS, TSP, TPP, and HRQoL measured with FACT-P — were the focus of this reimbursement review (refer to the section GRADE Summary of Findings and Certainty of Evidence).

Some baseline patient characteristics in the *BRCA* subgroup, such as body location of metastases, metastasis stage, Gleason scores, and Eastern Cooperative Oncology Group Performance Status (ECOG PS) score were not balanced between the treatment groups. The population was predominately white (72%), with an approximate mean age of 68 years. Most patients had a tumour stage of T3 (41.8%), a Gleason score of 8 or more (69.2%), and an ECOG PS score of 0 (66.2%). A similar proportion of patients in both groups had prior prostate cancer therapy.

Efficacy Results

All results are from the second interim analysis of the MAGNITUDE trial, with a data cut-off date of June 17, 2022.

Overall Survival

The median follow-up time was 24.80 months for all patients in the *BRCA* subgroup. The median duration of follow-up with patients was 20.18 months in the niraparib and abiraterone acetate with prednisone group and 19.98 months in the placebo and abiraterone acetate with prednisone group. More patients had died in the placebo and abiraterone acetate group (44%) than in the niraparib and abiraterone acetate group (38%) by the data cut-off date. The median OS was 29.27 months in the niraparib and abiraterone acetate with

prednisone group and 28.55 months in the placebo and abiraterone acetate with prednisone group, with an adjusted hazard ratio (HR) of 0.68 (95% confidence interval [CI], 0.445 to 1.046) and a stratified HR of 0.881 (95% CI, 0.58 to 1.33). The probability of OS at 12 months was 84.1% (95% CI, 75.9% to 89.7%) and 83.9% (95% CI, 75.7% to 89.5%), and the probability of OS at 24 months was 65.6% (95% CI, 55.4% to 74.1%) and 56.6% (95% CI, 45.5% to 66.3%) in the niraparib and abiraterone acetate with prednisone group and the placebo and abiraterone acetate with prednisone group, respectively. The results from the nonstratified sensitivity analysis of OS for the *BRCA* subgroup were consistent with the stratified analysis.

Radiographic Progression-Free Survival

The between–treatment group difference in rPFS met the prespecified criteria for declaring the primary analysis successful at the first interim analysis, and therefore no formal statistical testing was performed at the second interim analysis. At the second interim analysis, approximately 50% of patients receiving niraparib and abiraterone acetate with prednisone had progression events compared with nearly 70% of those in the placebo and abiraterone acetate with prednisone group by the June 17, 2022, data cut-off date in the *BRCA* subgroup. The median rPFS was 19.52 months in the niraparib and abiraterone acetate with prednisone group and 10.87 months in the placebo and abiraterone acetate with prednisone group, with a stratified HR of 0.55 (95% CI, 0.39 to 0.78) favouring the niraparib and abiraterone acetate with prednisone group. The probability of being event-free at 12 months was [redacted] (95%CI, [redacted] to [redacted]) and [redacted] ([redacted] to [redacted]), and the probability of being event-free at 24 months was [redacted] (95% CI, [redacted] to [redacted]) and [redacted] (95% CI, [redacted] to [redacted]) in the niraparib and abiraterone acetate with prednisone group and the placebo and abiraterone acetate with prednisone group, respectively.

Time to Symptomatic Progression

More patients who received placebo and abiraterone acetate with prednisone (46%) than who received niraparib and abiraterone acetate with prednisone (27%) reported symptom progression in the *BRCA* subgroup. The median TSP in the niraparib and abiraterone acetate with prednisone group was not estimable and was 23.56 months in the placebo and abiraterone acetate with prednisone group. The stratified HR of 0.54 (95% CI, 0.34 to 0.85) favoured niraparib and abiraterone acetate with prednisone. The probability of TSP at 12 months was 83.4% (75% to 89.2%) and 75.1% (65.7% to 82.2%), and the probability of TSP at 24 months was 68% (95% CI, 57.3% to 76.6%) and 47.8% (95% CI, 36.1% to 58.5%) in the niraparib and abiraterone acetate with prednisone group and in the placebo and abiraterone acetate with prednisone group, respectively.

Time to Pain Progression

The median TPP in the niraparib and abiraterone acetate with prednisone group was not estimable and was 22.11 months in the placebo and abiraterone acetate with prednisone group, with a stratified HR of 0.70 (95% CI, 0.43 to 1.12). The probability of TPP at 12 months was 72.90% (62.9% to 80.6%) and 69.4% (59.3% to 77.5%), and the probability of TPP at 24 months was 66.9% (95% CI, 55.9% to 75.8%) and 49.9% (95% CI, 36.2% to 61.3%) in the niraparib and abiraterone acetate with prednisone group and the placebo and abiraterone acetate with prednisone group, respectively.

Change From Baseline in FACT-P Total Score

The difference in the least squares mean for the change from baseline in FACT-P total score at cycle 25 between the 2 treatment groups was [redacted] points (95% CI, [redacted] to [redacted]). Data were available for only 26 of 133 patients in the niraparib and abiraterone acetate with prednisone group and for 13 of 112 patients in the placebo and abiraterone acetate with prednisone group at the latest (cycle 25) analysis time point.

Harms Results

At least 1 treatment-emergent adverse event (TEAE) was reported in almost all patients in both treatment groups (99.1% of patients in the niraparib and abiraterone acetate with prednisone group, and 97.3% of patients in the placebo and abiraterone acetate with prednisone group). The most common TEAEs in the niraparib and abiraterone acetate with prednisone group versus the placebo and abiraterone acetate with prednisone group, respectively, were anemia ([redacted]versus [redacted]), constipation (33.6% versus 19.6%), hypertension (32.7% versus 24.1%), and nausea (32.7% versus 20.5%). A larger proportion of patients in the niraparib and abiraterone acetate with prednisone group experienced at least 1 TEAE of a grade 3 or grade 4 compared to the placebo and abiraterone acetate with prednisone group (68.1% versus 50.9%). At least 1 serious adverse event (SAE) was reported in 40.7% of patients in the niraparib and abiraterone acetate with prednisone group, and 25% of patients in the placebo and abiraterone acetate with prednisone group. The most common SAE in both groups was COVID-19 (4.4% and 2.7% in the niraparib and abiraterone acetate with prednisone group and the placebo and abiraterone acetate with prednisone group, respectively). Overall, 15% of patients in the niraparib and abiraterone acetate with prednisone group versus 5.4% of patients in the placebo and abiraterone acetate with prednisone group withdrew from study treatment due to TEAEs. During the follow-up time where death occurred more than 30 days after the last dose of the study drug, deaths were reported in [redacted] of patients in the niraparib and abiraterone acetate with prednisone group, and [redacted] of patients in the placebo and abiraterone acetate with prednisone group. Most deaths were attributed to disease progression in both treatment groups ([redacted] with niraparib and abiraterone acetate with prednisone; [redacted] with placebo and abiraterone acetate with prednisone).

Notable harms identified in the CADTH review included anemia, which occurred in [redacted] of patients treated with niraparib and abiraterone acetate with prednisone and [redacted] of patients treated with placebo and abiraterone acetate with prednisone, followed by hypertension (32.7% versus 24.1%, respectively), fatigue ([redacted] versus [redacted], respectively), thrombocytopenia ([redacted] versus [redacted], respectively), asthenia ([redacted] versus [redacted], respectively), fluid retention ([redacted] versus [redacted], respectively), neutropenia ([redacted] versus [redacted], respectively), and peripheral edema ([redacted] versus [redacted], respectively).

Critical Appraisal

Although the MAGNITUDE study was a randomized trial, several key baseline factors were imbalanced between the 2 treatment groups, such as body location of metastases, metastasis stage at diagnosis, and ECOG PS score, which confounds the results and makes it difficult to determine the true effects of the treatments. The relatively small sample sizes in the trial and in the prespecified *BRCA* subgroup may partially account for the between-group differences. Multivariate Cox regression analysis (only for OS) and other analysis methods were used to try to balance differences between the groups. The clinical experts

consulted by CADTH indicated that the differences in baseline characteristics signalled that the niraparib and abiraterone acetate with prednisone group had more serious disease than the control group. Therefore, if the identified differences in characteristics were not fully accounted for in the analyses, then the likely direction of the bias would be to the null (i.e., against niraparib and abiraterone acetate with prednisone). There were major protocol deviations identified in the trial; however, the magnitude and direction of potential bias was unclear due to the lack of reported patient numbers affected by these deviations within the *BRCA* subgroup. Furthermore, the niraparib and abiraterone acetate with prednisone group received more treatment cycles than the placebo and abiraterone acetate with prednisone group (33.0% versus 23. 7%, respectively), which could lead to artificially inflating the perceived effectiveness of the niraparib and abiraterone acetate with prednisone group. However, this difference in cycles of treatment received also reflects the observed higher percentage of patients in the placebo and abiraterone acetate with prednisone group who had disease progression. The difference in treatment cycles may also increase the likelihood of reporting AEs with additional treatments in the niraparib and abiraterone acetate with prednisone group. CADTH reviewers could not determine whether the efficacy and safety results were influenced by this imbalance based on the available information, although it is anticipated to have a limited effect, if any.

According to clinical experts, patients in the MAGNITUDE trial were considered generally representative of patients with mCRPC. Patients in the cohort 1 *BRCA* subgroup of the MAGNITUDE trial all had *BRCA* mutations confirmed before being enrolled in the trial, which aligns with the indicated population and reimbursement request. However, there were potential gaps and implementation challenges related to the evidence from the MAGNITUDE trial versus the population of patients included in the approved indication. CADTH noted that the indication is line-agnostic, whereas no patients in the MAGNITUDE trial had received prior systemic therapy in an mCRPC setting (i.e., received niraparib and abiraterone acetate with prednisone or placebo and abiraterone acetate with prednisone as first-line treatment in this setting). Additionally, the clinical experts indicated that although asymptomatic patients could be easily identified, determining whether a patient is “mildly symptomatic” is a subjective judgment and may vary between clinicians. It is unclear if patients enrolled in the MAGNITUDE trial would be classified as asymptomatic or mildly symptomatic because the trial did not have eligibility criteria or report baseline characteristics directly related to this. Likewise, the clinical experts indicated that there is no objective definition for patients “in whom chemotherapy is not clinically indicated.” Health Canada reported that the definition of this component of the indication is based on the clinical judgment of the treating physician and was included to reflect the MAGNITUDE study exclusion criteria, where no prior chemotherapy in an mCRPC setting was allowed. However, the clinical experts consulted by CADTH for this review noted that any patient with mCRPC who was well enough for cytotoxic chemotherapy could be interpreted as having a clinical indication for it, although they and/or their clinicians might not wish to treat these patients with chemotherapy due to the associated adverse effects.

In addition, the clinical experts noted that the exclusion criteria of the MAGNITUDE trial reduce the generalizability of the results as many patients with mCRPC in Canada now would have received a second-generation androgen receptor (AR) targeted therapy in an earlier stage of the disease. The clinical experts indicated this might impact the choice of niraparib and abiraterone acetate in the mCRPC setting because

there would be a small population that would not be considered for taxane chemotherapy as first-line mCRPC treatment. Therefore, the CADTH review team noted that the trial population could reflect a relatively small population in clinical settings based on treatment history and eligibility. Outcomes measured in the MAGNITUDE trial are those recommended by Prostate Cancer Clinical Trials Working Group 3 (PCWG3)[11] (i.e., OS, rPFS, and patient-reported outcomes such as symptoms and HRQoL) and some are clinically relevant and important to patients. According to clinical experts consulted by CADTH, although rPFS is a relevant end point for assessing efficacy in trials, it is not an ideal primary efficacy outcome. It should be noted that despite the improvement in rPFS, there did not appear to be a substantial OS advantage. This is because the emphasis on radiographic results to determine disease progression and treatment benefit in an mCRPC setting does not adequately reflect clinical practice, which involves a broader and more holistic assessment of determining treatment benefit. Although the experts noted that abiraterone acetate with prednisone was an appropriate comparator when the MAGNITUDE trial was designed, there are gaps in the direct comparative evidence since there are additional clinically relevant comparators used to treat patients with mCRPC in Canada that are now more commonly used (e.g., chemotherapy). Therefore, the absence of head-to-head evidence between niraparib and abiraterone acetate versus chemotherapy represents an evidence gap. Clinical experts also noted that enrolling patients with only an ECOG PS score of 0 and 1 in the MAGNITUDE study is not entirely representative of patients with mCRPC as they expect to find patients with higher ECOG PS scores in Canadian practice.

GRADE Summary of Findings and Certainty of Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.[12,13]

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for OS and rPFS were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review; for the FACT-P total score, reference points were set according to the presence or absence of an important effect based on thresholds identified in the literature. The target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for the TSP and TPP due to the lack of

a formal minimal important difference (MID) estimate; for harms events, due to the unavailability of the absolute difference in effects, the certainty of evidence was summarized narratively.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, on CADTH's consultation with clinical experts, and on input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- survival outcomes (OS, rPFS, TSP, TPP)
- HRQoL outcome (FACT-P total score)
- harms (withdrawals due to adverse events [WDAEs], SAEs).

Results of GRADE Assessments

Table 2 presents the GRADE summary of findings for niraparib and abiraterone acetate with prednisone versus placebo and abiraterone acetate with prednisone.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

Description of Studies

The sponsor provided 1 indirect treatment comparison (ITC)[17] described as an unanchored matching-adjusted indirect comparison (MAIC). In the analysis, individual participant data (IPD) from patients with mCRPC treated with niraparib and abiraterone acetate with prednisone in the MAGNITUDE pivotal trial (N = 113) was compared with the IPD from patients with mCRPC treated with first-line enzalutamide in the CAPTURE study (N = 19). The CAPTURE study was an observational, multiple-cohort database study focusing on Spanish patients. Patients from the CAPTURE study were reweighted using propensity score weighting in an attempt to match the distribution of patient characteristics of the patient cohort from the MAGNITUDE study. Outcomes presented in the ITC included OS, rPFS, and time to treatment discontinuation.

Results

The median follow-up time for patients in the MAGNITUDE trial was 26.8 months, while in the CAPTURE trial, the median follow-up time was 25.2 months. Efficacy and safety results from the primary analyses (i.e., base-case adjustment with simple imputation) in the scenario 1 population (i.e., patients selected from the CAPTURE study with first-line treatment mCRPC and *BRCA1* or *BRCA2* mutations) are presented in Table 20. The HR for OS among patients receiving enzalutamide only was [redacted]). However, the Kaplan-Meier curves for OS crossed, indicating that the proportional hazards assumption did not hold (Figure 7). The HR for rPFS among patients receiving enzalutamide only was [redacted]. The HR for time to treatment discontinuation among patients receiving enzalutamide only was [redacted]. The results of all sensitivity analyses (data not shown) in the scenario 1 population favoured niraparib and abiraterone acetate with prednisone over comparators.

Table 2: Summary of Findings for Niraparib and Abiraterone Acetate With Prednisone vs. Placebo and Abiraterone Acetate With Prednisone for Patients With mCRPC Having *BRCA* Mutation

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Niraparib and abiraterone acetate with prednisone	Placebo and abiraterone acetate with prednisone	Difference		
OS: Randomized analysis set							
Probability of death[a] at 12 months Median follow-up: 24.8 months	225 (1 RCT)	NR	159 per 1,000	161 per 1,000 (NR)	2 fewer per 1,000 (108 fewer to 104 more)	Low[b]	Niraparib and abiraterone acetate with prednisone may result in little to no clinically important difference in the probability of death at 12 months when compared with placebo and abiraterone acetate with prednisone.
Probability of death[a] at 24 months Median follow-up: 24.8 months	225 (1 RCT)	NR	344 per 1,000	434 per 1,000 (NR)	90 fewer per 1,000 (245 fewer to 65 more)	Low[c]	Niraparib and abiraterone acetate with prednisone may result in a clinically important decrease in the probability of death at 24 months when compared with placebo and abiraterone acetate with prednisone.
rPFS: Randomized analysis set							
Probability of radiographic progression[d] at 12 months Median follow-up: 24.8 months	225 (1 RCT)	NR	309 per 1,000	539 per 1,000 (NR)	230 fewer per 1,000 (370 fewer to 89 fewer)	Moderate[e, f]	Niraparib and abiraterone acetate with prednisone likely increases the probability of rPFS at 12 months when compared with placebo and abiraterone acetate with prednisone. The clinical importance of the difference is unknown.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Niraparib and abiraterone acetate with prednisone	Placebo and abiraterone acetate with prednisone	Difference		
Probability of radiographic progression[d] at 24 months Median follow-up: 24.8 months	225 (1 RCT)	NR	579 per 1,000	748 per 1,000 (NR)	169 fewer per 1,000 (329 fewer to 8 fewer)	Moderate[e, f]	Niraparib and abiraterone acetate with prednisone likely increases the probability of rPFS at 24 months when compared with placebo and abiraterone acetate with prednisone. The clinical importance of the difference is unknown.
TSP: Randomized analysis set							
Probability of symptom progression[g] at 12 months Median follow-up: 24.8 months	225 (1 RCT)	NR	166 per 1,000	249 per 1,000 (NR)	83 fewer per 1,000 (203 fewer to 35 more)	Low[h, i]	Niraparib and abiraterone acetate with prednisone may result in a decrease in the probability of symptomatic progression at 12 months when compared with placebo and abiraterone acetate with prednisone. There is some uncertainty about the clinical importance of the estimates.
TPP: Randomized analysis set							
Probability of pain progression[j] at 12 months Median follow-up: 24.8 months	225 (1 RCT)	NR	271 per 1,000	306 per 1,000 (NR)	35 fewer per 1,000 (174 fewer to 105 more)	Very low[h, k]	The evidence is very uncertain about the effect of niraparib and abiraterone acetate with prednisone on pain progression at 12 months when compared with placebo and abiraterone acetate with prednisone.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Niraparib and abiraterone acetate with prednisone	Placebo and abiraterone acetate with prednisone	Difference		
FACT-P questionnaire (total score): Randomized analysis set							
LSM change from baseline in FACT-P (total score); range of scores is 0 to 156 and a higher overall score indicates better HRQoL Time point: At cycle 25	225 (1RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[h, l]	Niraparib and abiraterone acetate with prednisone likely result in little to no difference in HRQoL at cycle 25 when compared with placebo and abiraterone acetate with prednisone. There is some uncertainty about the clinical importance of the estimates.
Harms							
SAEs	225 (1 RCT)	**Effects:** In the total population, there were 46 (40.7%) SAEs in the niraparib and abiraterone acetate with prednisone group vs. 28 (25%) SAEs in the placebo and abiraterone acetate with prednisone group.				Moderate[m]	Niraparib and abiraterone acetate with prednisone likely results in an increase in the proportion of patients who experience SAEs when compared with placebo and abiraterone acetate with prednisone. The clinical significance of the magnitude of the effect is uncertain.
WDAEs	225 (1 RCT)	**Effects:** In the total population, there were 17 (15%) withdrawal adverse events in the intervention group vs. 6 (5.4%) withdrawal adverse events in the comparator group.				Moderate[m]	Niraparib and abiraterone acetate with prednisone likely results in an increase in the proportion of patients who withdraw due to adverse events when compared with placebo and abiraterone acetate with prednisone. The clinical

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Niraparib and abiraterone acetate with prednisone	Placebo and abiraterone acetate with prednisone	Difference		
							significance of the magnitude of the effect is uncertain.

CI = confidence interval; FACT-P = Functional Assessment of Cancer Therapy–Prostate; HR = hazard ratio; HRQoL = health-related quality of life; NA = not applicable; LSM = least squares mean; mCRPC = metastatic castration-resistant prostate cancer; NR = not reported; OS = overall survival; RCT = randomized controlled trial; rPFS = radiographic progression-free survival; TPP = time to pain progression; TSP = time to symptomatic progression; SAE = serious adverse event; vs. = versus; WDAE = withdrawal due to adverse event.

Notes: Details included in Table 2 are from the sponsor's Summary of Clinical Evidence.[14]

Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, the imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]The sponsor provided the probability of an event at the time point (i.e., death).

[b]Rated down 2 levels for very serious imprecision. The 95% CI for the difference between groups included the possibility of both benefit and harm when compared with placebo and abiraterone acetate with prednisone. A between-group difference of greater than 5% was clinically significant according to the clinical experts. We did not rate down OS due to the risk of bias since there was a multivariate analysis for OS, adjusting for important imbalanced characteristics.

[c]Rated down 2 levels for very serious imprecision. The 95% CI for the difference between groups included the possibility of a trivial effect (little to no difference) and important harm when compared with placebo and abiraterone acetate with prednisone. A between-group difference of 5% (50 fewer or 50 more events per 1,000 patients) was clinically significant according to the clinical experts.

[d]The sponsor provided the probability of an event at the time point (i.e., radiographic progression).

[e]We did not rate down for the risk of bias due to important baseline imbalances since differences in baseline characteristics signalled that the niraparib and abiraterone acetate group had more serious disease than the control group and the point estimate was showing a benefit, we are then more confident that the result was true. Results were based on an interim analysis. However, we did not detect potential overestimation of the true effect.

[f]Rated down 1 level for serious imprecision and because clinical experts were uncertain of what the exact threshold for clinical importance would be. Therefore, the null was used as the threshold. The point estimate and entire CI excluded the null. However, it was based on a small number of events.

[g]The sponsor provided the probability of an event at the time point (i.e., symptomatic progression).

[h]Rated down 1 level for serious risk of bias due to important baseline imbalances; the direction of bias was potentially toward the placebo and abiraterone acetate with prednisone group. The point estimate was showing little to no difference.

[i]Rated down 1 level for serious imprecision. The 95% CI included the possibility of little to no difference. There was no known MID so the target of certainty appraisal was any effect.

[j]The sponsor provided the probability of an event at the time point (i.e., pain progression).

[k]Rated down 2 levels for very serious imprecision due to the 95% CI, which included the possibility of both important benefit and important harm. There was no known MID so the target of certainty appraisal was any effect.

[l]There was no imprecision in the estimate (the entire CI showed little to no difference). The point estimate and both the lower and upper boundaries of the 95% CI of the between-group comparison indicated trivial or no clinically meaningful difference. Based on literature, a 10-point change from baseline in FACT-P total score was clinically important.

[m]Rated down 1 level for serious imprecision. The number of events did not meet the optimal information size.

Sources: MAGNITUDE Second Interim Analysis Clinical Study Report[15] and the sponsor's response to requested additional information.[16]

Critical Appraisal

CADTH noted that the ITC analysis carried out by the sponsor was not a typical unanchored MAIC based on comparing IPD from 1 study with aggregate-level data from the other study. The analysis submitted to CADTH was more like a single exposure cohort (i.e., the niraparib and abiraterone acetate with prednisone group of the MAGNITUDE study) compared with an external comparator (e.g., enzalutamide-only group from the CAPTURE study), using population adjustment methods based on IPD from both groups.

One major concern that decreased CADTH's certainty in the ITC estimates related to patient comparability. In the sponsor-submitted ITC analysis, more than 20 potential prognostic and effect modifying factors were identified from the literature (Table 17) that were considered relevant and comprehensive by the clinical experts consulted by CADTH. However, of these factors identified, only 9 factors (6 factors adjusted for the base-case analysis and an additional 3 factors for the sensitivity analysis) were involved in the propensity score weighting. It is understandable that many prognostic and effect modifying factors identified were not reported in the MAGNITUDE or CAPTURE study, which made it impossible to adjust. Yet, with many relevant factors unadjusted, it is likely that the differences unaccounted for would bias the results, although the degree of the bias remains unknown. Additionally, after adjustment in the base-case analysis, the absolute values of the standardized mean differences (SMDs) greater than 0.2 were identified for several prognostic factors such as age (SMD = 0.269), baseline PSA (SMD = 0.250), Gleason score at initial diagnosis (SMD = 0.460), and the presence of visceral metastases (SMD = 0.513), which suggested the existence of insufficient balance.

Another concern was that the Kaplan-Meier curves for OS, which was considered the most clinically relevant end point for patients with mCRPC, signalled that the proportional hazards assumption had been violated, and no further analyses addressing the nonproportional hazard issue were found. In addition, a lack of information in the sponsor-submitted ITC report made it challenging for CADTH to determine, for example, whether the discrepancy in the definitions of disease progression (and therefore rPFS) between the MAGNITUDE and CAPTURE studies would impact the ITC estimates and whether data from the CAPTURE study was temporally relevant to the data from the MAGNITUDE study.

Lastly, findings from the ITC focused on the comparison between niraparib and abiraterone acetate with prednisone versus enzalutamide in the first-line treatment setting only. Therefore, there remains a gap in the indirect comparative evidence related to the later lines of therapy.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps in the systematic review evidence were submitted by the sponsor.

Conclusions

mCRPC is an advanced stage of prostate cancer, and there is an unmet need for new treatments to prolong life, prevent disease progression, improve HRQoL, and reduce adverse events (AEs). The MAGNITUDE trial is an ongoing, double-blind, phase III RCT evaluating the efficacy and safety of first-line treatment with niraparib and abiraterone acetate with prednisone in patients with mCRPC. The trial did not demonstrate a benefit with niraparib and abiraterone acetate with prednisone compared to placebo and abiraterone acetate with

prednisone on OS or HRQoL, which were identified as important outcomes by patients and clinical experts. Moderate certainty of evidence showed niraparib and abiraterone acetate with prednisone likely resulted in an increase in rPFS when compared with placebo and abiraterone acetate with prednisone; however, the clinical importance of this difference was uncertain. Results for TSP and TPP suggested that niraparib and abiraterone acetate with prednisone were favoured over placebo and abiraterone acetate with prednisone but the results for these efficacy outcomes were affected by concerns for imprecision and limitations in the trial, such as imbalanced baseline characteristics between treatment groups. Niraparib and abiraterone acetate with prednisone appeared to be associated with a higher frequency of TEAEs, grade 3 or grade 4 AEs, SAEs, withdrawals from treatment due to an AE (WDAEs), and notable harms compared with placebo and abiraterone acetate with prednisone. Findings from the sponsor-conducted indirect comparison with enzalutamide were considered of high uncertainty due to several major limitations, such as the fact that many relevant prognostic and effect modifying factors were not adjusted as well as the fact that the proportional hazards assumption was likely violated for OS.

Introduction

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of niraparib 200 mg and abiraterone acetate 1,000 mg (oral tablet) used with prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA* mutated (germline and/or somatic) mCRPC who are asymptomatic or mildly symptomatic, and in whom chemotherapy is not clinically indicated.

Disease Background

Content in this section has been informed by materials submitted by the sponsor and clinical expert input. The following has been summarized and validated by the CADTH review team.

Prostate cancer is the most common cancer among Canadian males, affecting 1 in 8 males during their lifetime[1] and accounting for 10% of cancer-related deaths.[18] The 10-year prevalence of prostate cancer was 993.7 per 100,000 among those assigned male at birth in Canada (excluding Quebec) (492.7 per 100,000 people) in 2018.[19] It was estimated that in 2022, 24,600 males in Canada would be diagnosed with prostate cancer.[1] The stages of prostate cancer are classified in terms of localized, locally advanced, or metastatic disease, with further subcategorization according to hormone therapy status, whether hormone-naive or hormone-sensitive, or mCRPC.[11] A patient may progress from mCSPC to mCRPC based on biochemical recurrence (characterized by rising PSA levels despite medical or surgical castration) or from nmCRPC based on the presentation of metastases (assessed radiographically).[2,3] Progressing to mCRPC is characterized by increased symptomatic burden and reduced HRQoL,[4-6] and goals of treatment include delaying progression and improving HRQoL.[5] As per a recent systematic literature review of the epidemiology of advanced prostate cancer, the prevalence of mCRPC was estimated at 1.2% to 2.1% of prostate cancer cases.[20]

Even though the expected 5-year survival for males diagnosed with prostate cancer in Canada is 91% for all stages combined,[21] when the disease progresses to the mCRPC stage, the 5-year survival rate reduces

to approximately 26% to 28%.[8,9] With current mCRPC treatments, median survival is low, ranging from approximately 9 months to 3 years in more recent studies.[22-26] Approximately 20% to 30% of patients with metastatic prostate cancer have pathogenic variants in DNA repair genes (e.g., *BRCA1, BRCA2*, *ATM*) that are associated with the HRR pathway.[27,28] When these mutations occur in the HRR pathway specifically, cancer cells rely on PARP to correct DNA damage and prevent cell death.[29]

Approximately 10% of all patients with mCRPC harbour *BRCA* alterations.[7] Half of pathogenic variants are of germline (inherited) origin and the other half are of somatic (acquired in tumour cells during tumourigenesis) origin.[28] Patients with *BRCA* gene–mutated mCRPC are more likely to present with advanced disease, nodal involvement, and distant metastases at diagnosis.[10]

Standards of Therapy

Content in this section has been informed by materials submitted by the sponsor and clinical expert input. The following has been summarized and validated by the CADTH review team.

Clinical experts consulted by CADTH indicated that there are several systemic therapies that are approved for the treatment of patients with mCRPC, and the sequencing of these treatments depends on patient and disease factors, prior treatments used in the mCSPC setting, and access, which varies across Canada. Docetaxel, cabazitaxel, abiraterone acetate, enzalutamide, olaparib (for patients with *BRCA1, BRCA2,* and/or *ATM* mutations), radium-223 (for patients with bone-predominant disease and no visceral metastasis) and lutetium vipivotide tetraxetan are all Health Canada–approved and, with the exception of lutetium vipivotide tetraxetan, are widely available in all provinces across Canada. abiraterone acetate, enzalutamide, and docetaxel are treatment options in all lines of therapy for mCRPC. In addition, clinical experts noted that triplet therapy is an option in the first-line mCSPC setting. According to the clinical experts consulted by CADTH, chemotherapy is now the most commonly used first-line treatment for mCRPC since most patients have already received an ARPi in the mCSPC setting. Clinical experts indicated that in some rare situations, radium-223 is directly chosen in the first-line mCRPC setting. In a response to an additional information request, the sponsor indicated that niraparib and abiraterone acetate with prednisone could be used in all lines of mCRPC based on a physician's clinical judgment.[30] The sponsor submitted an algorithm of current treatments for mCRPC in which the most common treatments used to treat castration-resistant prostate cancer (first-line to third-line treatments and beyond) are abiraterone, enzalutamide, docetaxel, and radium-223. Additionally, cabazitaxel, radium-223, lutetium vipivotide tetraxetan, and olaparib were reported as treatment options in second-line treatment, third-line treatment, and lines beyond of treatment, with olaparib for patients with *BRCA* gene–mutated or *ATM*-mutated mCRPC. This was aligned with a published CADTH provisional funding algorithm,[31] a CADTH health technology review,[32] recently published Canadian guidelines, recent Canadian publications detailing practice of care, and current international guidelines.[33-38]

According to the literature, the goals of treatment in mCRPC include delaying disease progression, ameliorating symptoms, and improving HRQoL.[5] Likewise, clinical experts consulted by CADTH noted that the goals of treatment in the mCRPC setting include prolonged life, improved quality of life, and reduced toxicity.

Drug Under Review

The drug under review is a fixed-dose dual combination of niraparib and abiraterone acetate. Niraparib is a highly selective PARP inhibitor, with potent activity against PARP-1 and PARP-2; abiraterone acetate is a CYP17 inhibitor.[39] This combination targets 2 oncogenic dependencies in patients with mCRPC and HRR gene alterations.[39] Niraparib and abiraterone acetate is an oral medication administered as a single daily dose and is used with 10 mg prednisone or prednisolone daily.[39] The recommended dose is 200 mg niraparib and 1,000 mg abiraterone acetate (two 100 mg/500 mg tablets). Niraparib and abiraterone acetate tablets are also available as a low-dose strength (50 mg niraparib and 500 mg abiraterone acetate) for dose adjustment.[39]

The Health Canada–approved indication for niraparib and abiraterone acetate with prednisone or prednisolone is for the treatment of adult patients with deleterious or suspected deleterious *BRCA* gene–mutated (germline and/or somatic) mCRPC who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated.[39] Patients must have confirmation of *BRCA* mutation before niraparib and abiraterone acetate treatment is initiated as per the product monograph. The sponsor's reimbursement request aligns with the Health Canada–approved indication.

Key characteristics of niraparib, abiraterone acetate, and enzalutamide are summarized in the Table 3.

Table 3: Key Characteristics of Niraparib, Abiraterone Acetate, and Enzalutamide

Characteristic	Niraparib[a, 39]	Abiraterone acetate[b, 40]	Enzalutamide[41]
Mechanism of action	Inhibitor of PARP-1 and PARP-2	Prodrug of abiraterone, an androgen biosynthesis inhibitor	Competitive androgen receptor inhibitor
Indication[c]	Combined with abiraterone acetate and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA* gene–mutated (germline and/or somatic) mCRPC who are asymptomatic or mildly symptomatic, and in whom chemotherapy is not clinically indicated	For the treatment of mCRPC in patients who: • are asymptomatic or mildly symptomatic after the failure of androgen deprivation therapy • have received prior chemotherapy containing docetaxel after failure of androgen deprivation therapy	For the treatment of mCRPC in patients who: • are chemotherapy-naive with asymptomatic or mildly symptomatic disease after the failure of androgen deprivation therapy • have received docetaxel therapy
Route of administration	Oral	Oral	Oral
Recommended dosage	200 mg niraparib and 1,000 mg abiraterone acetate (two 100 mg/500 mg tablets) administered once daily	500 mg (four 125 mg tablets) administered once daily	160 mg (four 40 mg tablets) administered once daily
Serious adverse effects or safety issues	May cause hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess. Should be used with caution	May cause hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess. Should be used with caution	Should only be prescribed by a qualified health care professional who is experienced with the treatment of prostate cancer and the use

Characteristic	Niraparib[a, 39]	Abiraterone acetate[b, 40]	Enzalutamide[41]
	in patients with a history of cardiovascular disease. Myelodysplastic syndrome and acute myeloid leukemia have been reported with PARP inhibitor treatment.	in patients with a history of cardiovascular disease. Patients with severe and moderate hepatic impairment should not receive this drug. Hepatotoxicity, including fatal cases, has been observed.	of antineoplastic endocrine therapies. The following are clinically significant adverse events: seizures and Posterior Reversible Encephalopathy Syndrome.
Other	Must be taken on an empty stomach	NA	NA

mCRPC = metastatic castration-resistant prostate cancer; NA = not applicable; PARP = poly-(ADP [adenosine diphosphate]-ribose) polymerase; PARP-1 = poly-(ADP [adenosine diphosphate]-ribose) polymerase 1; PARP-2 = poly-(ADP [adenosine diphosphate]-ribose) polymerase 2.

[a]Given in combination with abiraterone acetate and prednisone or prednisolone.

[b]Given in combination with niraparib and prednisone or prednisolone.

[c]Health Canada–approved indication.

Sources: Akeega, Zytiga, and Xtandi product monographs.[39-41]

Stakeholder Perspectives

Patient Group Input

This section was prepared by the CADTH review team based on the input provided by patient groups. The full original patient input received by CADTH has been included in the Stakeholder section of this report.

Two patient groups, CCS and CCSN, provided input for the review of niraparib and abiraterone acetate for the treatment of adult patients with deleterious or suspected deleterious *BRCA* gene–mutated (germline and/or somatic) mCRPC who are asymptomatic or mildly symptomatic, and in whom chemotherapy is not clinically indicated. Patient input was gathered from surveys that were conducted from April until May 2023 by CCS and in June 2023 by CCSN. In total, 24 responses were gathered by CCS (from 21 patients and 3 caregivers), and 8 responses (from 8 patients) were gathered by CCSN. Overall, 97% of respondents in the CCS survey and 6 of the patients in the CCSN survey were living in Canada. One patient from the CCSN survey had experience with the drug under review.

With the use of currently available treatments, patients reported that the following symptoms affected their quality of life and day-to-day living: changes in libido, sexual function or fertility, hot flushes, fatigue, low energy, difficulties with urination, loss of appetite, bone or skeletal pain, indigestion, bowel problems, peripheral neuropathy, dizziness, and muscle loss. Patients from the CCS survey noted difficulty travelling to access treatment, costs associated with travelling to appointments, and difficulty managing side effects as some of the issues they expect to be improved. Maintaining quality of life, prolonging life, providing a cure, and reducing side effects from current medications or treatments were some of the expected outcomes that most CCSN survey patients hoped a new drug would address to manage their disease.

While describing the considerations regarding balancing the advantages and disadvantages of a treatment, CCSN survey patients reported life extension and cures, severity of side effects, quality of life, high mental

stress, and living a healthy life as important. When asked about disease experience and its impact on day-to-day activities, 14 (67%) patients from the CCS survey mentioned that the ability to engage in sexual activity was most affected, along with the ability to work, to exercise, and to maintain positive mental health being moderately to significantly impacted. On the other hand, respondents from the CCSN survey reported identifying the cause, working toward the cure, avoiding metabolic syndrome, avoiding having metastases progressing to other body locations, preventing or mitigating the spread of cancer in the bones, and avoiding erectile dysfunction (which inhibits intimacy) and incontinence as the most important aspects of their disease to control. While patients from the CCS survey identified transportation costs associated with appointments as the largest barrier while receiving treatments, followed by lack of familiarity with navigating the health care system and long wait times to receive tests or treatments, CCSN survey respondents noted that limited availability in the community, financial hardship due to cost, travel costs associated with accessing therapy, supplies, and challenges with administration were some issues they faced while accessing therapies.

While describing the experience with the current drug under review, the sole patient from the CCSN survey who had taken niraparib reported constipation and decreased appetite as adverse effects. When asked in comparison to other therapies how was their treatment experience with niraparib in treating their prostate cancer, the respondent noted that there was little or no difference in symptom management, side effects, and ease of use. The patient also noted that the experience regarding disease progression was much better compared to other therapies.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of mCRPC.

Unmet Needs

The clinical experts indicated that since mCRPC is a terminal phase of prostate cancer, the unmet needs of patients would be prolonged OS, improved quality of life, and reduced toxicity. Both clinical experts highlighted that the balance between treatment efficacy and quality of life would be important. In addition, the clinical experts noted a need for new treatments since these patients have primary or acquired resistance to offered treatments in the mCRPC setting.

Place in Therapy

Clinical experts agreed that it remains unclear whether niraparib and abiraterone acetate would lead to a shift in the current treatment paradigm. This uncertainty stems from the increased use of ARPis. They noted that niraparib and abiraterone acetate would not be coadministered with systematic treatments

except for androgen deprivation therapy. However, it could be administrated with palliative external beam radiotherapy (EBRT). One of the experts highlighted that although there is some biological theory that abiraterone acetate would increase the efficacy of a PARP inhibitor when they are coadministrated, this has not been investigated clinically. While niraparib and abiraterone acetate are used in patients who have been treated with enzalutamide, apalutamide, and darolutamide in the nmCRPC or mCSPC settings, many medical oncologists would favour a change to chemotherapy in patients progressing on an ARPi. They noted that if a treatment was used in mCSPC, it is not likely that the patient would receive it again in mCRPC (with the occasional exception of docetaxel). The clinical experts noted that niraparib and abiraterone acetate may have a limited role as a first-line or later-line treatment in the mCRPC setting due to the decreasing number of patients who are ARPi-naive and the few patients who would be clinically ineligible for docetaxel.

Patient Population

The clinical experts agreed with the *BRCA* gene–mutated mCRPC population specified in the Health Canada–approved indication. Testing for the *BRCA* mutation is usually conducted at an early stage for patients with mCRPC. It was noted that most patients with mCRPC, especially those who are otherwise well, would be considered for treatment with cytotoxic chemotherapy. However, it is rare for patients to have an absolute contraindication to chemotherapy. Clinicians may consider alternatives to chemotherapy in patients whose disease is asymptomatic or minimally symptomatic and palliative to minimize the toxic effects of treatments. Niraparib and abiraterone acetate may be a treatment option for those patients with mCRPC who are *BRCA*-positive and for whom chemotherapy was not a treatment of choice.

Assessing the Response Treatment

The clinical experts indicated that in clinical practice, a combination of radiographic, biochemical, and clinical parameters is used to determine whether a patient with mCRPC is responding to treatment.

Discontinuing Treatment

The clinical experts indicated that treatment with niraparib and abiraterone acetate should be discontinued if treatment is intolerable, if the patient experiences disease progression, or if the patient prefers to discontinue treatment.

Prescribing Considerations

According to the clinical experts consulted by CADTH, PARP inhibitors have the potential to be toxic. Therefore, patients receiving niraparib and abiraterone acetate must be under the care of a medical oncologist to manage toxicity. They noted that to manage toxicity, it is required to involve medical oncologists in the community setting and other oncology professionals in academic settings.

Clinician Group Input

This section was prepared by the CADTH review team based on the input provided by clinician groups. The full original clinician group input received by CADTH has been included in the Stakeholder section of this report.

Clinician group input on the review of niraparib and abiraterone acetate with prednisone was received from the OH-CCO Genitourinary Cancer Drug Advisory Committee. A total of 8 clinicians provided input on behalf of OH-CCO.

OH-CCO highlighted the need to have therapies in the first-line mCRPC setting that can prolong life, considering there is currently no cure and no targeted treatments available at this setting. They also mentioned the need for treatments that can maximize quality of life. The group noted that niraparib and abiraterone acetate with prednisone would become a SOC in treatment-naive patients with mCRPC with HRR mutation, although the CADTH review team noted that the Health Canada–approved indication is for patients with *BRCA* mutations only. The group indicated that while PSA will be used to determine the burden of disease and to monitor response to therapy, serial radiographic imaging will also be used to monitor response and to determine progression as per SOC. They also noted they would discontinue treatment in cases of significant side effects or disease progression.

The clinician group highlighted that niraparib and abiraterone acetate with prednisone should be administered by oncologists with experience using PARP inhibitors, as well as with expertise in the management of PARP inhibitor side effects. The clinician group noted that niraparib and abiraterone acetate with prednisone is a novel combination of therapies that would benefit a targeted population of patients with prostate cancer.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 4.

Table 4: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
The MAGNITUDE phase III clinical trial compared niraparib and abiraterone acetate vs. placebo and abiraterone acetate. In both arms of the study, patients also received prednisone or prednisolone. First-line treatment of mCRPC in Canada includes ARAT drugs (i.e., abiraterone acetate [in combination with prednisone] or enzalutamide), taxane-based chemotherapy (i.e., docetaxel), or radium-223 (funded in some provinces, but used minimally and only for patients with bone-predominant disease). Olaparib may also be used as a first-line treatment of mCRPC in patients with a *BRCA* and/or *ATM* gene mutation if a patient was previously treated with an ARAT in the nmCRPC or mCSPC setting.	This is a comment from the drug plans to inform pERC deliberations.

Drug program implementation questions	Clinical expert response
Considerations for initiation of therapy	
In the MAGNITUDE clinical trial, patients had to have metastatic prostate cancer in the setting of castrate levels of testosterone ≤ 50 ng/dL on a Gn-RH analogue or bilateral orchiectomy, and evidence of PSA progression or radiographic progression. Is this the same definition of "castration-resistant" that should be used to determine eligibility for niraparib and abiraterone acetate with prednisone?	The clinical experts consulted by CADTH indicated that this definition could be used to determine eligibility for niraparib and abiraterone acetate with prednisone.
Is there a specific definition of "mildly symptomatic" to determine eligibility for niraparib and abiraterone acetate with prednisone?	The clinical experts consulted by CADTH reported that there is no specific definition of "mildly symptomatic" to determine eligibility. The clinical experts noted that determining whether a patient is symptomatic vs. mildly symptomatic is subjective and determined by the patient and their treating clinician. They reported that asymptomatic patients are easily identified, however; the definition of mildly symptomatic may vary considerably between patients and clinicians.
Should patients with previously untreated mCRPC who have a deleterious *BRCA* mutation and who are candidates for chemotherapy or where chemotherapy is clinically indicated, but who decline chemotherapy, be eligible for niraparib and abiraterone acetate with prednisone?	Clinical experts consulted by CADTH replied that patients who are candidates for chemotherapy or where chemotherapy is clinically indicated but who decline chemotherapy should be eligible for niraparib and abiraterone acetate. However, the clinical experts highlighted that it is challenging to define "in whom chemotherapy is not clinically indicated" because they reported that all patients are eligible for chemotherapy unless they are too unwell to receive chemotherapy. In addition, the clinical experts noted that if a patient declines chemotherapy, they would consider that as chemotherapy is not indicated for the patient.
Should patients who received abiraterone acetate and prednisone in the metastatic castration-sensitive setting be eligible for niraparib and abiraterone acetate with prednisone in the mCRPC setting?	The clinical experts consulted by CADTH responded that if patients have been on abiraterone acetate for more than 4 months, or if they have progressed from mCSPC to mCRPC while on abiraterone, they should not be eligible for niraparib and abiraterone acetate in the mCRPC setting.
Should patients who received apalutamide, enzalutamide, or darolutamide in the nonmetastatic castration-resistant setting or metastatic castration-sensitive setting be eligible for niraparib and abiraterone acetate with prednisone in the mCRPC setting?	The clinical experts consulted by CADTH indicated that these patients should not be eligible.
Should patients who have more symptomatic disease (greater than mildly symptomatic) who otherwise meet all eligibility criteria but are not candidates for chemotherapy due to comorbidities be eligible for niraparib and abiraterone acetate with prednisone? Would patients with this subtype benefit equally from niraparib and abiraterone acetate with prednisone as those who are asymptomatic or mildly symptomatic?	The clinical experts consulted by CADTH replied that these patients should be eligible for niraparib and abiraterone acetate with prednisone. Although they were not studied in the trial, the clinical experts indicated there is no biological reason to believe that they would respond differently to niraparib and abiraterone acetate with prednisone.

Drug program implementation questions	Clinical expert response
Considerations for discontinuation of therapy	
The product monograph recommends that treatment should be continued until disease progression, unequivocal clinical progression, or unacceptable toxicity. What are the definitions of disease progression (e.g., radiographic, biochemical) that should be used to discontinue niraparib and abiraterone acetate with prednisone?	The clinical experts consulted by CADTH noted that the definition of disease progression used to discontinue treatment is subjective. The clinical experts reported that clinicians typically use a composite end point of biochemical, symptomatic, and radiologic progression to determine progression, and these 3 parameters can be weighed differently across clinicians.
Generalizability	
Patients with an ECOG PS score of 0 or 1 were eligible for the MAGNITUDE clinical trial. Should patients with an ECOG PS score > 1 be eligible for niraparib and abiraterone acetate with prednisone?	The clinical experts consulted by CADTH highlighted that it should be left to clinical judgment. The clinical experts suggested that patients who are expected to tolerate niraparib and abiraterone acetate should be eligible.
Should patients currently receiving alternate first-line treatment for mCRPC who otherwise meet all eligibility criteria be able to switch to niraparib and abiraterone acetate with prednisone?	The clinical experts consulted by CADTH noted that if patients are receiving first-line treatment to which they are responding and find tolerable, they would not switch therapy.
Funding algorithm	
The drug plans noted the following items that may require the development of a provisional funding algorithm by CADTH: • the drug may change place in the therapy of drugs reimbursed in subsequent lines • this is a complex therapeutic space with multiple lines of therapy, subpopulations, or competing products • olaparib plus abiraterone for the first-line treatment of patients with mCRPC for whom chemotherapy is not clinically indicated is also under CADTH review.	This is a comment from the drug plans to inform pERC deliberations.
Care provision issues	
Additional patients may require access to *BRCA*-mutation testing before initiating first-line therapy in the mCRPC setting. Currently, some jurisdictions may only test for *BRCA* and/or *ATM* mutations after first-line therapy is initiated. How many patients with mCRPC harbour deleterious *BRCA* mutations?	The clinical experts consulted by CADTH estimated that the proportion of patients with an HRR mutation is approximately 25% to 30% overall, and approximately 15% for *BRCA* mutations specifically. CADTH identified literature that reports that approximately 10% of all patients with mCRPC harbour *BRCA* alterations.[7]
Can patients be switched to niraparib and abiraterone acetate with prednisone if there are delays in accessing *BRCA*-mutation results and patients are initiated on abiraterone acetate and prednisone? Is there a time limit for switching in this situation (e.g., 2 months to 4 months)?	The clinical experts consulted by CADTH noted that adding niraparib to abiraterone acetate with prednisone within 4 months of starting the abiraterone acetate with prednisone is appropriate.
The recommended dosage of niraparib and abiraterone acetate with prednisone is 200 mg niraparib and 1,000 mg abiraterone acetate (two 100 mg/500 mg tablets) as a single daily dose that must be taken on an empty stomach at approximately the same time every day. For dose reduction to 100 mg niraparib and 1,000 mg abiraterone acetate, a low-strength tablet (two 50 mg/ 500 mg tablets) is recommended. If a further dose reduction below 100 mg per day niraparib	The clinical experts consulted by CADTH noted that as long as patients are still responding to treatment, abiraterone acetate could continue if niraparib is stopped due to toxicity.

Drug program implementation questions	Clinical expert response
is required, it is recommended to discontinue niraparib and abiraterone acetate with prednisone. If toxicity is attributable to niraparib only, could single-drug abiraterone acetate (with prednisone) be prescribed and continued on its own?	
System and economic issues	
The sponsor estimates the increase in net expenditures attributable to Akeega to be $6,671,716 in year 1, $11,987,626 in year 2, and $13,327,095 in year 3 for a total estimated net budget impact over the first 3 years of $31,986,438. PAG members are concerned about the budget impact if CADTH estimates the budget impact to be substantially higher, and due to the high volume of patients with mCRPC. Some drug wastage may be expected to occur due to the fixed-dose combination and a separate strength to be used in the event of toxicity. In patients who require a dose reduction, the 100 mg niraparib/500 mg abiraterone acetate strength would be wasted if already dispensed.	This is a comment from the drug plans to inform pERC deliberations.
Generic versions of abiraterone acetate and docetaxel are available. Confidential pCPA pricing is available for enzalutamide and olaparib.	This is a comment from the drug plans to inform pERC deliberations.

ARAT = androgen receptor axis-targeted; ECOG PS = Eastern Cooperative Oncology Group Performance Status; Gn-RH = gonadotropin-releasing hormone; HRR = homologous recombination repair; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer; PAG = CADTH Provincial Advisory Group; pCPA = pan-Canadian Pharmaceutical Alliance; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; PSA = prostate-specific antigen; vs. = versus.

Clinical Evidence

The objective of CADTH's Clinical Review Report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of niraparib 200 mg and abiraterone acetate 1,000 mg (oral tablet) with prednisone 10 mg once daily for the treatment of adult patients with deleterious or suspected deleterious *BRCA* gene–mutated (germline and/or somatic) mCRPC who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated. The focus has been placed on comparing niraparib and abiraterone acetate to relevant comparators and identifying gaps in the current evidence.

A summary of the clinical evidence included by the sponsor in the review of niraparib and abiraterone acetate with prednisone is presented in 2 sections, with CADTH's critical appraisal of the evidence included at the end of each section. The first section, the systematic review, includes pivotal studies and RCTs that were selected according to the sponsor's systematic review protocol. CADTH's assessment of the certainty of the evidence in this first section using the GRADE approach followed the critical appraisal of the evidence. The second section includes indirect evidence from the sponsor. No long-term extension studies or studies addressing gaps in the systematic review evidence section were submitted by the sponsor.

Included Studies

Clinical evidence from the following is included in the CADTH review and appraised in this document:

- 1 pivotal RCT
- 1 ITC.

Systematic Review

Content in this section has been informed by materials submitted by the sponsor. The following has been summarized and validated by the CADTH review team.

Description of Studies

The MAGNITUDE study is an ongoing phase III, randomized, double-blind, placebo-controlled, multicentre trial. The aim of the trial is to assess the efficacy and safety of niraparib 200 mg and abiraterone acetate 1,000 mg and prednisone 10 mg administered orally once daily for the treatment of adult patients with mCRPC who had not received prior systemic therapy in the mCRPC setting. Patients were prospectively screened for HRR gene alterations and then enrolled in either cohort 1 if they had presence of HRR gene alterations (either monoallelic or biallelic pathogenic gene alterations in ≥ 1 of the following genes: *ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2*, or *PALB2*) or cohort 2 if they did not have HRR gene alterations or if they were patients whose gene testing failed. Cohort 2 enrolment and follow-up was stopped based on the threshold for futility being met in a preplanned futility analysis. Patients from cohort 1 and cohort 2 could continue to a third open-label cohort of patients with HRR gene alterations (cohort 3) to obtain descriptive data on the clinical experience with a fixed-dose combination tablet formulation of niraparib and abiraterone acetate. Cohort 1 was the focus of this review because it aligns with the Health Canada indication and the sponsor's reimbursement request.

The trial included a screening period of up to 28 days, a treatment period of until disease progression or unacceptable toxicity, and a follow-up period of up to 60 months, until death or loss to follow-up. Following discontinuation of the treatment, patients were followed for survival, initiation of subsequent prostate cancer therapy, and disease progression; patients were followed for up to 5 years or until death, loss to follow-up, withdrawal of consent, or study termination. Characteristics of the MAGNITUDE study are summarized in Table 5.

Given the Health Canada indication for niraparib and abiraterone acetate specifies patients with deleterious or suspected deleterious *BRCA* gene–mutated mCRPC and that patients must have confirmation of *BRCA* mutation before treatment is initiated, this review will report on a subgroup of patients from cohort 1 with *BRCA* gene alterations.

Table 5: Details of Studies Included in the Systematic Review

Detail	MAGNITUDE study
Designs and populations	
Study design	Phase III, double-blind, placebo-controlled RCT
Locations	**205 sites in 26 countries** 3 countries in North America including Canada (5 sites), 15 countries in Europe, 6 countries in Asia, and 2 countries in South America
Patient enrolment dates	**Start date:** February 5, 2019 **End date:** Study is ongoing and estimated to end in February 2027
Randomized (N)	Patients in cohort 1 (N = 423) • Niraparib and abiraterone acetate with prednisone: N = 212 • Placebo and abiraterone acetate with prednisone: N = 211 Patients in cohort 1 with *BRCA1* or *BRCA2* gene alterations[a] (N = 225) • Niraparib and abiraterone acetate with prednisone: N = 113 • Placebo and abiraterone acetate with prednisone: N = 112 **Additional cohorts (not relevant to this reimbursement review)** Patients in cohort 2 (N = 247) • Niraparib and abiraterone acetate with prednisone: N = 123 • Placebo and abiraterone acetate with prednisone: N = 124 Patients in cohort 3 (N = 95)
Inclusion criteria	• Older than 18 years • Positive for HRR gene alteration, including *BRCA1* or *BRCA*2 • Metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI • Metastatic prostate cancer in the setting of castrate levels of testosterone ≤ 50 ng/dL on a Gn-RH analogue or bilateral orchiectomy as evidenced by PSA progression or radiographic progression • Able to continue Gn-RH analogue during the study if not surgically castrate • ECOG PS score of 0 or 1 • Score of ≤ 3 on the BPI-SF question #3 (worst pain in last 24 hours) • Clinical laboratory values at screening: ANC ≥ 1.5 × 10^9/L, hemoglobin ≥ 9.0 g/dL (independent of transfusions for at least 30 days), and platelet count ≥ 100 × 10^9/L
Exclusion criteria	• Prior treatment with a PARP inhibitor • Systemic therapy (i.e., novel second-generation AR targeted therapy such as enzalutamide, apalutamide, or darolutamide; taxane-based chemotherapy or more than 4 months of AAP before randomization) in the mCRPC setting; or AAP outside of the mCRPC setting • Presence of uncontrolled hypertension (persistent systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg) • Any of the following ≤ 28 days before randomization: transfusion (platelets or red blood cells), hematopoietic growth factors, investigational drug for prostate cancer, major surgery, or radiotherapy

Detail	MAGNITUDE study
Drugs	
Intervention	Niraparib (200 mg daily oral administration) with abiraterone acetate (1,000 mg daily oral administration) and prednisone (10 mg daily administration)
Comparator	Placebo (daily oral administration) with abiraterone acetate (1,000 mg daily oral administration) and prednisone (10 mg daily administration)
Study duration	
Screening phase	Up to 28 days before randomization
Double-blind treatment phase	Until death, radiographic progression, or clinical progression per protocol definition, or unacceptable toxicity
Follow-up phase	Up to 60 months (5 years) or until death, lost to follow-up, withdrawal of consent, or study termination (study is ongoing)
Outcomes	
Primary end point	rPFS
Secondary and exploratory end points	**Secondary** • TCC • TSP • OS **Exploratory** • TPSA according to PCWG3 criteria • PFS2 • Time to initiation of subsequent therapy • TPP • ORR • DOR • PSA response rate • TEAEs (up to 66 months)
Publication status	
Publications	Chi et al. (2023)[42]

AAP = abiraterone acetate with prednisone; ANC = absolute neutrophil count; AR = androgen receptor; BP = blood pressure; BPI-SF = Brief Pain Inventory (Short Form); DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; Gn-RH = gonadotropin-releasing hormone; HRR = homologous recombination repair; mCRPC = metastatic castration-resistant prostate cancer; ORR = objective response rate; OS = overall survival; PARP = poly-(ADP [adenosine diphosphate]-ribose) polymerase; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; PFS2 = progression-free survival on first subsequent therapy; PSA = prostate-specific antigen; RCT = randomized controlled trial; rPFS = radiographic progression-free survival; TCC = time to initiation of cytotoxic chemotherapy; TEAE = treatment-emergent adverse event; TPP = time to pain progression; TPSA = time to prostate-specific antigen progression; TSP = time to symptomatic progression.

Note: Details from Table 5 have been taken from the sponsor's Summary of Clinical Evidence.[14]

[a]To align with the Health Canada indication for niraparib and abiraterone acetate with prednisone, the population of the MAGNITUDE study that was considered herein was patients with a *BRCA* gene alteration who were randomized to receive niraparib and abiraterone acetate with prednisone or placebo and abiraterone acetate with prednisone (a subgroup of cohort 1, which consisted of patients positive for HRR gene alterations).

Sources: MAGNITUDE Second Interim Analysis Clinical Study Report[43] and ClinicalTrials.gov entry.[44]

A total of 765 patients were enrolled in the MAGNITUDE study; of these, 423 patients had HRR gene alterations and were enrolled in cohort 1. Of the 423 patients with HRR alterations, 225 patients were enrolled in the *BRCA* subgroup. Patients enrolled in cohort 1 were randomized 1:1 at 205 sites across 26

countries, including Canada (5 sites), to receive niraparib 200 mg and abiraterone acetate 1,000 mg and prednisone 10 mg daily (N = 113 in the *BRCA* subgroup) or placebo and abiraterone acetate 1,000 mg and prednisone 10 mg (N = 112 in the *BRCA* subgroup). Randomization was balanced using randomly permuted blocks and stratified by past taxane-based chemotherapy exposure (yes versus no), past AR-targeted therapy exposure (yes versus no), and prior abiraterone acetate with prednisone use (yes versus no). For cohort 1, stratification by gene alteration group (i.e., *BRCA1* or *BRCA2* versus all other HRR gene alterations) was also performed. The MAGNITUDE study was initiated on February 5, 2019. This study is ongoing, with results available from 2 prespecified interim analyses with data cutoff dates of April 5, 2022, and June 17, 2022.

Populations

Inclusion and Exclusion Criteria

A detailed description of the inclusion and exclusion criteria for the MAGNITUDE trial is provided in Table 5. Patients eligible for enrolment in cohort 1 were adults with mCRPC and positive for HRR gene alteration, including *BRCA* mutation, and had an ECOG PS score grade of 0 or 1. Patients were excluded if they had had prior treatment with a PARP inhibitor, systemic therapy (i.e., novel second-generation AR targeted therapy such as enzalutamide, apalutamide, or darolutamide; taxane-based chemotherapy; or more than 4 months of abiraterone acetate with prednisone before randomization) in the mCRPC setting; or abiraterone acetate with prednisone outside of the mCRPC setting. Patients who had previously been treated and progressed on an ARPi in the mCSPC and nmCRPC settings were eligible for the MAGNITUDE trial. Patients who had received 2 months to 4 months of abiraterone acetate with prednisone before randomization for the treatment of mCRPC should have had no evidence of progression by PSA during screening (i.e., required to have 2 PSA values during the prescreening and screening phases) or had uncontrolled hypertension.

Interventions

Patients received niraparib 200 mg and abiraterone acetate 1,000 mg with prednisone 10 mg or placebo and abiraterone acetate 1,000 mg with prednisone 10 mg taken orally daily. Treatment began at cycle 1, day 1, in the treatment phase and continued in 28-day cycles until the study treatment was discontinued.[15] Placebo for niraparib was provided as a capsule formulation and was matched in size, colour, and shape to maintain the study blind. Study treatments were administered together, except for prednisone, which was taken twice daily. Treatments were to be discontinued for unequivocal clinical progression, unacceptable toxicity, death, or sponsor termination of the study.

In the MAGNITUDE trial, dose interruptions and modifications of niraparib and abiraterone acetate and placebo and abiraterone acetate were generally done if patients experienced GRADE 3 or higher toxicities. Treatment was also interrupted before procedures that required hospitalization. Grade 1 or grade 2 toxicities were managed symptomatically without requiring dose adjustments or dose interruptions. The dose of prednisone remained unchanged with dose modifications of niraparib, placebo, or abiraterone acetate.

If either study drug (i.e., niraparib/placebo or abiraterone acetate) was permanently discontinued due to toxicity, the other study drug could be continued. Prednisone was discontinued (with a taper if clinically indicated) if abiraterone acetate was permanently discontinued.

Supportive concomitant therapies (e.g., endocrine therapy, analgesics, antihypertensives, antacids, antibacterials) were allowed. The following concomitant treatments were prohibited: investigational drugs other than the study treatments; other anticancer therapies; other drugs that targeted the androgen axis (e.g., antiandrogens such as enzalutamide and apalutamide, CYP17 inhibitors such as ketoconazole); testosterone; radiotherapy for tumour progression (patients may have received palliative radiotherapy in selected cases after discussion with the sponsor); chemotherapy; immunotherapy; diethylstilbestrol or similar estrogen receptor agonists; pomegranates and pomegranate juice; spironolactone; radiopharmaceuticals such as radium-223, strontium, or samarium; and strong inducers of CYP3A4 (e.g., rifampin). Concomitant treatment with substrates of CYP2D6 and CYP2C8 were restricted due to the potential for drug-drug interactions.

Outcomes

A list of efficacy end points assessed in this Clinical Review Report is provided in Table 6, followed by descriptions of the outcome measures. Summarized end points are based on outcomes included in the sponsor's Summary of Clinical Evidence[14] as well as any outcomes identified as important to this review according to the clinical experts consulted by CADTH and stakeholder input from patient and clinician groups and public drug plans. Using the same considerations, the CADTH review team selected end points that were considered to be most relevant to inform CADTH's expert committee deliberations and finalized this list of end points in consultation with members of the expert committee. All summarized efficacy end points were assessed using GRADE. Select notable harms outcomes considered important for informing CADTH's expert committee deliberations were also assessed using GRADE.

Table 6: Efficacy Outcomes Summarized From the Study Included in the Systematic Review

Outcome measure	Time point	MAGNITUDE study
OS[a]	At 12 months and 24 months	Secondary
rPFS by BICR[a]	At 12 months and 24 months	Primary
TSP	At 12 months	Secondary
TPP	At 12 months	Exploratory
FACT-P	At cycle 25, day 1	Exploratory

BICR = blinded independent central review; FACT-P = Functional Assessment of Cancer Therapy–Prostate; OS = overall survival; rPFS = radiographic progression-free survival; TPP = time to pain progression; TSP = time to symptomatic progression.

Note: Details included in Table 6 are from the sponsor's Summary of Clinical Evidence.[14]

[a]Statistical testing for these end points was adjusted for multiple comparisons (e.g., hierarchal testing).

Sources: MAGNITUDE Second Interim Analysis Clinical Study Report[15] and ClinicalTrials.gov entry.[44]

Efficacy Outcomes

Overall Survival

The secondary outcome of OS was defined as the time from date of randomization to date of death from any cause. Patients alive at the time of analysis would be censored on the last date the patient was known to be alive.

rPFS by BICR

The primary end point for this study was rPFS as assessed by BICR. This outcome was defined as the time interval from the date of randomization to the first date of radiographic progression or death due to any cause, whichever occurred first. Radiographic progression was determined by the first occurrence of progression by bone scan (according to PCWG3 criteria) or progression of soft tissue lesions by CT or MRI scan (according to RECIST 1.1 criteria), both assessed by BICR.

Time to Symptomatic Progression

The secondary end point of TSP was defined as the date of randomization to the date of the first of any of the following:

- EBRT for skeletal symptoms
- tumour-related orthopedic surgical intervention
- other cancer-related procedures (e.g., nephrostomy insertion, bladder catheter insertion, EBRT, surgery for tumour symptoms other than skeletal)
- cancer-related morbid events (e.g., fracture [symptomatic and/or pathologic], cord compression, urinary obstructive events)
- initiation of a new systemic anticancer therapy because of cancer pain.

Time to Pain Progression

The exploratory end point of TPP was defined as the time from the date of randomization to the date of the first observation of pain progression. Pain progression was defined as an average increase by 2 points from baseline in the Brief Pain Inventory (Short Form) tool, worst pain intensity (item 3), observed at 2 consecutive evaluations 3 or more weeks apart.

FACT-P Questionnaire

FACT-P was an exploratory end point evaluating prostate cancer–specific HRQoL. A summary of its measurement properties is in Table 7. FACT-P consists of the 27 items from the Functional Assessment of Cancer Therapy–General (FACT-G), of which 10 items are prostate cancer–specific concerns. This questionnaire assesses physical, social/family, emotional, and functional well-being. Patients respond by selecting 1 of 5 response categories ranging from "not at all" to "very much." Decreasing scores indicate worsening and/or deterioration (i.e., worse HRQoL). The MID for total score was estimated at 10.[15]

Table 7: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
BPI-SF	Patient-reported generic questionnaire for pain intensity and impact. Each item is scored on an 11-point scale from 0 to 10, where 0 is no pain or no interference and 10 is the worst pain or complete	**Validity:** Strong correlations between worst pain and average pain items (r = 0.79) and between the worst pain item and PPI (r = 0.52)[46] Support for content validity via	An MID estimate of 2 or more points or 30% change in pain intensity items from baseline was previously used in

Outcome measure	Type	Conclusions about measurement properties	MID
	interference.[45] The BPI is available as a long and short version, the latter of which has a 24-hour recall period for both worst pain and least pain items.[46] A composite of the 4 pain items (a mean severity score) can be presented and pain interference is typically scored as the mean of the 7 interference items.[45]	in-depth interviews for worst pain item in a study of patients with CRPC and bone metastases[47] **Reliability:** Good internal consistency reliability in study of patients with mCRPC with alpha ≥ 0.89 and good internal consistency reliability with ICC values ≥ 0.73[46] **Responsiveness:** Not assessed in indicated population	studies in patients with mCRPC.[48,49]
FACT-P	The FACT-P is a validated questionnaire used to assess HRQoL in males with prostate cancer. The instrument was tested in 3 independent samples: a subscale development sample (n = 43), validity sample 1 (n = 34), and validity sample 2 (n = 96).[50] FACT-P consists of FACT-G, a 27-item self-reported questionnaire measuring general HRQoL in patients with cancer, and a 12-item PCS, designed specifically to measure prostate cancer–specific quality of life. The FACT-P total score includes the FACT-G and the PCS.[51] A higher overall score indicates better HRQoL; the range of these scores is 0 to 156 for the FACT-P total score.[52]	**Validity:** Concurrent validity of the FACT-P instrument was confirmed by the ability to distinguish patients with prostate cancer by disease stage, performance status, and baseline PSA level.[50] **Reliability:** Internal consistency of the PCS ranged from 0.65 to 0.69, with coefficients for FACT-G subscales and aggregated scores ranging from 0.61 to 0.90.The coefficients for the FACT-G total score ranged from 0.85 to 0.87, and the range for FACT-P was from 0.87 to 0.89.[50] **Responsiveness:** Sensitivity to change in performance status and PSA score over a 2-month period suggested that some subscales of the FACT-P (including the PCS) are sensitive to meaningful clinical change.[50]	Clinically meaningful changes were estimated as 6 to 10 for the FACT-P total score.[52]

BPI = Brief Pain Inventory; BPI-SF = Brief Pain Inventory (Short Form); CRPC = castration-resistant prostate cancer; FACT-G = Functional Assessment of Cancer Therapy–General; FACT-P = Functional Assessment of Cancer Therapy–Prostate; HRQoL = health-related quality of life; ICC = intraclass correlation coefficient; mCRPC = metastatic castration-resistant prostate cancer; MID = minimal important difference; PCS = prostate cancer subscale; PPI = Present Pain Intensity; PSA = prostate-specific antigen.

Harms Outcomes

TEAEs included any untoward medical occurrence that occurred or worsened on or after the first dose of study treatment through 30 days after the last dose of study treatment and are included in the analysis in the MAGNITUDE trial. SAEs were defined as an untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, was persistent or a significant disability, was a congenital anomaly or birth defect, or was medically important per medical and scientific judgment. WDAEs were defined as events related to discontinued study treatment due to TEAEs in the MAGNITUDE trial. Deaths that occurred within 30 days of the last dose of study treatment in the MAGNITUDE trial were reported.

Statistical Analysis

Sample Size and Power Calculation

It was estimated that for cohort 1 of the MAGNITUDE study, approximately 400 patients with mCRPC and HRR gene alterations were to be randomized 1:1 to receive niraparib and abiraterone acetate with prednisone or placebo and abiraterone acetate with prednisone. A target subgroup within cohort 1, the *BRCA* subgroup, would consist of patients with *BRCA1* or *BRCA2* mutations; this subgroup was planned to consist of at least 50% of patients from cohort 1 who would undergo randomization.

The target sample size for cohort 1 was event-driven, with approximately 220 rPFS events required to provide 87% power in detecting an HR of 0.65 for rPFS in patients with mCRPC and HRR gene alterations (median rPFS of 13 months for the placebo and abiraterone acetate with prednisone treatment group versus 20 months for the niraparib and abiraterone acetate with prednisone treatment group) at a 2-tailed level of significance of 0.05. With a 21-month accrual period and an additional 7 months of follow-up, the study duration to reach the required number of rPFS events would be approximately 28 months. Assuming that approximately 50% of patients in cohort 1 belonged to the *BRCA* subgroup, with the proposed sample size and study duration, approximately 102 rPFS events were planned to be observed in the *BRCA* subgroup to provide 93% power to detect an HR of 0.5 (median 13 months versus 26 months) at a 2-tailed level of significance of 0.05.

Statistical Testing and Sensitivity Analysis

A summary of statistical analysis appears in Table 8. The primary end point (rPFS by BICR) was tested using stratified log-rank test at the overall 2-tailed significance level of 0.05. The Kaplan-Meier product limit method and a stratified Cox model were used to estimate the median rPFS and to obtain the HR along with the associated 95% CIs, respectively. Sensitivity analyses were carried out using a nonstratified log-rank test, using an investigator-assessed radiographic progression, and having no censoring for subsequent therapy.

A post hoc covariate-adjusted sensitivity analysis was conducted for rPFS and OS using a propensity-based method because of the observed differences in baseline characteristics despite randomization. The inverse probability treatment weighting method with an estimate of average treatment effect was used as the statistical approach for comparing outcomes between the niraparib and abiraterone acetate with prednisone group and the placebo and abiraterone acetate with prednisone group to adjust for imbalances in the population characteristics. Propensity score weighting was performed to obtain adjusted estimates of treatment effects and to limit the potential confounding effect of unbalanced patient characteristics between the 2 groups in the MAGNITUDE study. Propensity scores (i.e., based on the probability of receiving treatment) were used to obtain weights after adjustment by relevant covariates.

Table 8: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
rPFS	• Stratified log-rank test • Kaplan-Meier analysis • Stratified Cox model	NR	No imputation method was used for handling missing or incomplete data	• Nonstratified log-rank test • Post hoc covariate-adjusted sensitivity analysis • Investigator-assessed radiographic progression • No censoring for subsequent therapy
OS	• Stratified log-rank test • Kaplan-Meier analysis • Stratified and multivariate Cox model	NR	NR	• Nonstratified log-rank test • Post hoc covariate-adjusted sensitivity analysis • Censoring death due to COVID-19 • IPCW analysis
TSP	• Stratified log-rank test • Kaplan-Meier analysis • Stratified Cox model	NR	NR	• Nonstratified log-rank test
TPP	• Stratified log-rank test • Kaplan-Meier analysis • Stratified Cox model	NR	NR	• Nonstratified log-rank test

IPCW = inverse probability of censoring weighting; NR = not reported; OS = overall survival; rPFS = radiographic progression-free survival; TPP = time to pain progression; TSP = time to symptomatic progression.

Note: Details included in Table 8 are from the sponsor's Summary of Clinical Evidence.[14]

Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[15]

The final analysis of the primary end point rPFS was performed when approximately 220 rPFS events were observed in cohort 1 and approximately 102 rPFS events were observed in the *BRCA* subgroup within cohort 1. The second preplanned interim analysis of secondary end points was performed on June 17, 2022, after observing 179 OS events. Prespecified sensitivity analyses were performed in accordance with the statistical analysis plan. The efficacy analysis began by testing rPFS in the *BRCA* subgroup of cohort 1 using a 2-sided alpha level of 0.05. If statistical significance was met in the *BRCA* subgroup, then rPFS in all of cohort 1 was to be tested, also at a 2-sided alpha level of 0.05 based on the predefined testing hierarchy. If rPFS in cohort 1 was statistically significant, then the secondary end points were to be tested using a group sequential method with 2 interim analyses and the final analysis. After testing for the primary end point of rPFS in the *BRCA* subgroup and cohort 1, an alpha of 0.05 was split between the secondary end points, which were analyzed for all of cohort 1 with an alpha of 0.025 allocated to OS and an alpha of 0.0125 allocated to time to initiation of cytotoxic chemotherapy (TCC) and TSP separately. The alpha for the secondary end points was further subdivided between the 2 planned interim analyses and the final analysis. For the secondary end points, the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method were used, and interim boundary cutoffs were calculated using the information fraction for the OS end point. Given that the study met the primary end point of rPFS by BICR and the results of the first interim

analysis were publicly presented, a change in the prescribing pattern of subsequent therapies was possible; hence, a revised alpha spending function for TCC and TSP at the second interim analysis was prospectively implemented before the database lock for the second interim analysis. This revision was designed to minimize the impact on secondary end points based on the likely increased use of subsequent anticancer therapy with a PARP inhibitor (essentially a crossover for patients treated with SOC therapy). The preplanned analysis of OS, including the alpha spending for OS, remained unchanged from the originally planned O'Brien-Fleming boundaries for the second interim analysis and the final analysis. The overall study wise type I error rate remained adequately controlled at the 2-sided level of 0.05 with the revised alpha spending function for TCC and TSP, and the original alpha spending function for OS. As per the preplanned testing procedure, the initial statistical significance boundaries at the second interim analysis were 0.012 for both TSP and TCC, and 0.0067 for OS (based on 179 observed OS events at the second interim analysis). If either TCC or TSP met statistical significance, its alpha would be recycled, with the significance boundary for the other of TCC or TSP at the second interim analysis becoming 0.0183; as described earlier, the significance boundary for OS would remain at 0.0067.

Data Imputation Methods

Data for which quality issues were detected were excluded, when deemed necessary, from the sensitivity analysis for efficacy and safety. The strength of association between rPFS and OS was evaluated for the *BRCA* subgroup using the iterative multiple imputation approach when data were missing. Missing data for patient-reported outcomes were analyzed by accounting for change from baseline with a mixed model of repeated measures and using a pattern-mixture model as a sensitivity analysis.

Subgroup Analyses

Subgroup analyses were conducted only for the HRR study population in the MAGNITUDE study. Per the Health Canada indication and sponsor's reimbursement request, this review was limited to the prespecified *BRCA* subgroup.

Secondary Outcomes

The testing of the key secondary efficacy end points (TSP and OS) was based on the stratified log-rank test. These end points were summarized using the Kaplan-Meier method. Cox proportional hazard models were used to estimate the HR and its 95% CI. A sensitivity analysis using a nonstratified log-rank test was performed for each end point. For OS, an additional sensitivity analysis censoring death due to COVID-19 was performed. The multiplicity of testing secondary outcomes was carried out.

For other efficacy end points (e.g., TPP), estimates of the time-to-event end points were obtained using the Kaplan-Meier estimates and stratified log-rank test of the survival distributions and a stratified Cox model was used to obtain the HR along with the associated 95% CIs. A sensitivity analysis using a nonstratified log-rank test was performed for each end point.

A prespecified multivariate Cox regression analysis, adjusting for important selected prognostic factors, was performed for OS. Each baseline prognostic factor from a predefined list was assessed individually for the prognostic value ($P < 0.05$) using a univariate Cox regression model. The selected factors with a prognostic

value were included as covariates in a multivariate Cox regression model to assess their significance in the presence of the other factors. Backward selection methods were used to identify the final set of prognostic factors (exit P value = 0.10). The treatment group was then added to the final multivariate Cox proportional hazards model to assess the effect of treatment when adjusted for the selected prognostic factors. For OS in the *BRCA* population, PSA (P = 0.079), lactate dehydrogenase (P = 0.017), the ECOG PS score (0 versus 1) at baseline (P = 0.0103), the number of bone lesions at baseline (≤ 10 versus > 10) (P = 0.003), and the presence of visceral disease (yes versus no) (P = 0.002) were included as covariates in the final multivariate Cox regression model.

Analysis Populations

The analysis population is summarized in Table 9. The efficacy outcomes were analyzed based on the randomized analysis set for cohort 1. The safety analysis set included all randomized patients who received at least 1 dose of study treatment in cohort 1. The safety analysis was performed separately by cohort.

Results

Patient Disposition

A summary of patient disposition for the second interim analysis (data cut-off date of June 17, 2022) is presented in Table 10. Overall, 946 patients were screened, and 423 patients with HRR gene alterations were randomized to cohort 1. The reasons for screening failure specifically for the cohort 1 *BRCA* subgroup were not reported. Of the 423 patients with HRR alterations, 225 patients were enrolled in the *BRCA* subgroup. In the *BRCA* subgroup, 113 patients were randomized to the niraparib and abiraterone acetate with prednisone group and 112 patients to the placebo and abiraterone acetate with prednisone group. At the second interim analysis, 47 (41.6%) patients in the niraparib and abiraterone acetate with prednisone group and 29 (25.9%) patients in the placebo and abiraterone acetate with prednisone group were still receiving treatment. The rate of treatment discontinuation was higher in the placebo and abiraterone acetate with prednisone group compared to the niraparib and abiraterone acetate with prednisone group. The most common reason for discontinuation in both groups was disease progression (niraparib and abiraterone acetate with prednisone = 41.6%; placebo and abiraterone acetate with prednisone = 67.9%).

Table 9: Analysis Populations of MAGNITUDE Study

Study	Population	Definition	Application
MAGNITUDE study	Randomized analysis set	All randomized patients	Used for evaluating efficacy
	Safety analysis set	All randomized patients who received at least 1 dose of study medication	Used for evaluating safety and treatment compliance

Note: Details included in Table 9 are from the sponsor's Summary of Clinical Evidence.[14]
Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[15]

Table 10: Summary of Patient Disposition of Cohort 1 *BRCA* Subgroup — MAGNITUDE Study, Second Interim Analysis

Patient disposition	Niraparib and abiraterone acetate with prednisone (N = 113)	Placebo and abiraterone acetate with prednisone (N = 112)
Screened, N	946	
Randomized, N	423 for cohort 1, of which 225 had *BRCA* gene alterations	
Patients ongoing, n (%)	47 (41.6)	29 (25.9)
Discontinued from study treatment, n (%)	66 (58.4)	83 (74.1)
Reason for discontinuation, n (%)		
Progressive disease	47 (41.6)	76 (67.9)
Adverse event	14 (12.4)	4 (3.6)
Lost to follow-up	NR	NR
Adverse event (COVID-19 related)	5 (4.4)	0
Patient refused further study treatment	4 (3.5)	2 (1.8)
Physician decision	0	1 (0.9)
Nonadherence with study drug	NR	NR
Other	1 (0.9)	0
FAS, N	113 (100.0)	112 (100.0)
PP, N	NR	NR
Safety, N	113 (100.0)	112 (100.0)

FAS = full analysis set; NR = not reported; PP = per-protocol.

Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[15]

Baseline Characteristics

A summary of baseline patient demographics and disease characteristics of the cohort 1 *BRCA* subgroup are in Table 11. The baseline characteristics outlined in Table 11 are limited to those that are most relevant to this review or were felt to affect the outcomes or interpretation of the study results. There are some important imbalances in the baseline characteristics between the 2 treatment groups. Some of those important imbalances included, between the niraparib and abiraterone acetate with prednisone group and the placebo and abiraterone acetate with prednisone group, respectively, a tumour stage of T3 at initial diagnosis ([redacted] versus [redacted]), a metastasis stage of M0 (33.6% versus 50%) and M1 (61.9% versus 44.6%), a Gleason score of 7 (14.4% versus 24.1%) and a score of 8 or more (74.1% versus 64.3%), having surgery as a prior prostate cancer therapy [redacted], an ECOG PS score of 0 (61.1% versus 71.4%) and a score of 1 (38.9% versus 28.6%), and extent of disease in nodal at baseline (54.9% versus 44.6%). The study population was predominately white (72%), with an approximate mean age of 68 years. Most patients had a tumour stage of T3 ([redacted]), a Gleason score of 8 or more (69.2%), and an ECOG PS score of 0 (66.2%). A similar

proportion of patients in both groups had prior prostate cancer therapy, in which hormone therapy was the most common therapy (approximately 95%), followed by surgery (approximately [redacted]).

Exposure to Study Treatments

A summary of treatment exposure is presented in Table 12. The median duration of treatment observed by the second interim data cut-off date (June 17, 2022) was longer in the niraparib and abiraterone acetate with prednisone group ([redacted] months) compared to the placebo and abiraterone acetate with prednisone group ([redacted] months). More patients received 24 or more cycles of treatment in the niraparib and abiraterone acetate with prednisone group [redacted] compared to the placebo and abiraterone acetate with prednisone group (16.1%).

Table 11: Summary of Baseline Characteristics of Cohort 1 *BRCA* Subgroup — MAGNITUDE Study, Second Interim Analysis

Characteristic	Niraparib and abiraterone acetate with prednisone (N = 113)	Placebo and abiraterone acetate with prednisone (N = 112)
Age, years, mean (SD)	67.9 (9.34)	67.9 (8.43)
< 65	39 (34.5)	37 (33)
≥ 65 to 74	44 (38.9)	52 (46.4)
≥ 75	30 (26.5)	23 (20.5)
Race, n (%)		
White	78 (69.0)	84 (75.0)
Asian	18 (15.9)	20 (17.9)
Black or African American	3 (2.7)	0
American Indian or Alaska Native	NR	NR
Other	14 (12.4)	8 (7.1)
Weight (kg), mean (SD)	[redacted]	[redacted]
Mean time from initial diagnosis to randomization, years (SD)	3.09 (2.796)	3.68 (3.506)
Tumour stage at initial diagnosis, n (%)		
T0	[redacted]	[redacted]
T1	[redacted]	[redacted]
T2	[redacted]	[redacted]
T3	[redacted]	[redacted]
T4	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Metastasis stage at initial diagnosis, n (%)		
M0	38 (33.6)	56 (50.0)

Characteristic	Niraparib and abiraterone acetate with prednisone (N = 113)	Placebo and abiraterone acetate with prednisone (N = 112)
M1	70 (61.9)	50 (44.6)
Unknown	5 (4.4)	6 (5.4)
Gleason score at initial diagnosis, n (%)		
Number of patients	112	112
< 7, n (%)	8 (7.1)	8 (7.1)
7, n (%)	16 (14.3)	27 (24.1)
3 + 4, n (%)	6 (5.4)	7 (6.3)
4 + 3, n (%)	10 (8.9)	19 (17.0)
Unknown, n (%)	0	1 (0.9)
≥ 8, n (%)	83 (74.1)	72 (64.3)
Unknown	5 (4.5)	5 (4.5)
Prior prostate cancer therapy, n (%)		
Hormonal therapy	108 (95.6)	107 (95.5)
Surgery	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
AAP	30 (26.5)	29 (25.9)
Past taxane-based chemotherapy	26 (23.0)	29 (25.9)
Prior novel AR targeted therapy	6 (5.3)	5 (4.5)
Other	26 (23.0)	37 (33.0)
ECOG PS score at baseline, n (%)		
0	69 (61.1)	80 (71.4)
1	44 (38.9)	32 (28.6)
Extent of disease at study entry, n (%)[a]		
Bone	99 (87.6)	93 (83.0)
Nodal[b]	62 (54.9)	50 (44.6)
Visceral	26 (23.0)	22 (19.6)
Soft tissue	5 (4.4)	7 (6.3)
Prostate[c]	1 (0.9)	2 (1.8)
Number of bone lesions at study entry, n (%)		
≤ 10 lesions[d]	68 (60.2)	67 (59.8)
> 10 lesions	45 (39.8)	45 (40.2)
PSA at initial diagnosis (mcg/L)		

Characteristic	Niraparib and abiraterone acetate with prednisone (N = 113)	Placebo and abiraterone acetate with prednisone (N = 112)
Number of patients	104	101
Mean (SD)	219.83 (553.871)	252.83 (693.698)

AAP = abiraterone acetate with prednisone; ECOG PS = Eastern Cooperative Oncology Group Performance Status; M0 = metastasis stage 0; M1 = metastasis stage 1; NR = not reported; PSA = prostate-specific antigen; SD = standard deviation; T0 = tumour stage 0; T1 = tumour stage 1; T2 = tumour stage 2; T3 = tumour stage 3; T4 = tumour stage 4.

Note: Details included in Table 11 are from the sponsor's Summary of Clinical Evidence.[14]

[a]Patients having multiple lesions within each category are counted only once in the category but may be represented in more than 1 category.

[b]Includes lymph nodes not specified as pelvic or nonpelvic.

[c]Prostate local recurrence or progression.

[d]Includes patients with no bone lesions.

Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[15]

Table 12: Summary of Patient Exposure of Cohort 1 *BRCA* Subgroup — MAGNITUDE Study, Second Interim Analysis

Exposure	Niraparib and abiraterone acetate with prednisone (N = 113)	Placebo and abiraterone acetate with prednisone (N = 112)
Total, treatment months[a]		
Duration, mean (SD)	[redacted]	[redacted]
Duration, median (range)	[redacted]	[redacted]
Total number of cycles		
Duration, mean (SD)	[redacted]	[redacted]
Duration, median (range)	[redacted]	[redacted]
Duration of follow-up (months)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
AA adherence, %	[redacted]	[redacted]

AA = abiraterone acetate; SD = standard deviation.

Note: Details included in Table 12 are from the sponsor's Summary of Clinical Evidence.[14]

[a]Treatment duration is defined as the following: (duration from the date of the first dose of study drug to the date of the last dose of study drug + 1) ÷ 30.4375. The study is ongoing.

Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[15]

Concomitant Medications and Subsequent Therapies

Concomitant medications taken by more than 10% of patients in the *BRCA* subgroup of the MAGNITUDE trial are presented in Table 13. Most patients ([redacted] took 1 or more concomitant medications during study treatment. Endocrine therapy was the most common concomitant treatment ([redacted] in the niraparib and abiraterone acetate with prednisone group versus [redacted] in the placebo and abiraterone acetate with prednisone group). Other anticancer therapies were prohibited during the study.

Of those patients who discontinued study treatment as of the second data cut-off date, more patients had received subsequent therapy for prostate cancer in the placebo and abiraterone acetate with prednisone group (66 [58.9%] patients) compared to the niraparib and abiraterone acetate with prednisone group (35 [31%] patients). The most common type of subsequent therapy was chemotherapy, with 28 (24.8%) patients in the niraparib and abiraterone acetate with prednisone group versus 44 (39.3%) patients in the placebo and abiraterone acetate with prednisone group. The most common chemotherapy used was docetaxel (15.9% versus 32.1%) followed by cabazitaxel (7.1% versus 11.6%) for the niraparib and abiraterone acetate with prednisone group and the placebo and abiraterone acetate with prednisone group, respectively. There were some imbalances between the groups in terms of subsequent therapies. In general, a higher percentage of patients in the placebo and abiraterone acetate with prednisone group received subsequent therapy compared to those in the niraparib and abiraterone acetate with prednisone group (58.9% versus 31%). The most prominent therapy was PARP inhibitor therapy in the placebo and abiraterone acetate with prednisone group — 22 of 66 (19.6%) patients, compared with 1 such patient in the niraparib and abiraterone acetate with prednisone group.

Table 13: Summary of Subsequent Treatment and Concomitant Medication of Cohort 1 *BRCA* Subgroup — MAGNITUDE Study, Second Interim Analysis

Exposure	Niraparib and abiraterone acetate with prednisone (N = 113)	Placebo and abiraterone acetate with prednisone (N = 112)
Subsequent therapies		
Received subsequent therapy, n (%)	35 (31.0)	66 (58.9)
Chemotherapy, n (%)	28 (24.8)	44 (39.3)
Docetaxel	18 (15.9)	36 (32.1)
Cabazitaxel	8 (7.1)	13 (11.6)
Carboplatin	6 (5.3)	4 (3.6)
Etoposide	1 (0.9)	1 (0.9)
Carboplatin and docetaxel	1 (0.9)	1 (0.9)
Cisplatin	1 (0.9)	2 (1.8)
Carboplatin and etoposide	1 (0.9)	0
Cyclophosphamide	NR	NR
Estramustine	0	1 (0.9)
Docetaxel and prednisone	0	1 (0.9)
Mitoxantrone	0	1 (0.9)
Vinorelbine	0	1 (0.9)
Novel AR targeted therapy, n (%)	7 (6.2)	11 (9.8)
Enzalutamide	7 (6.2)	10 (8.9)
Apalutamide	0	1 (0.9)

Exposure	Niraparib and abiraterone acetate with prednisone (N = 113)	Placebo and abiraterone acetate with prednisone (N = 112)
Hormonal, n (%)	2 (1.8)	9 (8.0)
Abiraterone	2 (1.8)	6 (5.4)
Bicalutamide	0	2 (1.8)
Flutamide	0	1 (0.9)
PARP inhibitor, n (%)	1 (0.9)	22 (19.6)
Olaparib	1 (0.9)	18 (16.1)
Fluzoparib	0	1 (0.9)
Niraparib	0	2 (1.8)
Rucaparib	0	1 (0.9)
Talazoparib	0	1 (0.9)
Other, n (%)	11 (9.7)	18 (16.1)
Concomitant medication		
Endocrine therapy, n (%)	[redacted]	[redacted]
Analgesics, n (%)	[redacted]	[redacted]
Drugs acting on the renin-angiotensin system, n (%)	[redacted]	[redacted]
Drugs for acid-related disorders, n (%)	[redacted]	[redacted]
Antibacterials for systemic use, n (%)	[redacted]	[redacted]

AR = androgen receptor; NR = not reported; PARP = poly-(ADP [adenosine diphosphate]-ribose) polymerase.
Note: Details included in Table 13 are from the sponsor's Summary of Clinical Evidence.[14]
Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[15]

Efficacy

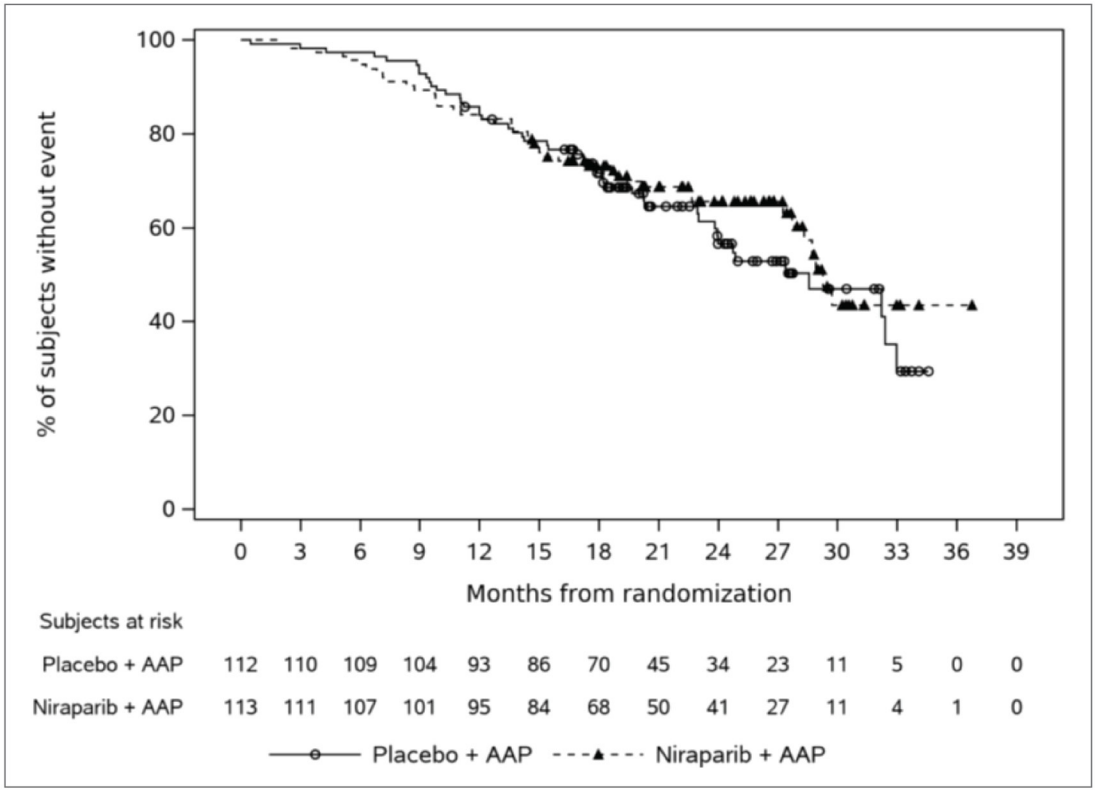
Only those efficacy outcomes identified as important to this review are reported. The main findings presented for the *BRCA* subgroup of cohort 1 in the MAGNITUDE trial are from the second interim analysis (with a June 17, 2022, data cut-off date). Table 14 provides a summary of the efficacy results.

Overall Survival

The median follow-up time was 24.80 months for all patients in the *BRCA* subgroup. The median duration of follow-up was 20.18 months in the niraparib and abiraterone acetate with prednisone group and 19.98 months in the placebo and abiraterone acetate with prednisone group. Overall, 92 deaths occurred in both groups. The median OS was 29.27 months in the niraparib and abiraterone acetate with prednisone group and 28.55 months in the placebo and abiraterone acetate with prednisone group, with an adjusted HR of 0.68 (95% CI, 0.445 to 1.046) and stratified HR of 0.881 (95% CI, 0.58 to 1.33). The probability of OS at 12 months was 84.1% (95% CI, 75.9% to 89.7%) and 83.9% (95% CI, 75.7% to 89.5%), and the probability of OS at 24 months was 65.6% (95% CI, 55.4% to 74.1%) and 56.6% (95% CI, 45.5% to 66.3%) in the niraparib and abiraterone acetate with prednisone group and in the placebo and abiraterone acetate with prednisone

group, respectively. Kaplan-Meier curves for OS are shown in Figure 1. The results from the nonstratified sensitivity analysis of OS for the *BRCA* subgroup were consistent with the stratified analysis.

Figure 1: MAGNITUDE Study, Kaplan-Meier Plot of OS — Cohort 1 *BRCA* Subgroup, FAS, Second Interim Analysis

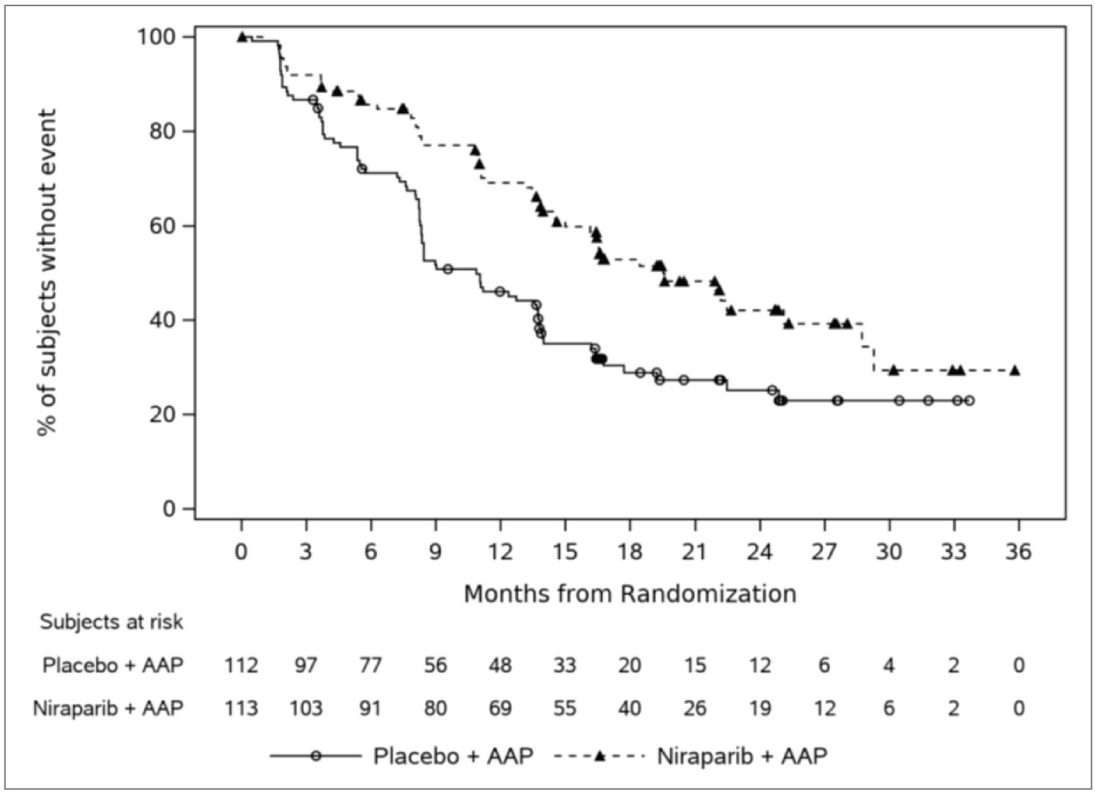


AAP = abiraterone acetate with prednisone; FAS = full analysis set; OS = overall survival.
Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[15]

Radiographic Progression-Free Survival

As rPFS was found to be statistically significant at the first interim analysis, no formal statistical testing was performed at the second interim analysis. By the time of the second interim analysis, 135 events had occurred overall. The median rPFS was 19.52 months in the niraparib and abiraterone acetate with prednisone group and 10.87 months in the placebo and abiraterone acetate with prednisone group, with a stratified HR of 0.55 (95% CI, 0.39 to 0.78) favouring niraparib and abiraterone acetate with prednisone. The probability of being event-free at 12 months was [redacted] and [redacted], and the probability of being event-free at 24 months was [redacted] and [redacted] in the niraparib and abiraterone acetate with prednisone group and the placebo and abiraterone acetate with prednisone group, respectively. Kaplan-Meier curves for rPFS are shown in Figure 2.

Figure 2: MAGNITUDE Study, Kaplan-Meier Plot of rPFS — Cohort 1 *BRCA* Subgroup, FAS, Second Interim Analysis

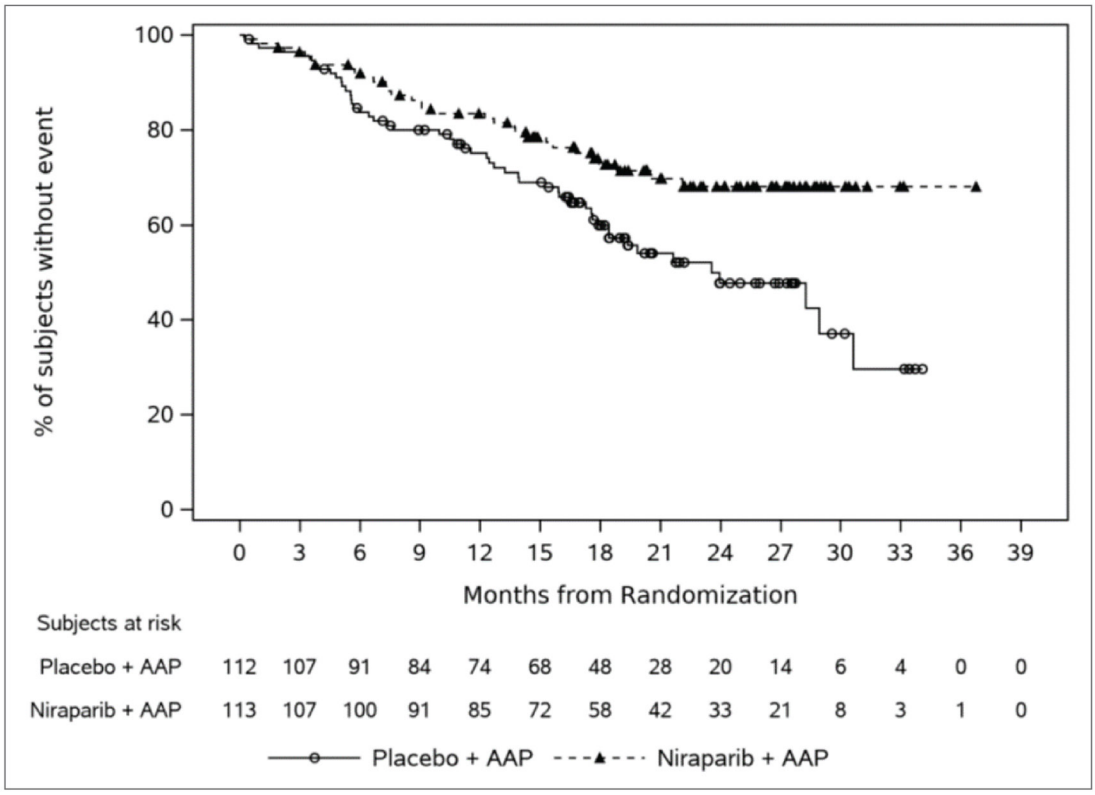


AAP = abiraterone acetate with prednisone; FAS = full analysis set; rPFS = radiographic progression-free survival.
Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[15]

Time to Symptomatic Progression

Overall, 82 events had occurred by the time of the second interim analysis. The median TSP in the niraparib and abiraterone acetate with prednisone group was not estimated while the median TSP was 23.56 months in the placebo and abiraterone acetate with prednisone group, with a between-group HR of 0.54 (95% CI, 0.35 to 0.85; P = 0.0071). The probability of being event-free at 12 months was 83.4% (75% to 89.2%) and 75.1% (65.7% to 82.2%), and the probability of being event-free at 24 months was 68% (95% CI, 57.3% to 76.6%) and 47.8% (95% CI, 36.1% to 58.5%) in the niraparib and abiraterone acetate with prednisone group and the placebo and abiraterone acetate with prednisone group, respectively. Kaplan-Meier curves for TSP are shown in Figure 3.

Figure 3: MAGNITUDE Study, Kaplan-Meier Plot of TSP — Cohort 1 *BRCA* Subgroup, FAS, Second Interim Analysis

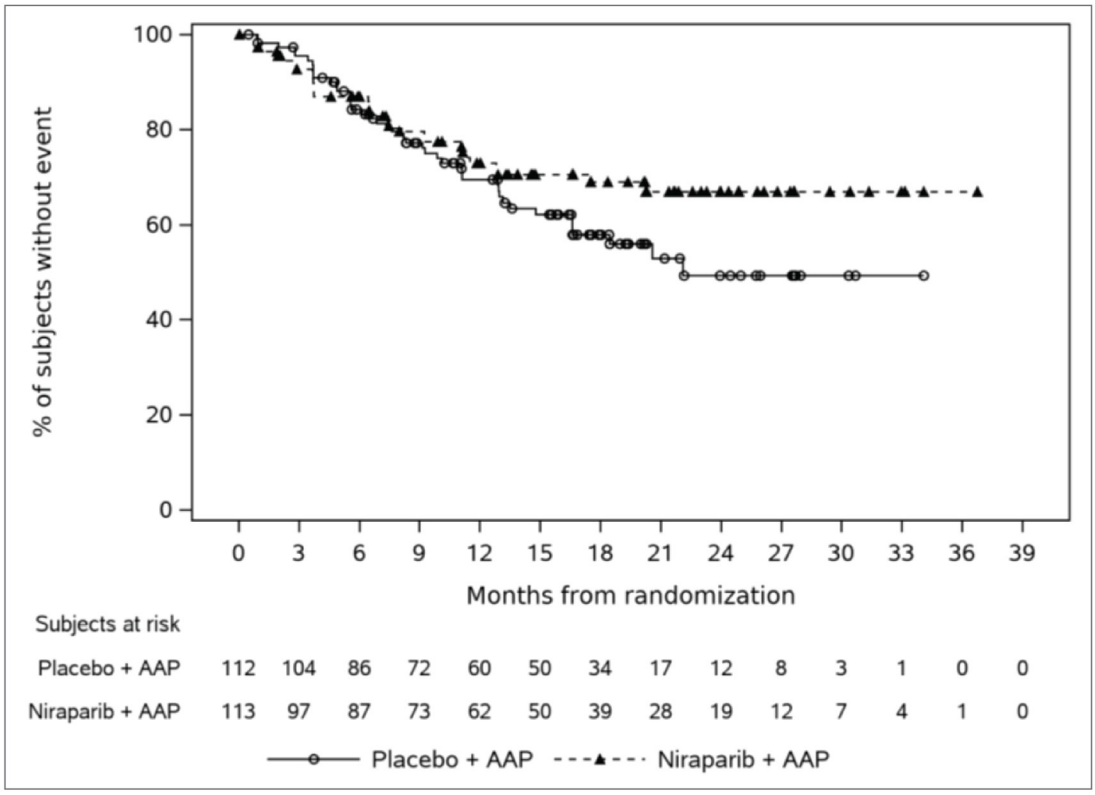


AAP = abiraterone acetate with prednisone; FAS = full analysis set; TSP = time to symptomatic progression.
Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[15]

Time to Pain Progression

Overall, 74 events had occurred in both groups. The median TPP in the niraparib and abiraterone acetate with prednisone group was not estimated while the median TPP was 22.11 months in the placebo and abiraterone acetate with prednisone group, with a stratified HR of 0.70 (95% CI, 0.44 to 1.12; P = 0.133). The probability of being event-free at 12 months was 72.90% (62.9% to 80.6%) and 69.4% (59.3% to 77.5%), and the probability of being event-free at 24 months was 66.9% (95% CI, 55.9% to 75.8%) and 49.9% (95% CI, 36.2% to 61.3%) in the niraparib and abiraterone acetate with prednisone group and the placebo and abiraterone acetate with prednisone group, respectively. Kaplan-Meier curves for TPP are shown in Figure 4.

Figure 4: MAGNITUDE Study, Kaplan-Meier Plot of TPP — Cohort 1 *BRCA* Subgroup, FAS, Second Interim Analysis



AAP = abiraterone acetate with prednisone; FAS = full analysis set; TPP = time to pain progression.
Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[15]

Change From Baseline in FACT-P Total Score

Results for the change from baseline in the FACT-P total score observed at cycle 25 (exploratory end point) are presented in Table 14 and Figure 5. The change from baseline in the FACT-P total score was an exploratory end point. The mean difference in absolute change from baseline in the FACT-P total score at cycle 25 between the 2 treatment groups was [redacted].

Table 14: Summary of Key Efficacy Results of Cohort 1 *BRCA* Subgroup — MAGNITUDE Study, Second Interim Analysis

Variable	Niraparib and abiraterone acetate with prednisone (N = 113)	Placebo and abiraterone acetate with prednisone (N = 112)
OS		
Events, n (%)	43 (38.1)	49 (43. 8)
Censored, n (%)	70 (61.9)	63 (56.3)
Stratified HR (95% CI)	0.881 (0.58 to 1.33)	
Log-rank test P value	0.5505	
Adjusted HR (95% CI)[a]	0.68 (0.445 to 1.046)	
Log-rank test P value[b]	0.0793	
Median OS, months (95% CI)	29.27 (27.70 to NR)	28.55 (23.82 to 32.95)
Number of patients at risk at 12 months	95	93
OS rate at 12 months, % (95% CI)	84.1 (75.9 to 89.7)	83.9 (75.7 to 89.5)
Number of patients at risk at 24 months	41	34
OS rate at 24 months, % (95% CI)	65.6 (55.4 to 74.1)	56.6 (45.5 to 66.3)
rPFS		
Events, n (%)	57 (50.4%)	78 (69.6%)
Censored, n (%)	56 (49.6%)	34 (30.4%)
Stratified HR (95% CI)	0.553 (0.392 to 0.782)	
Log-rank test P value[b]	0.0007	
Median rPFS, months (95% CI)	19.52 (14.98 to 28.71)	10.87 (8.31 to 13.73)
Number of patients at risk at 12 months	[redacted]	[redacted]
Event-free at 12 months, % (95% CI)	[redacted]	[redacted]
Number of patients at risk at 24 months	[redacted]	[redacted]
Event-free at 24 months, % (95% CI)	[redacted]	[redacted]
TSP		
Events, n (%)	31 (27.4)	51 (45.5)
Censored, n (%)	82 (72.6)	61 (54.5)
HR (95% CI)	0.544 (0.347 to 0.853)	
Log-rank test P value[b]	0.0071	
Median TSP, months (95% CI)	NE (NE to NE)	23.56 (17.91 to 30.62)
Number of patients at risk at 12 months	85	74
Event-free at 12 months, % (95% CI)	83.4 (75 to 89.2)	75.1 (65.7 to 82.2)
Number of patients at risk at 24 months	33	20

Variable	Niraparib and abiraterone acetate with prednisone (N = 113)	Placebo and abiraterone acetate with prednisone (N = 112)
Event-free at 24 months, % (95% CI)	68 (57.3 to 76.6)	47.8 (36.1 to 58.5)
TPP		
Events, n (%)	31 (27.4)	43 (38.4)
Censored, n (%)	82 (72.6)	69 (61.6)
HR (95% CI)	0.701 (0.439 to 1.118)	
Log-rank test P value[c]	0.1338	
Median TPP, months (95% CI)	NE (NE to NE)	22.11 (16.59 to NE)
Number of patients at risk at 12 months	62	60
Event-free at 12 months, % (95% CI)	72.90 (62.9 to 80.6)	69.4 (59.3 to 77.5)
Number of patients at risk at 24 months	19	12
Event-free at 24 months, % (95% CI)	66.9 (55.9 to 75.8)	49.4 (36.2 to 61.3)
FACT-P (total score)		
Number of randomized patients	113	112
Number of patients at cycle 25		
LSM change from baseline at cycle 25 (95% CI)[d]		
Difference in LSM at cycle 25 (95% CI)		
P value[e]		

AAP = abiraterone acetate with prednisone; BICR = blinded independent central review; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FACT-P = Functional Assessment Cancer Therapy–Prostate; HR = hazard ratio; LSM = least squares mean; NE = not estimable; NR = not reported; OS = overall survival; PFS2 = progression-free survival on first subsequent therapy; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; SE = standard error; TPP = time to pain progression; TSP = time to symptomatic progression; vs. = versus.

Note: Details included in Table 14 are from the sponsor's Summary of Clinical Evidence.[14]

[a]Based on a multivariate analysis, which accounted for PSA, lactate dehydrogenase, ECOG PS grade (0 vs. 1), number of bone lesions at baseline (≤ 10 vs. > 10), and the presence of visceral disease (yes vs. no).

[b]The P value was from a log-rank test stratified by stratification factors and was part of multiplicity adjustment.

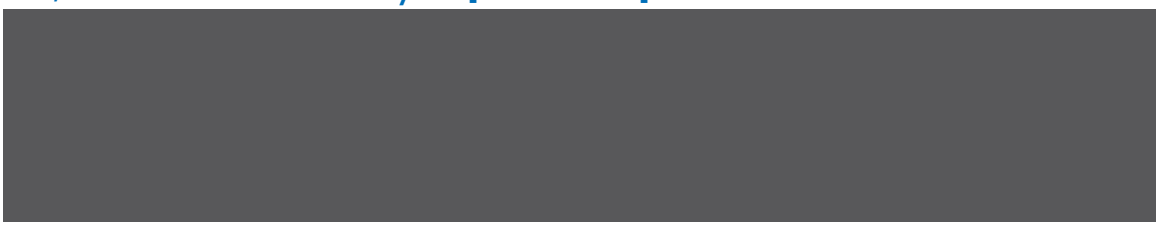
[c]The P value was from a log-rank test stratified by stratification factors.

[d]LSMs were derived based on the mixed-effects model with baseline, visit, treatment, and visit by treatment interaction as fixed effects, and individual patient as a random effect.

[e]Based on an F-test comparing niraparib and AAP vs. placebo and AAP. For the fixed-effects test, the P value was used for testing the significance of the main fixed effects.

Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[15]

Figure 5: Least Squares Mean Change from Baseline in FACT-P (Total Score) to Cycle 25, Mixed Model of Repeated Measures — Cohort 1 *BRCA* Subgroup, Randomized Analysis Set, Second Interim Analysis [Redacted]



AAP = abiraterone acetate with prednisone; FACT-P = Functional Assessment Cancer Therapy–Prostate.
Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[15]

Harms

Harms data were reported for the safety analysis set from the second interim analysis (data cut-off date of June 17, 2022). The key harms results for the cohort 1 *BRCA* subgroup are presented in Table 15. Any AE occurring at or after the initial administration of study medication through the day of the last dose plus 30 days was considered treatment-emergent.

Adverse Events

Almost all patients in the study reported at least 1 TEAE (99.1% of patients in the niraparib and abiraterone acetate with prednisone group; 97.3% of patients in the placebo and abiraterone acetate with prednisone group). The most common TEAEs in the niraparib and abiraterone acetate with prednisone group versus the placebo and abiraterone acetate with prednisone group, respectively, were anemia (46.9% versus 25.9%), constipation (33.6% versus 19.6%), hypertension (32.7% versus 24.1%), and nausea (32.7% versus 20.5%). A larger proportion of patients in the niraparib and abiraterone acetate with prednisone group experienced at least 1 TEAE at a level of grade 3 and grade 4 compared to the placebo and abiraterone acetate with prednisone group (68.1% versus 50.9%).

Serious Adverse Events

At least 1 treatment-emergent SAE was reported in 40.7% of patients in the niraparib and abiraterone acetate with prednisone group, and in 25% of patients in the placebo and abiraterone acetate with prednisone group. Anemia and COVID-19 were the most common SAEs in the niraparib and abiraterone acetate with prednisone group (4.7%). In the placebo and abiraterone acetate with prednisone group, COVID-19 was the most frequent SAE (2.7%).

Withdrawals Due to Adverse Events

Study treatment withdrawal due to a TEAE was reported in 15% of patients in the niraparib and abiraterone acetate with prednisone group, and in 5.4% of patients in the placebo and abiraterone acetate with prednisone group. The most common TEAEs that led to treatment discontinuation in both treatment groups was COVID-19 (13.3% in the niraparib and abiraterone acetate with prednisone group versus 8.9% in the placebo and abiraterone acetate with prednisone group).

Mortality

In the niraparib and abiraterone acetate with prednisone group, deaths were reported for [redacted] of patients on study treatment and [redacted] in follow-up. In the placebo and abiraterone acetate with prednisone group, deaths were reported for [redacted] of patients on study treatment and [redacted] of patients in follow-up. The majority of deaths coded as AEs in both groups was attributed to progressive disease in follow-up ([redacted] in the niraparib and abiraterone acetate with prednisone group; [redacted] in the placebo and abiraterone acetate with prednisone group).

Notable Harms

Notable harms were selected based on serious warnings and precautions in the Health Canada product monograph for niraparib and abiraterone acetate with prednisone.[39] Anemia occurred in [redacted] of patients treated with niraparib and abiraterone acetate with prednisone and [redacted] of patients treated with placebo and abiraterone acetate with prednisone. The incidence of hypertension was [redacted] in the niraparib and abiraterone acetate with prednisone group and [redacted] in the placebo and abiraterone acetate with prednisone group. The percentage of patients who experienced fatigue in the niraparib and abiraterone acetate with prednisone group versus the placebo and abiraterone acetate with prednisone group was [redacted] and [redacted] respectively. Other notable harms reported in at least 1% of patients in the niraparib and abiraterone acetate with prednisone group and the placebo and abiraterone acetate with prednisone group, respectively, were the following: asthenia ([redacted] versus [redacted]), fluid retention ([redacted] versus [redacted]), neutropenia ([redacted] versus [redacted]), and hypokalemia ([redacted] versus [redacted]).

Table 15: Summary of Harms Results — MAGNITUDE Study, Cohort 1 *BRCA* Subgroup, Safety Analysis Set, Second Interim Analysis

Harm	Niraparib and abiraterone acetate with prednisone (N = 113)	Placebo and abiraterone acetate with prednisone (N = 112)
[redacted]		
Patients with ≥ 1 AE	[redacted]	[redacted]
Anemia	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Hyperglycemia	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]

Harm	Niraparib and abiraterone acetate with prednisone (N = 113)	Placebo and abiraterone acetate with prednisone (N = 112)
Patients with ≥ 1 grade 3 or grade 4 AE	[redacted]	[redacted]
Anemia	32 (28.3)	[redacted]
Hypertension	[redacted]	[redacted]
Thrombocytopenia	9 (8.0)	[redacted]
Neutropenia	8 (7.1)	[redacted]
[redacted]		
Patients with ≥ 1 SAE	[redacted]	[redacted]
Anemia	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
COVID-19 pneumonia	[redacted]	[redacted]
Hematuria	[redacted]	[redacted]
[redacted]		
Patients who stopped study treatment due to AEs	17 (15.0)	[redacted]
[redacted]		
Patients who died on study treatment[d]	[redacted]	[redacted]
AE	[redacted]	[redacted]
COVID-19–related	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Patients who died in follow-up[e]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
AE	[redacted]	[redacted]
COVID-19–related	[redacted]	[redacted]
Other	[redacted]	[redacted]
Notable harm,[a, f] n (%)		
Patients with ≥ 1 AE of special interest	[redacted]	[redacted]
Anemia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]

Harm	Niraparib and abiraterone acetate with prednisone (N = 113)	Placebo and abiraterone acetate with prednisone (N = 112)
Fluid retention	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Peripheral edema	[redacted]	[redacted]
Hypokalemia	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]
Hypoglycemia	[redacted]	[redacted]
Hepatic impairment	[redacted]	[redacted]
Anaphylactic reactions	[redacted]	[redacted]

AA = abiraterone acetate; AE = adverse event; SAE = serious adverse event.

[a]There was a frequency of 15% or greater in at least 1 treatment group.

[b]There was a frequency of 2% or greater in at least 1 treatment group.

[c]Aggregated data were from *BRCA* Clinical Study Report: supplement.[43]

[d]"On–study treatment death" was defined as death that occurs within 30 days of the last dose of the study drug.

[e]"Follow-up death" was defined as death that occurs more than 30 days after the last dose of the study drug.

[f]This was from the product monograph on niraparib and abiraterone acetate with prednisone.[39]

Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[15]

Critical Appraisal

Internal Validity

The MAGNITUDE study is an ongoing phase III, double-blind, multicentre RCT in which randomization has been performed using an Interactive Web Response System and stratification has been based on relevant prognostic factors. However, despite randomization, several key baseline factors were imbalanced between the 2 treatment groups, such as (but not limited to) body location of metastases, metastasis stage, and ECOG PS score. Differences in the baseline characteristics reduce the benefits of randomization and increase the probability that these measured and unmeasured factors would confound the results and make it difficult to determine the true effects of the treatments. In addition, there were imbalances in subsequent treatment between the 2 groups, which clinical experts noted could potentially confound the results. However, a multivariate Cox regression analysis was not performed to adjust for important prognostic factors within the *BRCA* subgroup, except for the OS outcome. For OS, an analysis was conducted to control for the following factors based on a stepwise approach: treatment (niraparib versus placebo), PSA levels, lactate dehydrogenase levels, ECOG PS grade (0 versus 1), number of bone lesions at baseline (≤ 10 versus > 10), and the presence of visceral disease (yes versus no). Therefore, imbalanced baseline characteristics may have introduced confounding effects on the remaining outcomes. The clinical experts consulted by CADTH indicated that the differences in baseline characteristics signalled the niraparib and abiraterone acetate group had more serious disease than the control group. Therefore, CADTH reviewers determined that any potential bias arising from the imbalances would go toward the null (i.e., against niraparib and

abiraterone acetate with prednisone). There were major protocol deviations both in the first and second interim analyses, including enrolling patients in the study without satisfying the eligibility criteria, receiving disallowed concomitant treatments, administering the wrong treatment or incorrect doses, missing planned tumour assessments related to COVID-19, and having unblinded patients. The number of patients affected by protocol deviations in the *BRCA* subgroup specifically was not reported; therefore, it is unclear how the protocol deviations could influence the interpretation of the study results or pose a safety risk to the patients in this subgroup. Therefore, the magnitude and direction of potential bias cannot be determined.

To minimize the risk of differential measurement error, the trial performed tumour assessments using RECIST 1.1 criteria and radiographic scans were assessed by a BICR. There was low selective reporting bias, as the data were analyzed in accordance with the prespecified statistical plan. All interim analyses conducted were planned a priori with appropriately specified alpha spending methods, and secondary outcomes were adjusted for multiplicity. A number of patients were unblinded in both groups before the data cut-off date at the second interim analysis (11 [9.7%] patients in the niraparib and abiraterone acetate with prednisone group versus 21 [19%] patients in the placebo and abiraterone acetate with prednisone group), which could potentially increase the risk of detection bias, particularly for subjective assessment of patient-reported outcomes (i.e., TSP, TPP, FACT-P, and AEs). However, there was no apparent evidence that this biased the results in favour of niraparib and abiraterone acetate.

Furthermore, the niraparib and abiraterone acetate with prednisone group received more treatment cycles than the placebo and abiraterone acetate with prednisone group (33.0% versus 23. 7%), which can lead to biased or misleading conclusions about the effectiveness of the intervention. The longer treatment duration in the experimental group could lead to a larger observed effect because participants have been receiving the treatment for a longer period. This could artificially inflate the perceived effectiveness of the niraparib and abiraterone acetate with prednisone. However, it may also increase the likelihood of reporting AEs with additional treatments. The clinical experts noted that this also could indicate that patients stopped the treatment due to disease progression. CADTH reviewers could not determine whether the efficacy and safety results were influenced by this imbalance based on the available information, although it is anticipated to have had a limited effect, if any.

In terms of statistical analyses, all statistical analyses and interim analyses were prespecified in the MAGNITUDE study protocol and all planned outcomes were reported for the *BRCA* subgroup. Although the utility of the few sensitivity analyses is uncertain, they generally supported the results of the primary rPFS analysis. Interim analyses were prespecified in the protocol. However, the use of the group sequential design can potentially lead to operational bias in cases where knowledge of the interim analysis exists. O'Brien-Fleming boundaries were employed in the trial as a strategy wherein the level of statistical significance becomes progressively smaller in each analysis, while still reserving the majority of the alpha allocation for the concluding analysis.[53] However, the alpha spending only applied to the secondary outcomes (OS and TSP) and the primary objective related to rPFS was still considered to have been met at the first interim analysis. While the rPFS results appeared to have been maintained at the second interim, no formal statistical comparisons or thresholds were set. While the trial appears to have met its primary objective, given that there was limited supporting evidence from secondary outcomes — notably a lack of OS

benefit for niraparib and abiraterone acetate with prednisone versus placebo and abiraterone acetate with prednisone — longer follow-up for the rPFS analyses would have been preferred to determine the clinical value of treatment with niraparib and abiraterone acetate with prednisone.

External Validity

The clinical experts consulted by CADTH considered the eligibility criteria and baseline characteristics of the MAGNITUDE trial generalizable to adult patients with mCRPC in the Canadian setting, although they identified some differences and the CADTH review team identified limitations to the external validity in comparison to the Health Canada–indicated population. The dosing and administration of niraparib and abiraterone acetate with prednisone in the MAGNITUDE trial was consistent with the Health Canada–approved product monograph. The experts also noted that abiraterone acetate with prednisone, an approved treatment option for patients with mCRPC in Canada, was an appropriate comparator.

The drug under review is indicated for "the treatment of adult patients with deleterious or suspected deleterious *BRCA* mutated (germline and/or somatic) mCRPC, who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated." Patients in the cohort 1 *BRCA* subgroup of the MAGNITUDE trial all had *BRCA* mutations confirmed before being enrolled in the trial, which aligns with the indicated population and reimbursement request. However, there were potential gaps and implementation challenges related to the evidence from the MAGNITUDE trial versus the population of patients included in the approved indication. First, CADTH noted that the indication is line-agnostic, whereas no patients in the MAGNITUDE trial had received prior systemic therapy in the mCRPC setting (i.e., received niraparib and abiraterone acetate with prednisone or placebo and abiraterone acetate with prednisone as first-line treatment in this setting). As a result, there is no direct comparative evidence for the use of niraparib and abiraterone acetate in the second-line, third-line, and later-line settings. Additionally, the clinical experts indicated that although asymptomatic patients can be easily identified, determining whether a patient is "mildly symptomatic" is a subjective judgment and may vary between clinicians. It is unclear if patients enrolled in the MAGNITUDE trial would be classified as asymptomatic or mildly symptomatic because the trial did not have eligibility criteria or report baseline characteristics directly related to this. Likewise, the clinical experts indicated that there is no objective definition for patients "in whom chemotherapy is not clinically indicated." Health Canada reported that this component of the indication is based on the clinical judgment of the treating physician and was included to reflect the MAGNITUDE study exclusion criteria, where no prior chemotherapy in the mCRPC setting was allowed. However, the clinical experts consulted by CADTH for this review noted that any patient with mCRPC who is well enough for cytotoxic chemotherapy could be interpreted as having a clinical indication for it, although they and/or their clinicians may not wish to treat these patients with chemotherapy due to the associated adverse effects.

The clinical experts consulted by CADTH noted that excluding patients from the MAGNITUDE trial who previously received a novel second-generation AR targeted therapy, taxane-based chemotherapy, or more than 4 months of abiraterone acetate with prednisone before randomization in the mCRPC setting was appropriate in terms of establishing a purely mCRPC treatment-naive population to evaluate the efficacy of niraparib and abiraterone acetate with prednisone. However, they noted that the exclusion criteria reduce

the generalizability of the trial results to the current population of patients with mCRPC in Canada as many patients would have received a second-generation AR targeted therapy in an earlier stage of the disease. The clinical experts noted that this might impact the choice of niraparib and abiraterone acetate with prednisone in the mCRPC setting because there would be a small population of these patients that would not be considered for taxane chemotherapy as first-line mCRPC treatment. Therefore, the CADTH review team noted that the trial population may reflect a relatively small population in clinical settings based on treatment history and eligibility. But, as also mentioned, implementing conditions to define the exact population may be difficult because of the lack of objective criteria for defining the characteristics aligned with the indication and MAGNITUDE trial eligibility.

Outcomes measured in the MAGNITUDE trial are those recommended by PCWG3[11] (i.e., OS, rPFS, and patient-reported outcomes such as symptoms and HRQoL) and some are clinically relevant and important to patients, based on the input received from stakeholders for this review. According to clinical experts, although rPFS is a relevant end point for assessing efficacy in trials, it is not an ideal primary outcome to assess the primary efficacy. This is because the emphasis on radiographic results to determine disease progression and treatment benefit in the mCRPC setting does not adequately reflect clinical practice, which involves a broader and more holistic assessment of determining treatment benefit. While there are data emerging that rPFS is a predictor of OS,[54-56] CADTH reviewers concluded that the association was difficult to interpret at the time of this review because of the varying definitions of rPFS used, relatively short follow-up periods used for the comparisons, and lack of prospective evidence. The clinical experts agreed that given the advancements in therapies and understanding of the natural history of prostate cancer, OS remains the most clinically relevant outcome.

Although abiraterone acetate with prednisone is an appropriate comparator as per the clinical experts consulted by CADTH, there are additional clinically relevant comparators used to treat patients with mCRPC in Canada. The clinical experts indicated that the treatment paradigm in the mCRPC setting has changed substantially since the MAGNITUDE trial began to become chemotherapy-focused in recent years due to emerging evidence and because most patients have received an ARPi in the mCSPC setting. The clinical experts consulted by CADTH for this review noted that they would not offer an alternate ARPi in the first-line setting in mCRPC if the patient received an ARPi in the nmCRPC or mCSPC settings, and they reported that almost every patient could theoretically receive chemotherapy in the mCRPC setting unless patients preferred not to receive it. Therefore, the absence of head-to-head evidence between niraparib and abiraterone acetate with prednisone versus chemotherapy represents an evidence gap.

The CADTH review team identified some aspects of the MAGNITUDE trial that may reduce its generalizability. First, clinical experts noted that the subsequent anticancer therapies patients received after their first-line treatment failed in this study are not fully representative of currently Canadian clinical practice. They indicated that in recent years, docetaxel has become the most common first-line treatment for mCRPC. Moreover, the MAGNITUDE trial did not include patients with a poor ECOG PS while clinical experts noted that enrolling patients with only an ECOG PS score of 0 and 1 is not entirely representative of patients with mCRPC as they expect to find patients with higher ECOG PS scores in Canadian practice. Additionally, based

on the baseline characteristics of patients enrolled in the MAGNITUDE trial, the CADTH review team noted that Black and African American individuals may be underrepresented.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.[12,13]

- **"High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate — The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. We use the word 'likely' for evidence of moderate certainty (e.g., 'X intervention likely results in Y outcome').
- **Low certainty**: Our confidence in the effect estimate is limited — The true effect may be substantially different from the estimate of the effect. We use the word 'may' for evidence of low certainty (e.g., 'X intervention may result in Y outcome').
- **Very low certainty**: We have very little confidence in the effect estimate — The true effect is likely to be substantially different from the estimate of effect. We describe evidence of very low certainty as 'very uncertain.'"

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for OS was set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review. Although 1 clinical expert suggested a reference point for the certainty of evidence assessment for rPFS could be 25%, both clinical experts were uncertain of what the exact threshold for clinical importance would be; therefore, the target of the certainty of evidence assessment for rPFS was the presence or absence of any (non-null) effect. The reference point for the certainty of the evidence assessment for the FACT-P total score was set according to the presence or absence of an important effect based on thresholds identified in the literature. The target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for the TSP and TPP due to the lack of a formal MID estimate; for harms events, due to the unavailability of the absolute difference in effects, the certainty of evidence was summarized narratively.

Results of GRADE Assessments

Table 2 presents the GRADE summary of findings for niraparib and abiraterone acetate with prednisone versus placebo and abiraterone acetate with prednisone.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Evidence

Content in this section has been informed by materials submitted by the sponsor. The following has been summarized and validated by the CADTH review team.

Objectives for the Summary of Indirect Evidence

The MAGNITUDE pivotal trial provides a head-to-head comparison between niraparib and abiraterone acetate with prednisone versus placebo and abiraterone acetate with prednisone in adult male patients with mCRPC with a *BRCA* gene alteration. However, direct evidence with respect to the comparative effectiveness of niraparib and abiraterone acetate with prednisone versus other mCRPC treatments in this population is currently unavailable. Therefore, an ITC is warranted to address this evidence gap.

Description of Indirect Comparison(s)

One ITC[17] — described as an unanchored MAIC — was determined feasible by the sponsor. In the analysis, IPD from patients treated with niraparib and abiraterone acetate with prednisone in the MAGNITUDE pivotal trial was compared with the IPD from patients with first-line treatment mCRPC in the CAPTURE study.

The CAPTURE trial (Figure 6) was an observational, multiple-cohort database study focusing on Spanish patients with localized prostate cancer, mCSPC, or first-line treatment mCRPC (defined as patients who received any treatment after interrupting continuous androgen deprivation therapy with a luteinizing hormone-releasing hormone agonist, gonadotropin-releasing hormone agonist, or those who were not surgically castrated)[57] to describe the trajectory of the disease and explore clinical management and outcomes based on the HRR mutation status.

The data source for patients with first-line treatment mCRPC in the CAPTURE trial included the PROREPAIR-B trial (NCT03075735; a start date of January 2013 and actual completion date of December 2018), the PROSTAC trial (NCT02362620; a start date of May 2014 and estimated completion date of December 2020), the PROSABI trial (NCT02787837; a start date of May 2014 and estimated completion date of December 2020), and the PROSENZA trial (NCT02922218; a start date of June 2016 and estimated completion date of December 2020).[57]

Figure 6: Schema of the CAPTURE Study [Redacted]

HRR = homologous recombination repair; LPC = localized prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; PCa = prostate cancer.

Source: Protocol of the CAPTURE study.[57]

ITC Design

Objectives

The objective of the unanchored MAIC was to determine the efficacy and safety of niraparib and abiraterone acetate with prednisone relative to other therapies in addition to placebo and abiraterone acetate with prednisone for the treatment of first-line adult patients with mCRPC and *BRCA* gene alterations.

Study Selection Methods

A systematic literature review of RCTs investigating niraparib and abiraterone acetate and other potentially relevant treatments was conducted by the sponsor. Details on the study selection criteria and methods are shown in Table 16. In total, 32 RCTs were identified. An assessment evaluating the feasibility of conducting an ITC with data from these trials was carried out.

Table 16: Study Selection Criteria and Methods for ITC Submitted by the Sponsor

Characteristics	Indirect comparison
Population	• Males (age ≥ 18 years) with mCRPC (including those who may have been treated previously with novel hormone therapy, chemotherapy, androgen deprivation therapy, and first-generation antiandrogens) • Excluded if the patient population was children, healthy volunteers, patients with only noncancerous prostate disease (such as benign prostatic hyperplasia), patients with malignancies other than prostate cancer, patients with localized or locally advanced prostate cancer, biochemical recurrence, hormone-sensitive or nonmetastatic prostate cancer (including nmCRPC), patients with metastatic prostate cancer who had not received prior endocrine manipulation

Intervention and/or comparator	• Antiandrogens:
	  ◦ apalutamide + abiraterone acetate with prednisone
	  ◦ abiraterone acetate with prednisone
	  ◦ enzalutamide
	  ◦ darolutamide
	• PARP inhibitor (monotherapy and combination therapy):
	  ◦ talazoparib
	  ◦ rucaparib
	  ◦ pamiparib

Characteristics	Indirect comparison
	◦ niraparib ◦ olaparib + abiraterone acetate with prednisone ◦ talazoparib + enzalutamide ◦ pembrolizumab + olaparib ◦ olaparib + radium-223 ◦ fluzoparib • Corticosteroids: ◦ prednisone or prednisolone • Radiopharmaceuticals: ◦ radium-223 (Xofigo) ◦ Lu-PSMA-617 • Chemotherapy: ◦ docetaxel ◦ cabazitaxel ◦ carboplatin • Immunotherapy: ◦ sipuleucel-T ◦ durvalumab ◦ tremelimumab ◦ denosumab ◦ nivolumab ◦ pembrolizumab ◦ ipilimumab ◦ autologous dendritic cell immunotherapy • Tyrosine kinase inhibitor: ◦ masitinib • AKT inhibitor: ◦ ipatasertib • Other non-PARP inhibitor combination therapy: ◦ ipatasertib + abiraterone acetate + prednisone ◦ isatuximab + cemiplimab ◦ durvalumab + tremelimumab ◦ cabozantinib + atezolizumab • Androgen receptor antagonist: ◦ rezvilutamide • Best supportive care • Placebo
Outcome	**Efficacy outcomes** • PFS (rPFS and other PFS [e.g., clinical, biochemical]) • PFS2 • OS

Characteristics	Indirect comparison
	• Time to symptomatic skeletal-related event or TSP (e.g., bone fracture or EBRT) • TPSAP • TPP • Time to chronic opioid use • TCC • Time to initiation of subsequent therapy **Harms outcomes** • Total number of patients with discontinuations • Treatment discontinuation due to AEs • Total all-cause AEs and SAEs • Total treatment-related AEs and SAEs • Individual AEs of interest such as hypertension, rash, cognitive or memory impairment, ischemic heart disease, fatigue, hepatotoxicity, fall, fracture, edema, hypokalemia, arrhythmia, cardiac failure, and so on **Patient-reported outcomes** • Brief Pain Inventory (Short Form) • Functional Assessment of Cancer Therapy–Prostate • EQ-5D-5L
Study designs	• RCTs (open-label extensions and post hoc analyses) • Single-arm interventional trials
Databases searched[a]	**Electronic literature database (via Ovid.com)** • Embase • MEDLINE and MEDLINE In-Process • Cochrane Database of Systematic Reviews • Cochrane Central Register of Clinical Trials **Conference** • American Society of Clinical Oncology Annual Meeting • American Society of Clinical Oncology Genitourinary Cancers Symposium • American Urological Association Annual Meeting • European Association of Urology Annual Congress • European Cancer Organisation, Congress • European Society for Medical Oncology Congress • American Association for Cancer Research Annual Meeting • European Multidisciplinary Congress on Urological Cancers • Advanced Prostate Cancer Consensus Conference **Other** • The bibliography list of relevant systematic literature reviews and meta-analyses identified by the database searches (published since 2017) • ClinicalTrials.gov
Selection process	Articles were screened and selected by 2 independent researchers. Any discrepancies were resolved via a third reviewer.

Characteristics	Indirect comparison
Data extraction process	Data were extracted by 1 reviewer and validated by a second senior reviewer. Any discrepancies were resolved through a third senior reviewer.
Quality assessment	All included RCTs that were reported in a full-text publication were assessed using the Cochrane Risk of Bias 2 assessment tool.[58] The assessment was performed by 1 reviewer and validated by a second senior reviewer.

AE = adverse event; EBRT = external beam radiotherapy; mCRPC = metastatic castration-resistant prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer; OS = overall survival; PARP = poly-(ADP [adenosine diphosphate]-ribose) polymerase; PFS = progression-free survival; PFS2 = progression-free survival on first subsequent therapy; RCT = randomized controlled trial; rPFS = radiographic progression-free survival; SAE = serious adverse event; TCC = time to initiation of cytotoxic chemotherapy; TPP = time to pain progression; TPSA = time to prostate-specific antigen progression; TSP = time to symptomatic progression.

[a]The latest literature search was conducted on March 14, 2023.

Source: Sponsor's indirect treatment comparison report.[17]

ITC Analysis Methods

It was determined by the sponsor that neither a network meta-analysis nor an anchored MAIC with identified RCTs was feasible due to high between-study heterogeneity or lack of a common comparator. Only an unanchored MAIC using IPD from the MAGNITUDE trial and IPD from the CAPTURE study (i.e., a retrospective observational database study that involved the Spanish patient population with first-line treatment mCRPC)[57] was potentially feasible after examining patient populations (including eligibility criteria and baseline characteristics), interventions, and comparators, as well as outcomes (e.g., definitions, frequency of assessment) between the *BRCA* populations from the MAGNITUDE trial and those from the CAPTURE study.

In the unanchored MAIC, the population selected from the MAGNITUDE trial was the patient subgroup with mCRPC and *BRCA1* or *BRCA2* mutations. Based on different eligibility criteria, 3 populations were selected from the CAPTURE study, including:

- patients with first-line treatment mCRPC and *BRCA1* or *BRCA2* mutations (scenario 1)
- patients with first-line treatment mCRPC and *BRCA1* or *BRCA2* mutations, and having an ECOG PS of 1 or less (scenario 2)
- patients with first-line treatment mCRPC and *BRCA1* or *BRCA2* mutations, having an ECOG PS of 1 or less, having an absolute neutrophil count of 1.5 or greater multiplied by 10^9/L, having hemoglobin of 9.0 g/dL or greater and being independent of transfusions for at least 30 days, having serum albumin of 3.0 g/dL or greater, having creatinine clearance of 30 mL per minute or greater, and having serum total bilirubin of 1.5 or less multiplied by the upper limit of normal (ULN) or direct bilirubin of 1 or less multiplied by the ULN (scenario 3).

In the unanchored MAIC, niraparib and abiraterone acetate with prednisone from the MAGNITUDE trial was compared with 3 treatments from the CAPTURE study, including enzalutamide only (160 mg once daily as continuous); a physician's choice of either abiraterone acetate, cabazitaxel, docetaxel, or enzalutamide; and novel hormone therapy which referred to abiraterone, enzalutamide, darolutamide, or apalutamide.

The following issues were of note:

- Although the scenario 2 and scenario 3 populations were more similar to the patient cohort from the MAGNITUDE study, evidence in these 2 populations was not presented by CADTH because the additional restriction criteria in these 2 populations were not specified in the proposed indication for reimbursement, and because there was a lack of information regarding the 2 scenario populations. For example, the number of patients in the scenario 2 and scenario 3 populations was not even reported.
- Evidence regarding the comparators — a physician's choice of either abiraterone acetate, cabazitaxel, docetaxel, or enzalutamide and novel hormone therapy — was not presented or appraised in the CADTH reimbursement review because these 2 comparators were referring to a group or category of treatments considered to be noninformative for the CADTH reimbursement review.

Table 17: List of Treatment Effect Modifiers and Prognostic Factors Identified by the Sponsor

Effect modifiers	Prognostic factors
• *BRCA1* mutation status • *BRCA2* mutation status • Concurrent prednisone use (with docetaxel) • Line of therapy • Eastern Cooperative Oncology Group Performance Status score • Previous treatment • Presence of visceral metastases • Pain	• Age • Albumin • Alkaline phosphatase • Creatinine • Eastern Cooperative Oncology Group Performance Status score • Gleason score • Hemoglobin • Lactate dehydrogenase • Presence of metastases, bone • Presence of metastases, liver • Presence of metastases, visceral • Neutrophil count • Pain • Prior antiandrogen therapy • Prior chemotherapy • Prostate-specific antigen • Testosterone • Tumour-nodes-metastasis score

Source: Sponsor's indirect treatment comparison report.[17]

The sponsor identified a list of treatment effect modifiers and prognostic factors from literature (Table 17). From those reported in both the MAGNITUDE study and the CAPTURE study, 9 effect modifiers and prognostic factors were selected for weighting adjustment by the clinical experts consulted by the sponsor and shown as follows (ordered by rank of adjustment importance):

1. alkaline phosphatase (≤ ULN, > ULN)

2. lactate dehydrogenase (≤ ULN, > ULN)
3. age
4. baseline ECOG PS (0, 1)
5. number of bone lesions at baseline (≤ 10, > 10)
6. metastasis stage M1 at diagnosis (yes, no)
7. baseline PSA (log)
8. Gleason score at initial diagnosis (≤ 7, > 7)
9. presence of visceral metastasis (yes, no).

The rank of adjustment importance of each covariate was determined by a combination of opinions of clinical experts consulted by the sponsor, by its association with treatment assignment, and by its association with the outcome. The association between each covariate and treatment assignment was assessed in a univariate logistic regression model, where treatment was regressed against each covariate separately.

The propensity scores were determined with a logistic regression model fitted to the combined MAGNITUDE and CAPTURE study data, where treatment was regressed against the main effects of included covariates. Three assumptions were evaluated to determine the valid use of propensity score, including the positivity assumption (which required all participants to be eligible to receive niraparib and abiraterone acetate with prednisone or the relevant comparators), the overlap assumption (which required the distributions of propensity scores between the niraparib and abiraterone acetate with prednisone and comparator groups to be similar), and the balance assumption (which required the populations of the niraparib and abiraterone acetate with prednisone and comparator groups to be sufficiently balanced). To assess the positivity assumption, all patients were assessed to determine if they were contraindicated to niraparib and abiraterone acetate with prednisone or the comparators. Histograms and density plots were visually inspected to evaluate the overlap assumption. Covariate balance was assessed via the change in SMD between the niraparib and abiraterone acetate with prednisone and comparator groups before and after adjustment; SMDs greater than 0.2 were indicative of unacceptable balance.

For each scenario and treatment comparator, base-case analyses (i.e., covariates number 1 to number 6 were adjusted) and sensitivity analyses (i.e., covariates number 1 to number 9 were adjusted) in combination with different methods dealing with missing data (i.e., simple imputation or complete case analysis) were carried out. In other words, the sponsor carried out base-case adjustment with simple imputation (presented as primary analysis by the sponsor), base-case adjustment with complete case analysis, sensitivity adjustment with simple imputation, and sensitivity adjustment with complete case analysis. Additionally, an analysis without adjustment of any covariate was also conducted.

OS, rPFS (by BICR), time to PSA progression, time to second progression on next line (progression-free survival on first subsequent therapy), time to subsequent therapy, and time to treatment discontinuation were used to determine the relative efficacy or safety. The comparative effectiveness was summarized as HR (95% CI). The summary of outcomes measured in the MAGNITUDE trial and the CAPTURE trial database

were presented in Table 18. The HR was estimated using a weighted Cox proportional hazards model, where the coefficient of the treatment coefficient informed the log-HR of niraparib and abiraterone acetate with prednisone versus the comparator. The corresponding standard error (SE) was estimated using a robust sandwich variance estimator to account for the uncertainty in the weights. A log-rank test was also conducted to test the null hypothesis that there was no difference in the survival observed between the niraparib and abiraterone acetate with prednisone and comparator groups.

Table 18: Summary of Outcomes Measured in MAGNITUDE and CAPTURE Studies

Outcome	MAGNITUDE study	CAPTURE study
OS		
Outcome definition	Time from date of randomization to date of death from any cause	Time from the baseline date to date of death from any cause. Patients who are alive at the date of last follow-up will be censored at this time.
rPFS		
Soft tissue lesion criteria	RECIST 1.1	RECIST 1.1
Bone lesion criteria	PCWG3	PCWG2
Assessor	• BICR • Investigator	BICR
Outcome definition	Time from randomization date to date of radiographic progression or death, whichever occurs first	Time from the baseline date to the date of radiographic progression or death from any cause, whichever occurs first[a]
Frequency of assessment	Baseline, week 9, week 17, week 25, and every 12 weeks thereafter	Every 8 weeks to 12 weeks during the first 6 months, and every 12 weeks thereafter
Time to treatment discontinuation		
Outcome definition	Time from treatment commencement to the date of treatment discontinuation due to any cause, including death	Time from the date of first dose to the date of last dose or discontinuation of the treatment regimen or death. Patients who did not stop treatment of the testing regimen at the time of the analysis were censored on last follow-up or known alive date.

BICR = blinded independent central review; OS = overall survival; PCWG2 = Prostate Cancer Working Group 2; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1; rPFS = radiographic progression-free survival.

[a]The exact definition of disease progression (and therefore rPFS) may vary across data sources and studies included in the CAPTURE trial.

Source: Sponsor's indirect treatment comparison report.[17]

Summary of Included Studies

The distribution of baseline characteristics before and after weighting the scenario 1 population (i.e., patients, selected from the CAPTURE study, with first-line treatment mCRPC and *BRCA1* or *BRCA2* mutations) is provided in Table 19. After weighting, characteristics such as age, baseline PSA, the Gleason score at initial diagnosis, and the presence of visceral metastases in the base-case analysis were still unbalanced between the MAGNITUDE study population and the CAPTURE study population.

Results

The median follow-up time for patients in the MAGNITUDE trial was 26.8 months while in the CAPTURE trial, the median follow-up time was 25.2 months. Efficacy and safety results from the primary analyses (i.e., base-case adjustment with simple imputation) in the scenario 1 population (i.e., patients, selected from the CAPTURE trial, with first-line treatment mCRPC and *BRCA1* or *BRCA2* mutations) are presented in Table 20. The results of all sensitivity analyses (data not shown) in the scenario 1 population favoured niraparib and abiraterone acetate with prednisone over comparators, with the majority showing statistical significance.

Overall Survival

The HR for OS among patients receiving enzalutamide only was [redacted] (Table 20). However, the Kaplan-Meier curves crossed, indicating that the proportional hazards assumption did not hold (Figure 7).

Table 19: Baseline Characteristics of MAGNITUDE and CAPTURE Studies Before and After Reweighting

Characteristic	Before adjustment			After adjustment (base-case analysis)		After adjustment (sensitivity analysis)	
	MAGNITUDE study	CAPTURE study	SMD	CAPTURE study	SMD	CAPTURE study	SMD
Niraparib and abiraterone acetate with prednisone from MAGNITUDE study (N = 113) vs. enzalutamide only from CAPTURE study (N = 19)							
ALP, %							
≤ ULN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> ULN	[redacted]	[redacted]		[redacted]		[redacted]	
LDH, %[a]							
≤ ULN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> ULN	[redacted]	[redacted]		[redacted]		[redacted]	
Age							
mean (SD)	67.89 (9.345)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of bone lesions at baseline, %							
≤ 10	68 (60.2%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 10	45 (39.8%)	[redacted]		[redacted]		[redacted]	
ECOG PS, %							
0	69 (61.1%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 to 2	44 (38.9%)	[redacted]		[redacted]		[redacted]	
Stage M1 at diagnosis, %[b]							
No	41 (36.3%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	72 (63.7%)	[redacted]		[redacted]		[redacted]	

Characteristic	Before adjustment			After adjustment (base-case analysis)		After adjustment (sensitivity analysis)	
	MAGNITUDE study	CAPTURE study	SMD	CAPTURE study	SMD	CAPTURE study	SMD
Baseline PSA (log)							
Mean (SD)	3.01 (2.15)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gleason score at initial diagnosis, %[c]							
≤ 7	24 (21.2%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 7	89 (78.8%)	[redacted]		[redacted]		[redacted]	
Presence of visceral metastases, %							
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]		[redacted]		[redacted]	

AAP = abiraterone acetate with prednisone; ALP = alkaline phosphatase; ECOG PS = Eastern Cooperative Oncology Group Performance Status; LDH = lactate dehydrogenase; M1 = metastasis stage 1; PSA = prostate-specific antigen; SD = standard deviation; SMD = standardized mean difference; ULN = upper limit of normal; vs. = versus.

Notes: Table 19 presents scenario 1, where all patients in the CAPTURE study with *BRCA* mutations were included.

SMDs with an absolute value of more than 0.2 are bolded.

Missing covariates were simply imputed in adjustments.

[a]One patient from the MAGNITUDE trial imputed to have LDH ≤ ULN, 1 MAGNITUDE patient imputed to have LDH > ULN .

[b]Three patients from the MAGNITUDE trial imputed to have "no" Stage M1 at diagnosis, 2 MAGNITUDE patients imputed to have "yes" Stage M1 at diagnosis.

[c]Six patients from the MAGNITUDE trial imputed to have Gleason score at initial diagnosis of > 7.

Source: Sponsor's indirect treatment comparison report.[17]

Table 20: Efficacy and Safety Results of the Sponsor-Submitted ITC

Outcome	Niraparib and abiraterone acetate with prednisone vs. enzalutamide	
	Niraparib and abiraterone acetate with prednisone (n = 113)	Enzalutamide only (n = 19)
OS		
Number of patients contributing to the analysis, n	113	[redacted]
Number of patients with events (%)	43 (38.05)	[redacted]
Number of patients censored (%)	70 (61.95)	[redacted]
Median, months (95% CI)	29.27 (27.70 to NE)	[redacted]
Hazard ratio (95% CI, P value)	[redacted]	
rPFS		
Number of patients contributing to the analysis, n	113	[redacted]
Number of patients with events (%)	57 (50.44)	[redacted]
Number of patients censored (%)	56 (49.56)	[redacted]
Median, months (95% CI)	19.52 (14.98 to 28.71)	[redacted]

Outcome	Niraparib and abiraterone acetate with prednisone vs. enzalutamide	
	Niraparib and abiraterone acetate with prednisone (n = 113)	Enzalutamide only (n = 19)
Hazard ratio (95% CI, P value)	[redacted]	
Time to treatment discontinuation		
Number of patients contributing to the analysis, n	113	[redacted]
Number of patients with events (%)	66 (58.41)	[redacted]
Number of patients censored (%)	47 (41.59)	[redacted]
Median, months (95% CI)	20.11 (16.56 to 22.31)	[redacted]
Hazard ratio (95% CI, P value)	[redacted]	

CI = confidence interval; ITC = indirect treatment comparison; NE = not estimable; OS = overall survival; rPFS = radiographic progression-free survival; vs. = versus.

Note: Results were obtained from the base-case model with simple imputation in the scenario 1 population, where all patients in the CAPTURE study with BRCA mutations were included.

Source: Sponsor's indirect treatment comparison report.[17]

Figure 7: Kaplan-Meier Curves of OS (Niraparib and Abiraterone Acetate With Prednisone vs. Enzalutamide, Scenario 1 Population, Base-Case Adjustment With Simple Imputation) [Redacted]

AAP = abiraterone acetate with prednisone; CI = confidence interval; Enza = enzalutamide; HR = hazard ratio; NE = not estimable; Nira = niraparib; OS = overall survival; sATT = average treatment effect on the treated in the sample; SE = standard error; vs. = versus.

Source: Sponsor's indirect treatment comparison report.[17]

Radiographic Progression-Free Survival

The HR for rPFS among patients receiving enzalutamide only was [redacted] (Table 20). The Kaplan-Meier curves are shown in Figure 8.

Time to Treatment Discontinuation

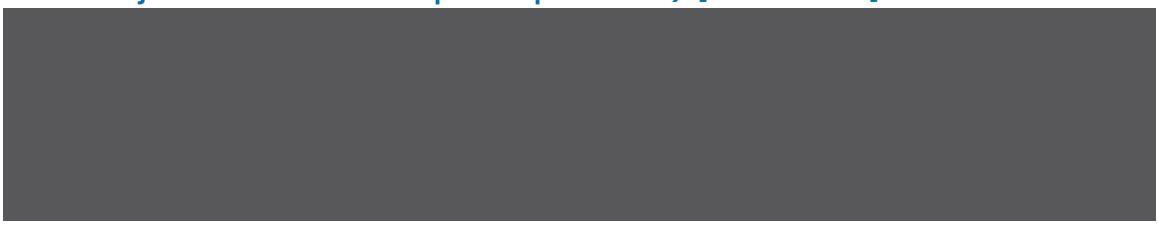
The HR (95% CI) for time to treatment discontinuation among patients receiving enzalutamide only was [redacted] (Table 20). The Kaplan-Meier curves are shown in Figure 9.

Figure 8: Kaplan-Meier Curves of rPFS (Niraparib and Abiraterone Acetate With Prednisone vs. Enzalutamide, Scenario 1 Population, Base-Case Adjustment With Simple Imputation) [Redacted]

AAP = abiraterone acetate with prednisone; CI = confidence interval; Enza = enzalutamide; HR = hazard ratio; NE = not estimable; Nira = niraparib; rPFS = radiographic progression-free survival; sATT = average treatment effect on the treated in the sample; SE = standard error; vs. = versus.

Source: Sponsor's indirect treatment comparison report.[17]

Figure 9: Kaplan-Meier Curves of Time to Treatment Discontinuation (Niraparib and Abiraterone Acetate With Prednisone vs. Enzalutamide, Scenario 1 Population, Base-Case Adjustment With Simple Imputation) [Redacted]



AAP = abiraterone acetate with prednisone; CI = confidence interval; Enza = enzalutamide; HR = hazard ratio; NE = not estimable; Nira = niraparib; sATT = average treatment effect on the treated in the sample; SE = standard error; vs. = versus.

Source: Sponsor's indirect treatment comparison report.[17]

Critical Appraisal of the Sponsor-Submitted ITC

The sponsor assessed the feasibility of conducting ITCs and determined that only an unanchored MAIC was feasible. However, CADTH noted that the ITC analysis carried out by the sponsor was not a typical unanchored MAIC based on comparing IPD from 1 study with aggregate-level data from the other study. The analysis submitted to CADTH was more like a single exposure cohort (i.e., the niraparib and abiraterone acetate with prednisone group of the MAGNITUDE study) compared with an external comparator (e.g., enzalutamide-only group from the CAPTURE study) using population adjustment methods based on IPD from both groups.

Regardless of the study design, to reduce bias in the estimation of relative effectiveness, it is essential to make the cohort of patients treated with enzalutamide comparable to the cohort of patients treated with niraparib and abiraterone acetate with prednisone in terms of patient characteristics such as prognostic and effect modifying factors. The propensity score weighting adopted by the sponsor was considered an appropriate method to adjust for patient characteristics. However, there were still concerns regarding patient comparability. First, in the sponsor-submitted ITC analysis, more than 20 potential prognostic and effect modifying factors were identified from the literature (Table 17) that were considered relevant and comprehensive by the clinical experts consulted by CADTH. However, of the identified factors, only 9 factors (6 factors adjusted for the base-case analysis and an additional 3 factors for the sensitivity analysis) were

involved in the propensity score weighting. It is understandable that many prognostic and effect modifying factors identified were not reported in the MAGNITUDE or CAPTURE trials, which made it impossible to adjust. Yet, with many relevant factors unadjusted, it is likely that the differences unaccounted for would bias the results, although the degree of the bias remains unknown. Second, the sponsor prespecified that it would be indicative of unacceptable imbalance in patient characteristics between groups if the absolute values of the SMDs between the weighted means or prevalence proportions of niraparib and abiraterone acetate with prednisone and comparator groups were greater than 0.2. After adjustment in the base-case analysis, the absolute values of the SMDs greater than 0.2 were identified for several prognostic factors such as age (SMD = 0.269), baseline PSA (SMD = 0.250), Gleason score at initial diagnosis (SMD = 0.460), and the presence of visceral metastases (SMD = 0.513), which suggested the existence of insufficient balance. Third, the sponsor attempted to use results from the scenario 2 and scenario 3 populations, which were more similar to the patient cohort from the MAGNITUDE study in terms of patient characteristics, to corroborate the findings from the scenario 1 population. However, evidence generated from these 2 scenario populations was not considered informative due to a lack of information (e.g., the number of patients in the scenario 2 and scenario 3 populations was not even reported).

There were other concerns that also increased CADTH's uncertainty on the ITC estimates. First of all, the extent to which the discrepancy in the definitions of disease progression between the MAGNITUDE and CAPTURE studies would impact the ITC estimates was unclear (Table 18). The sponsor stated that "(t)he exact definition of disease progression (and therefore rPFS) may vary across data sources and studies included in CAPTURE" but "there are no meaningful differences in the definitions and assessments used in MAGNITUDE and CAPTURE that would lead to considerable bias in an ITC."[17] However, due to a lack of information, the potential bias due to differences in outcome definitions could not be ruled out. In addition, the sponsor-submitted ITC did not provide clear information on whether data from the CAPTURE trial was temporally relevant to the data from the MAGNITUDE trial. For instance, 1 data source of the CAPTURE study for the enzalutamide-only group (i.e., the PROSENZA study) started on June 2016 and was expected to be completed in December 2020 (no update on the ClinicalTrials.gov website has appeared since January 2020), while the MAGNITUDE trial started in February 2019 and is expected to be complete in 2027. The clinical experts consulted by CADTH noted that in the enzalutamide-only group, the proportion of patients with OS events (93.35% [18 of 19] of patients) or rPFS events (89.7% [17 of 19] of patients) was higher than 1 would find in clinical practice in recent years. In other words, the prognosis (e.g., survival) of the patients with mCRPC has been improving over time, according to the clinical experts consulted by CADTH. As a result, due to the potential difference in time periods between the MAGNITUDE and CAPTURE studies, it was possible that the treatment effect of enzalutamide was underestimated. Similarly, the discrepancy in geographic regions between the MAGNITUDE study (26 countries) and the CAPTURE study (1 country only [Spain]) might also result in biased ITC estimates due to the potential differences in the pattern of care and other factors (e.g., access to care) across regions. Finally, there was no assessment or discussion provided in the ITC report with respect to treatment-related factors (e.g., treatment adherence, concomitant treatments) in the MAGNITUDE and CAPTURE trials, which might threaten the validity of the treatment estimates of the ITC.

Lastly, findings from the ITC focused on the comparison between niraparib and abiraterone acetate with prednisone versus enzalutamide in the first-line treatment setting only. Therefore, there remains a gap in the indirect comparative evidence related to later lines of therapy.

Studies Addressing Gaps in the Systematic Review Evidence

No studies addressing gaps in the systematic review evidence were submitted by the sponsor.

Discussion

Summary of Available Evidence

The evidence included in this review consisted of 1 pivotal phase III, double-blind RCT and 1 ITC submitted by the sponsor.

One trial, the MAGNITUDE study (N = 423), met the inclusion criteria for the systematic review conducted by the sponsor, and a subgroup of patients in cohort 1 of the MAGNITUDE trial who had *BRCA* mutation (N = 225) enrolled in the study. The objective of the MAGNITUDE trial was to evaluate the efficacy and safety of niraparib and abiraterone acetate with prednisone versus placebo and abiraterone acetate with prednisone in adult patients with mCRPC who had not received prior systemic therapy in the mCRPC setting except for androgen deprivation therapy and had a potentially limited exposure (≤ 4 months) to abiraterone acetate with prednisone. Eligible patients were randomized to receive niraparib 200 mg and abiraterone acetate 1,000 mg with 10 mg prednisone taken orally once daily, or placebo and abiraterone acetate 1,000 mg with prednisone 10 mg daily administration. The primary outcome was rPFS assessed by BICR, and secondary outcomes were OS, TSP, and safety. HRQoL measured by the FACT-P questionnaire was assessed as an exploratory outcome. Despite randomization, there were some baseline patient characteristics that were imbalanced between treatment groups, including the metastasis stage at initial diagnosis, Gleason score at initial diagnosis, and ECOG PS score at baseline. The population was predominately white (72%), with an approximate mean age of 68 years. Most patients had a tumour stage of T3 and a Gleason score of 8 or more (69.2%). A similar proportion of patients in both groups had prior prostate cancer therapy, in which hormone therapy was the most common therapy (approximately 95%), followed by surgery (approximately 63.6%).

The sponsor-submitted ITC provided comparative evidence of niraparib and abiraterone acetate with prednisone versus enzalutamide. The analysis used IPD from patients with mCRPC treated with niraparib and abiraterone acetate with prednisone in the MAGNITUDE pivotal trial (N = 113) with the IPD from patients with mCRPC treated with first-line enzalutamide in the CAPTURE observational study (N = 19). Patients from the CAPTURE study were reweighted using propensity score weighting in an attempt to match the distribution of patient characteristics of the patient cohort from the MAGNITUDE study. Outcomes presented in the analysis included OS, rPFS, and time to treatment discontinuation.

Interpretation of Results

Efficacy

Preventing or delaying disease progression as well as prolonging life were identified as being important to patients. OS and rPFS were captured in the MAGNITUDE study, which corresponds with these patient needs. Managing symptoms that affect patients' HRQoL and reducing skeletal pain were also highlighted by patient group input. In the MAGNITUDE trial, these outcomes were assessed by TSP, TPP, and FACT-P.

Outcomes assessed at given time points for OS, rPFS, TSP, TPP, and HRQoL (FACT-P total score) were mostly affected by concerns for imprecision (i.e., the 95% CIs crossed a threshold of clinical important benefit to include the potential for both benefit and harm) and study limitation (e.g., imbalanced baseline characteristics between the 2 treatment groups). As of the second interim analysis, there was no difference between the treatment groups for OS ([stratified HR = 0.88; 95% CI, 0.58 to 1.33] and [adjusted HR = 0.68; 95% CI, 0.44 to 1.04]). An empirically validated MID for OS has not been submitted to CADTH, but clinical experts suggested the clinical importance threshold of a 5% absolute difference between groups for OS rates at 12 months and 24 months. The probability of OS at 12 months was 84.1% for the niraparib and abiraterone acetate with prednisone group compared with 83.9% for the placebo and abiraterone acetate with prednisone group, with a 0.2% difference. The difference between the 2 groups for the probability of OS at 24 months was 9%, with a 95% CI that included both harm and benefit. It was noted that the OS results are still likely immature since they were based on 2 interim analyses and not on the final clinical cut-off. Health Canada issued a Notice of Compliance with conditions in part because of the immature nature of the OS data, although the regulator only had the results from the first interim analysis for its review. The Health Canada review report states the following: "…at Interim Analysis 1 with a *BRCA* subgroup specific OS HR = 0.96 [95% CI: 0.57, 1.63]), where the upper bound of the 95% CI exceeded 1. Given the uncertainty in the magnitude of survival benefit in the overall *BRCA* population, a Notice of Compliance with Conditions QN was recommended."[59] Despite the additional follow-up time included with the second interim analysis (from median 18.6 months to 24.8 months) for this reimbursement review, there remains a low degree of certainty regarding the OS effects of treatment with niraparib and abiraterone acetate with prednisone versus placebo and abiraterone acetate with prednisone at both 12 months and 24 months. The 95% CI for the HR for OS between niraparib and abiraterone acetate with prednisone versus placebo and abiraterone acetate with prednisone was wide and the upper limit still crossed 1 at the later time point. Therefore, there is considerable imprecision in the OS estimates. The clinical experts consulted by CADTH agreed that there was a high degree of uncertainty in the OS estimates and that a longer follow-up time for the outcome is needed.

The MAGNITUDE trial determined that niraparib and abiraterone with prednisone were superior to placebo and abiraterone acetate with prednisone for the primary outcome of rPFS, particularly in the *BRCA* subgroup. The stratified HR for rPFS at the second interim analysis was 0.553 (95% CI, 0.392 to 0.782) in favour of niraparib and abiraterone acetate with prednisone, with a median of nearly 20 months versus 11 months for the placebo and abiraterone acetate with prednisone group. The difference in probabilities of being event-free for rPFS between the 2 treatment groups was [redacted] at 12 months and at 24 months, respectively. An

empirically validated MID for absolute differences in rPFS has not been submitted to CADTH. The clinical experts consulted by CADTH suggested the clinical importance threshold of rPFS could be a 25% difference between groups, although they were uncertain what the exact threshold of clinical importance would be. Based on using the null as a threshold, CADTH determined there was moderate certainty for clinical benefit in rPFS at 12 months and 24 months when comparing niraparib and abiraterone acetate with prednisone to placebo and abiraterone acetate with prednisone. Since any potential bias arising from the imbalances in baseline characteristics would go toward the null according to the clinical experts consulted by CADTH, and considering that the findings showed benefit for rPFS, there was less concern with regard to risk of bias. The GRADE assessment of the evidence demonstrated niraparib and abiraterone acetate with prednisone likely increases rPFS at both 12 months and 24 months compared to placebo and abiraterone acetate with prednisone, although the clinical importance of the difference between the groups is unknown. Furthermore, the clinical importance of rPFS as an outcome was unclear. The clinical experts consulted by CADTH indicated that rPFS is not an ideal primary outcome to assess efficacy of new treatments for mCRPC in terms of clinical practice, due to the emphasis on radiographic results to define disease progression. The clinical expert reported that in regular practice, disease progression is assessed using a combination of biochemical, symptom, and radiological assessments.

Furthermore, it is unclear if benefits in rPFS would translate into improvements in OS. For many new drugs that reported improvement in progression-free survival, further analysis has demonstrated no improvement in OS.[60] On the other hand, some studies have reported the correlation coefficient between rPFS and OS ranges from 0.72[54] to 0.3 between progression-free survival and OS in patients with mCRPC,[61] which demonstrates inconsistent evidence on establishing the relationship between OS and rPFS. Therefore, CADTH reviewers concluded the association between rPFS and OS was difficult to interpret at the time of this review. This is due to different factors, including the varying definitions of rPFS used, the relatively short follow-up periods used for the comparisons, and a lack of prospective evidence. The clinical experts agreed that given the advancements in therapies and understanding of the natural history of prostate cancer, OS remains the most clinically relevant outcome.

Although Health Canada indicated that the primary efficacy results were supported by results suggesting TSP favoured niraparib and abiraterone acetate with prednisone,[59] there was low certainty for an increase in TSP at 12 months, and the evidence was very uncertain about the effect of niraparib and abiraterone acetate with prednisone on TPP at 12 months in comparison to placebo and abiraterone acetate with prednisone. A serious risk of bias due to a lack of balanced baseline characteristics between the 2 groups and concern for serious imprecision due to the 95% CI encompassing both important harm and important benefit decreased the certainty of the results. The clinical experts noted that differences between the 2 groups was not likely clinically meaningful for TSP and TPP; however, they considered the results for TSP and TPP to align with the direction of the results for the primary outcome (i.e., rPFS).

HRQoL was assessed based on the least squares mean change from baseline in the FACT-P total score. The trials demonstrated a trivial difference between the 2 groups in FACT-P total score at cycle 25. The established MID in the literature for the FACT-P total score is 10.[52] Hence, certain concerns arose regarding risk of bias due to the presence of imbalanced baseline characteristics and relatively wide 95% CIs that

crossed the null effect. These factors led to a downgrade of the certainty of evidence to moderate. The HRQoL outcomes were exploratory and as such, this evidence cannot support firm conclusions for this end point.

One concern noted by clinical experts consulted by CADTH was that the exclusion criteria might be restrictive and exclude a large number of patients in the mCRPC setting. Niraparib and abiraterone acetate with prednisone or prednisolone has a Health Canada–approved indication "for the treatment of adult patients with deleterious or suspected deleterious *BRCA* mutated (germline and/or somatic) mCRPC, who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated."[39] The participating drug programs and the CADTH review team identified potential gaps and implementation challenges related to the evidence from the MAGNITUDE trial versus the population of patients included in the approved indication. First, CADTH noted that the indication is line-agnostic, whereas no patients in the MAGNITUDE trial had received prior systemic therapy in the mCRPC setting (i.e., study treatment was first-line in this setting). As a result, there was no direct comparative evidence for the use of niraparib and abiraterone acetate with prednisone in the second-line, third-line, and later-line settings. Second, the clinical experts consulted by CADTH noted that determining whether a patient is mildly symptomatic is a subjective clinical decision and likely varies between clinicians and patients. Lastly, the clinical experts consulted by CADTH noted that it may be challenging to identify patients in whom chemotherapy is not clinically indicated. According to Health Canada, the "in whom chemotherapy is not clinically indicated" component of the indication is defined based on the clinical judgment of the treating physician, and this component of the indication was included to reflect the exclusion criteria of the MAGNITUDE study, which prohibited any prior chemotherapy in the mCRPC setting. However, the clinical experts consulted by CADTH noted that, in current practice, any patient who is well enough to receive cytotoxic chemotherapy would be considered clinically indicated for that type of treatment, but that chemotherapy may not be the patient's therapy of choice. The clinical experts noted that if patients are not well enough to receive chemotherapy, they also may not be well enough to receive treatment with a PARP inhibitor such as niraparib. Overall, the clinical experts reported that there is no clear definition to identify patients in whom chemotherapy is not clinically indicated in clinical practice. Both the clinical experts and Health Canada agreed that it is defined based on the clinical judgment of the treating physicians. The sponsor noted that the language "not clinically indicated for chemotherapy" in the indication was a decision made at the regulatory level. Regarding the definition, the sponsor notes that chemotherapy being not clinically indicated does not mean chemotherapy-ineligible, but rather that it is a physician's choice where the physician applies their clinical judgment to determine the right treatment option for their patient. The sponsor highlighted that the MAGNITUDE study did not specify inclusion criteria concerning chemotherapy ineligibility.

Although abiraterone acetate was an appropriate comparator when the MAGNITUDE trial was designed and started recruitment, the clinical experts highlighted that the treatment paradigm has substantially shifted since then toward the use of chemotherapy as the most common first-line treatment for patients with mCRPC. However, the evidence comparing niraparib and abiraterone acetate with prednisone and chemotherapy was not included in the submission to CADTH, which represents a gap in the available evidence, given the shared place in therapy for mCRPC. Of note, the clinician group noted that the drug

under review would become a SOC in treatment-naive patients with mCRPC. In contrast, the clinical experts consulted by CADTH noted that while niraparib and abiraterone acetate with prednisone is used in patients with mCRPC who have been treated with enzalutamide, apalutamide, and darolutamide in the mCSPC setting, many medical oncologists would favour a change to chemotherapy for the first-line mCRPC in patients progressing on an ARPi. Therefore, the clinical experts indicated that niraparib and abiraterone acetate with prednisone would be positioned as a second-line and beyond treatment due to the decreasing number of patients who are ARPi-naive and considering the current evidence that does not show an improvement in OS or disease-specific outcomes. In contrast, clinician group input noted that niraparib and abiraterone acetate with prednisone would become a SOC in treatment-naive patients with mCRPC with HRR mutation, although the CADTH review team noted that the Health Canada–approved indication is for patients with *BRCA* mutations only. The CADTH review team notes that differences in the clinical expert input and clinician group input signals that there could be regional differences in clinical practice across Canada.

Findings from the sponsor-conducted ITC were considered of high uncertainty due to several limitations. First, as discussed in the Critical Appraisal of the Sponsor-Submitted ITC section, there was a comparability concern between the cohort of patients treated with enzalutamide only from the CAPTURE trial and the cohort of patients treated with niraparib and abiraterone acetate with prednisone from the MAGNITUDE trial. Second, the Kaplan-Meier curves for OS, which was considered as the most clinically relevant end point for patients with mCRPC, signalled that the proportional hazards assumption was violated, and no further analyses addressing the nonproportional hazard issue were found. Third, there was a lack of information in the sponsor-submitted ITC report for CADTH to determine, for example, whether the discrepancy in the definitions of disease progression (and therefore rPFS) between the MAGNITUDE and CAPTURE studies would impact the ITC estimates and whether data from the CAPTURE study was temporally relevant to the data from the MAGNITUDE study.

Harms

The overall frequency of TEAEs was different between the niraparib and abiraterone acetate with prednisone group and the placebo and abiraterone with prednisone group in the MAGNITUDE trial. Almost all patients experienced at least 1 TEAE in both treatment groups, with the most frequently reported TEAEs being anemia, constipation, hypertension, and nausea. A greater proportion of patients in the niraparib and abiraterone acetate with prednisone group experienced grade 3 or grade 4 AEs compared to those in the placebo and abiraterone acetate with prednisone group (68% versus 51%, respectively).

The frequency of deaths was nearly 12% in the niraparib and abiraterone acetate with prednisone group and 8% in the placebo and abiraterone with prednisone group; the majority of deaths in both groups was attributed to disease progression. Likewise, the frequencies of SAEs and WDAEs was approximately 2 to 3 times higher with the niraparib and abiraterone acetate with prednisone group than the placebo and abiraterone acetate with prednisone group. Assessment of the certainty of evidence also revealed it is likely that niraparib and abiraterone acetate with prednisone results in an increase in the proportion of patients who experience WDAEs and SAEs. There are a number of serious warnings and precautions in the Health Canada product monograph,[39] some of which were considered as notable harms in the CADTH review,

including anemia, hypertension, fatigue, thrombocytopenia, asthenia, and fluid retention. In addition, the frequency of all notable harms was higher in the niraparib and abiraterone acetate with prednisone group. The patient groups that provided input for this review highlighted that there is a need for reducing side effects with treatments for mCRPC. However, the MAGNITUDE study harms results suggest that niraparib and abiraterone acetate with prednisone results in more clinically important AEs compared to placebo and abiraterone acetate with prednisone since a higher incidence of TEAEs, grade 3 or grade 4 AEs, SAEs, deaths, AEs leading to treatment discontinuation, and notable harms were reported with the niraparib and abiraterone acetate with prednisone group. This also signals a likely increase in the resources required to manage the AEs.

In the ITC, time to treatment discontinuation was defined in the MAGNITUDE trial as "time from treatment commencement to the date of treatment discontinuation due to any cause including death," while it was defined in the CAPTURE trial as "time from the date of first dose to the date of the last dose/discontinuation of the treatment regimen or death." Given that 18 of 19 patients in the enzalutamide group had OS events, there was only 1 patient who discontinued enzalutamide due to reasons other than death. However, the results showed that 43 of 113 patients in the niraparib and abiraterone acetate with prednisone group had OS events while 66 patients discontinued treatment due to any cause, including death, which indicated that 23 additional patients discontinued treatment due to nonfatal reasons. Therefore, due to a lack of further information, evidence regarding time to treatment discontinuation remained highly uncertain. Overall, there was a great deal of uncertainty as to the comparative safety of niraparib and abiraterone acetate with prednisone versus other treatments for mCRPC beyond what was observed in the MAGNITUDE trial.

Conclusion

mCRPC is an advanced stage of prostate cancer, and there is an unmet need for new treatments to prolong life, prevent disease progression, improve HRQoL, and reduce AEs. The MAGNITUDE trial is an ongoing, double-blind, phase III RCT, evaluating the efficacy and safety of first-line treatment with niraparib and abiraterone acetate with prednisone in patients with mCRPC. The trial did not demonstrate a benefit with niraparib and abiraterone acetate with prednisone compared to placebo and abiraterone acetate with prednisone on OS or HRQoL, which were identified as important outcomes by patients and clinical experts. Moderate certainty of evidence shows niraparib and abiraterone acetate with prednisone likely resulted in an increase in rPFS when compared with placebo and abiraterone acetate with prednisone; however, the clinical importance of this difference was uncertain. Results for TSP and TPP suggested that niraparib and abiraterone acetate with prednisone were favoured over placebo and abiraterone acetate with prednisone but the results for these efficacy outcomes were affected by concerns for imprecision and limitations in the trial, such as imbalanced baseline characteristics between treatment groups. Niraparib and abiraterone acetate with prednisone appeared to be associated with a higher frequency of TEAEs, grade 3 or grade 4 AEs, SAEs, WDAEs, and notable harms compared with placebo and abiraterone acetate with prednisone. Findings from the sponsor-conducted indirect comparison with enzalutamide were considered of high uncertainty due to

several major limitations, such as the fact that many relevant prognostic and effect modifying factors were not adjusted as well as the fact that the proportional hazards assumption was likely violated for OS.

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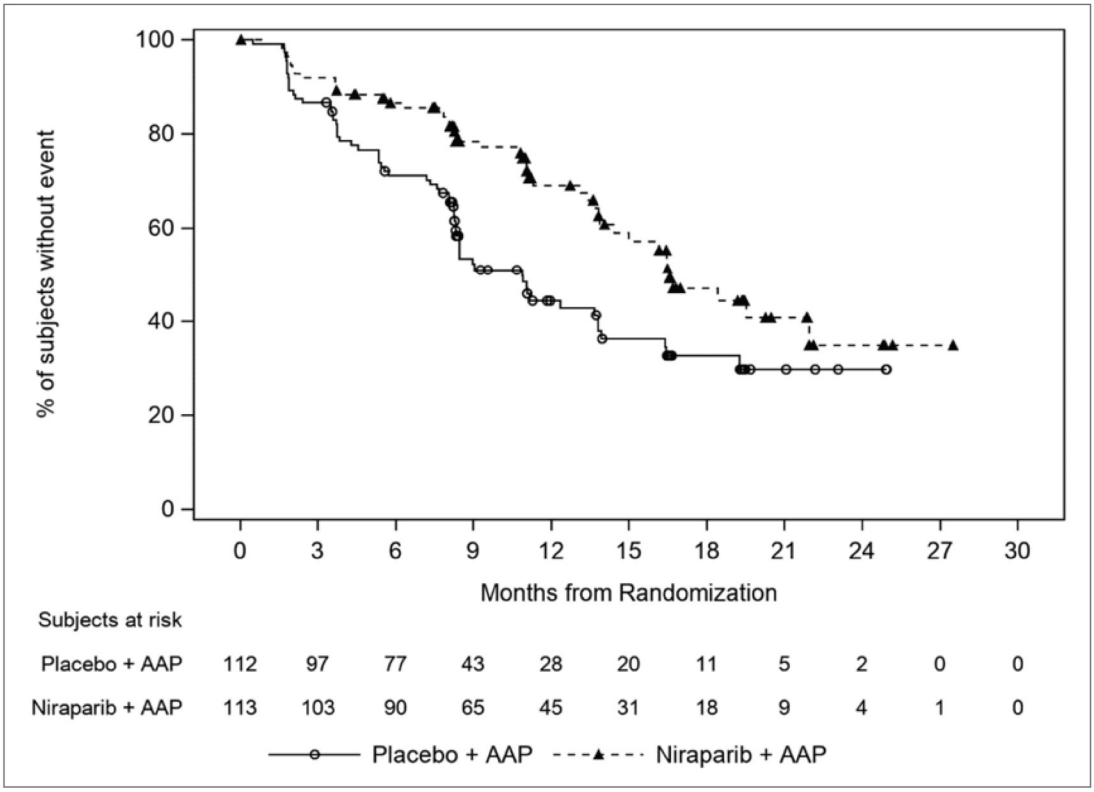
61. Halabi S, Vogelzang NJ, Ou SS, Owzar K, Archer L, Small EJ. Progression-free survival as a predictor of overall survival in men with castrate-resistant prostate cancer. *J Clin Oncol.* 2009;27(17):2766-2771. PubMed

Appendix 1: Detailed Outcome Data

Note that this appendix has not been copy-edited.

As rPFS was found to be statistically significant at first interim analysis, no formal statistical testing was performed at second interim analysis Figure 10 shows the Kaplan-Meier curves of rPFS for the cohort 1 *BRCA* subgroup at the first interim analysis.

Figure 10: Kaplan-Meier Plot of Radiographic Progression-Free Survival by Central Review — Cohort 1 *BRCA* Subgroup



AAP = abiraterone acetate plus prednisone.

Source: MAGNITUDE Second Interim Analysis Clinical Study Report.[43]

Pharmacoeconomic Review

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Abbreviations

ADT	androgen deprivation therapy
AE	adverse event
ARPi	androgen receptor pathway inhibitor
BIA	budget impact analysis
CI	confidence interval
CUA	cost-utility analysis
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
ITC	indirect treatment comparison
LY	life-year
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
OS	overall survival
PD	progressed disease
PH	proportional hazard
QALY	quality-adjusted life-year
RDI	relative dose intensity
rPFS	radiographic progression-free survival
SD	standard deviation
TTTD	time to treatment discontinuation

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Niraparib and abiraterone acetate (Akeega), 100 mg/500 mg and 50 mg /500 mg tablets
Submitted price	Niraparib and abiraterone acetate, 100 mg/500 mg: $147.10 per tablet Niraparib and abiraterone acetate, 50 mg/500 mg: $147.10 per tablet
Indication	For the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (germline and/or somatic) mCRPC who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated. Patients must have confirmation of *BRCA* mutation before niraparib and abiraterone acetate treatment is initiated.
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	June 12, 2023
Reimbursement request	As per indication
Sponsor	Janssen Inc.
Submission history	Previously reviewed: No

mCRPC = metastatic castration-resistant prostate cancer; NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with deleterious or suspected deleterious *BRCA*-mutated (germline and/or somatic) mCRPC who are asymptomatic or mildly symptomatic, and in whom chemotherapy is not clinically indicated
Treatment	Niraparib and abiraterone acetate with prednisone
Comparators	Abiraterone acetate with prednisone Enzalutamide
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (10 years)
Key data source	MAGNITUDE trial, second interim data analysis, to inform clinical efficacy of niraparib and abiraterone acetate with prednisone, and abiraterone acetate with prednisone Sponsor-conducted indirect treatment comparison to inform clinical efficacy of enzalutamide
Submitted results	• The ICER for niraparib and abiraterone acetate with prednisone compared to abiraterone acetate with prednisone was $149,066 per QALY gained (incremental costs = $136,932; incremental QALYs = 0.92).

Component	Description
	• The ICER for niraparib and abiraterone acetate with prednisone compared to enzalutamide was $131,972 per QALY gained (incremental costs = $114,894; incremental QALYs = 0.87).
Key limitations	• The sponsor modelled patients receiving first-line treatment for mCRPC. However, the indicated population for niraparib and abiraterone acetate with prednisone is line-agnostic, and thus broader than the modelled population. As such, the cost-effectiveness of niraparib and abiraterone acetate with prednisone used as a subsequent therapy is unknown. • The definition of chemotherapy eligibility in clinical practice is uncertain and based on the judgment of the treating physician rather than on consistent clinical criteria. This leads to uncertainty in cost-effectiveness in the patient population that is most likely to receive niraparib and abiraterone acetate with prednisone in Canada. • The long-term extrapolation of OS in the submitted model is uncertain and the methods used to select parametric survival curves did not align with best practices. • The relative efficacy of niraparib and abiraterone acetate with prednisone compared to enzalutamide was based on a sponsor-submitted indirect treatment comparison that was highly uncertain due to several major limitations, including patient comparability across studies, violation of the proportional hazard assumption, and outcome definitions. • Health state utility values used in the sponsor's submission lacked face validity, and methods to estimate them were not aligned with best practices. • The sponsor's selected time to treatment discontinuation distribution for abiraterone acetate with prednisone resulted in patients being treated until progression; however, niraparib and abiraterone acetate with prednisone was discontinued before progression. This resulted in patients receiving niraparib and abiraterone acetate with prednisone accruing health outcomes in the progression-free health state with no treatment cost. This introduced a bias that benefits niraparib and abiraterone acetate with prednisone. • The use of RDI estimates to calculate drug costs may underestimate the total treatment costs that would be seen in real-world clinical practice. • The health and cost outcomes associated with diagnostic tests were not adequately captured in the submitted model. The overall cost to the health care system was therefore underestimated.
CADTH reanalysis results	• To account for the identified key limitations, several changes were made to derive the CADTH base case: selecting the gamma distribution for OS for both niraparib and abiraterone acetate with prednisone and abiraterone acetate with prednisone; using the sponsor's EQ-5D-3L health state utility value from the MAGNITUDE trial for the progression-free health state; assuming that patients were treated until progression for all treatments; and removing RDI assumptions. • In the CADTH base case, the ICER for niraparib and abiraterone acetate with prednisone vs. abiraterone acetate with prednisone was $271,803 per QALY gained (incremental costs = $133,835; incremental QALYs = 0.49). A price reduction of approximately 61% would be required for niraparib and abiraterone with prednisone to be cost-effective at a $50,000 per QALY gained threshold.

ICER = incremental cost-effectiveness ratio; LY = life-year; mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; QALY = quality-adjusted life-year; RDI = relative dose intensity; vs. = versus.

Conclusions

Based on the CADTH clinical review of the MAGNITUDE trial, moderate certainty of evidence shows niraparib and abiraterone acetate with prednisone resulted in little improvement in radiographic progression-free survival (rPFS) when compared with abiraterone acetate with prednisone, although the findings are slightly below the clinically important threshold of a 25% difference suggested by clinical experts consulted by CADTH. CADTH's clinical review reported that treatment with niraparib and abiraterone acetate with

prednisone did not demonstrate a benefit in overall survival (OS) compared to abiraterone acetate with prednisone. Given the lack of direct comparative evidence, the sponsor submitted an indirect treatment comparison (ITC) using data from the CAPTURE study to estimate the relative clinical efficacy of niraparib and abiraterone acetate with prednisone versus enzalutamide. The CADTH clinical review reported that the results of this analysis were highly uncertain due to several major limitations, including patient comparability across studies, violation of the proportional hazards (PHs) assumption, outcome definitions, and the temporal relevance of the CAPTURE study.

In addition to these clinical limitations, CADTH identified several limitations with the sponsor's economic submission that could be addressed through reanalysis. For the CADTH base-case analysis, CADTH revised the assumptions about OS, which led to more plausible estimates of survival benefit; applied a more realistic health state utility value in the progression-free health state; assumed that patients were treated until progression for all treatments; and removed relative dose intensity (RDI) assumptions. In CADTH's base-case analysis, the incremental cost-effectiveness ratio (ICER) of niraparib and abiraterone acetate with prednisone compared to abiraterone acetate with prednisone was $271,803 per quality-adjusted life-year (QALY) gained (incremental costs = $133,835; incremental QALYs = 0.49). The probability of being cost-effective at a $50,000 per QALY gained threshold was 0%. For niraparib and abiraterone acetate with prednisone to be considered cost-effective at a $50,000 per QALY gained threshold compared to abiraterone acetate with prednisone, the price of niraparib and abiraterone acetate would need to be $3,213 per 28-day cycle, reflecting a price reduction of 61%. Given the limitations in the comparative clinical efficacy data for enzalutamide, a high degree of uncertainty remained in estimating the cost-effectiveness of niraparib and abiraterone acetate with prednisone versus enzalutamide. This comparison was explored through scenario analysis only.

CADTH identified key considerations regarding the alignment of the trial population, the reimbursement request, and the indicated population. First, the evidence generated by the MAGNITUDE trial was in patients receiving first-line treatment for metastatic castration-resistant prostate cancer (mCRPC), whereas the Health Canada indication does not specify treatment line. Clinical experts consulted by CADTH also indicated that a limited number of patients would meet the inclusion criteria of the MAGNITUDE trial, as they would have experienced prior exposure to abiraterone acetate with prednisone and enzalutamide in the castration-sensitive stage of their disease. In addition to the limitations in trial population alignment, there remains uncertainty regarding how "in whom chemotherapy is not clinically indicated" would be defined in clinical practice. Clinical experts consulted by CADTH noted that any patient with mCRPC fit enough for cytotoxic chemotherapy should be considered eligible for it, and that any decision that a patient is not indicated for chemotherapy is therefore based on the judgment of the treating physician rather than on consistent clinical criteria.

Consequently, CADTH was unable to estimate the cost-effectiveness of niraparib and abiraterone acetate with prednisone for the full population in which the treatment is likely to be used. CADTH's estimates of the ICER and the price reduction needed to reach cost-effectiveness at a given willingness-to-pay threshold only apply to the narrow subset of patients meeting the MAGNITUDE trial's inclusion criteria (i.e., first-line treatment in patients without prior exposure to abiraterone acetate or enzalutamide, and who had not

been previously treated with chemotherapy in the mCRPC setting). The cost-effectiveness of niraparib and abiraterone acetate with prednisone as a subsequent therapy or in patients for whom chemotherapy is clinically indicated remains unknown.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process. Patient input was received from the Canadian Cancer Society; it collected input from 24 patients and caregivers, the majority of whom were living in Canada, via an anonymous online survey. The majority of respondents (n = 21) identified as a person who has or has had mCRPC, and the remaining 3 identified as caregivers. No respondents had experience with niraparib and abiraterone acetate with prednisone. Patients with disease experience reported that they had experienced several physical and psychosocial struggles that impacted their quality of life. With regard to treatment experiences, the majority of patients had undergone 3 or more lines of therapy since their initial diagnosis with prostate cancer, with varying levels of side effects that impacted their daily life. The most common side effects reported by respondents were changes in libido, sexual function, or fertility, followed by hot flashes and fatigue. Patient input noted that there is a need for new therapies with fewer or less severe side effects.

Clinician input was received from the Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee. The clinician input highlighted that first-line therapy for mCRPC is aimed at prolonging life and maximizing quality of life given that there is no available cure. Current treatment options were noted to include abiraterone acetate, enzalutamide, docetaxel, and radium-223, all given concurrently with androgen deprivation therapy (ADT). The input noted that in treatment-naive patients with mCRPC with *BRCA* mutations, niraparib and abiraterone acetate with prednisone would become a standard of care, as there are no other combination therapies for first-line treatment of patients in this setting.

Drug plan input noted that first-line treatment of mCRPC in Canada includes abiraterone acetate with prednisone, enzalutamide, taxane-based chemotherapy (i.e., docetaxel), or radium-223 (used for a small group of patients). Drug plan input also noted that in Ontario, olaparib may be a relevant comparator used as a first-line treatment of patients with mCRPC with a *BRCA* mutation if the patient was previously treated with abiraterone acetate or enzalutamide in the nonmetastatic castration-resistant prostate cancer or metastatic castration-sensitive prostate cancer (mCSPC) setting; however, it is not currently reimbursed. Drug plan input raised questions regarding the eligibility of niraparib and abiraterone acetate with regard to defining "mildly symptomatic," and whether patients who are not clinically indicated for chemotherapy or patients who decline chemotherapy despite clinical eligibility should be considered for treatment with niraparib and abiraterone acetate.

Several of these concerns were addressed in the sponsor's model.

- The sponsor's submitted model accounted for quality of life and length of life.
- The sponsor's submitted model incorporated treatment-related adverse events (AEs).

CADTH was unable to address the following concerns raised from stakeholder input.

- The inclusion of olaparib as a comparator was not considered as it is not currently reimbursed for the relevant indication.

Economic Review

The current review is for niraparib and abiraterone acetate (Akeega) with prednisone for the treatment of adults with deleterious or suspected deleterious *BRCA*-mutated (germline and/or somatic) mCRPC who are asymptomatic or mildly symptomatic, and in whom chemotherapy is not clinically indicated.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis (CUA) comparing costs and outcomes for niraparib and abiraterone acetate with prednisone with abiraterone acetate with prednisone, and enzalutamide.[1] The model population comprised adults with deleterious or suspected deleterious *BRCA*-mutated (germline and/or somatic) mCRPC who are asymptomatic or mildly symptomatic, and in whom chemotherapy is not clinically indicated.

Niraparib and abiraterone acetate consists of niraparib, a selective poly-(ADP [adenosine diphosphate])-ribose polymerase inhibitor and abiraterone acetate, a *CYP17* inhibitor. Niraparib and abiraterone acetate is available in 2 strengths: a 100 mg niraparib/500 mg abiraterone acetate tablet or a 50 mg niraparib/500 mg abiraterone acetate tablet.[2] The recommended dose of niraparib and abiraterone acetate is 200 mg niraparib with 1,000 mg abiraterone acetate (i.e., two 100 mg/500 mg tablets) daily, to be taken with 10 mg prednisone or prednisolone. The cost per niraparib and abiraterone acetate tablet (regardless of strength) is $147.10, resulting in a daily cost of $294.20 and a corresponding annual cost of $107,457. The comparators in this analysis included abiraterone acetate with prednisone and enzalutamide, with corresponding annual per-patient costs of $11,186 and $42,654, respectively. The annual cost of prednisone is $16, to be taken with niraparib and abiraterone acetate, and abiraterone acetate. The sponsor applied RDI assumptions of 87.5% for niraparib and abiraterone acetate, 96% for abiraterone acetate, and 87.5% for enzalutamide, which resulted in the following annual treatment costs (including prednisone costs as indicated) in the submitted model: $94,039 for niraparib and abiraterone acetate, $10,754 for abiraterone acetate, and $37,323 for enzalutamide.[1]

The model used a 1-week cycle length and simulated costs, life-years (LYs), and QALYs for each treatment over a lifetime time horizon (10 years). The analysis was undertaken from the perspective of Canada's publicly funded health care system. Costs and QALYs were discounted at a rate of 1.5% per annum and a half-cycle correction was applied.[1]

Model Structure

The sponsor submitted a partitioned survival model with the following health states: progression-free, progressed disease (PD), and death (Figure 1). All patients entered the model in the progression-free state, at which time it was assumed they initiated first-line treatment for mCRPC. Patients could remain in the progression-free state or transition to the PD or death health states each cycle. Patients in the PD health state could remain in the PD state or transition to the death state. The proportion of patients who were progression-free, had PD, or were dead at any time was derived from survival extrapolations informed by rPFS and OS data from the MAGNITUDE trial and from an ITC. The proportion of patients in the PD health state was estimated as the difference between the proportion of living patients (estimated using the OS curve) and the proportion of progression-free patients (estimated from the rPFS curve).

Model Inputs

The baseline population characteristics used to inform the model were based on the MAGNITUDE trial and Institut national d'excellence en santé et en services sociaux (INESSS) Drug Submission Guidelines normative values for males.[1,3] The mean age applied in the model was 67.9 years (standard deviation [SD] = 8.9 years`), informed by the MAGNITUDE trial. The normative values for males from the INESSS Drug Submission Guidelines informed the mean weight (84.0 kg [SD = 8.4 kg]) and body surface area (1.98 m^2 [SD = 0.2 m^2]).[3]

Clinical efficacy for niraparib and abiraterone acetate with prednisone and abiraterone acetate with prednisone was informed by the MAGNITUDE trial (second interim analysis), which had a median duration of follow-up of 24.8 months. Evidence for abiraterone acetate with prednisone was generated alongside placebo. Parametric survival modelling was used to extrapolate rPFS, OS, and time to treatment discontinuation (TTTD). The submitted model used jointly fitted models for rPFS because the PHs assumption was not violated. The sponsor chose the Weibull distribution for the base-case analysis based on clinical plausibility and statistical assessment. For OS, the sponsor fitted models individually for niraparib and abiraterone acetate with prednisone and abiraterone acetate with prednisone, using the gamma distribution and Gompertz distribution, respectively, because the PHs assumption was considered to be violated. Similarly, the PHs assumption was considered violated for TTTD and thus the sponsor fitted individual models for niraparib and abiraterone acetate with prednisone and abiraterone acetate with prednisone, choosing the Gompertz and gamma models, respectively.

Clinical efficacy for enzalutamide was incorporated into the model via a hazard ratio (HR) approach, with values obtained from ITCs using patient-level data from both the MAGNITUDE study and the CAPTURE study (a real-world database study). The CAPTURE study was an observational study in Spanish patients that analyzed the disease trajectory in patients with prostate cancer, including patients with mCRPC who were treated with enzalutamide. The submitted model applied covariate-adjusted HRs for rPFS and OS of 2.78 (95% confidence interval [CI], 1.49 to 5.26) and 1.67 (95% CI, 0.78 to 3.33), respectively. It was assumed that patients were treated with enzalutamide until they experienced disease progression (i.e., TTTD was equal to rPFS). All parametric distributions (rPFS, OS, and TTTD) were limited by the general population mortality statistics derived from Statistics Canada life tables.[4]

A health state utility value of 0.93 was used for the progression-free health state, which was derived from the EQ-5D-5L analysis of MAGNITUDE trial data using the value set from Andrade et al. (2020).[5] The postprogression utility value applied in the sponsor's base-case analysis (0.60) was derived from an observational study conducted in Europe (n = 602) that used the EQ-5D-3L instrument.[6] The selected utility value represented patients with mCRPC who were post–chemotherapy treatment.[6]

The submitted model included costs associated with drug acquisition, treatment administration, diagnostic testing, end-of-life, medical resource use, AEs, and subsequent treatments. Drug acquisition and administration costs were estimated for both preprogression treatments (i.e., niraparib and abiraterone acetate with prednisone, abiraterone acetate with prednisone, and enzalutamide) and subsequent treatments, and incorporated RDI assumptions as follows: 87.5% for niraparib and abiraterone acetate with prednisone and enzalutamide, 96% for abiraterone acetate with prednisone, and 100% for all subsequent treatments. Disease management costs included physician visits, laboratory tests, imaging, and procedures, and were calculated using a micro-costing approach informed by published literature, expert opinion, and relevant schedules of benefits.[7-15] The submitted model included a 1-time cost of diagnostic testing for all patients of $1,300, applied in the first cycle of the model. A 1-time cost of $31,319 at the time of death was applied.[16]

The model included grade 3 to grade 5 AEs with an incidence of 5% or greater in both the preprogression and postprogression (i.e., subsequent therapies) settings. The AE frequencies for niraparib and abiraterone acetate with prednisone and abiraterone acetate with prednisone were obtained from the MAGNITUDE trial. Preprogression AEs for enzalutamide were obtained from the PREVAIL trial, a double-blind phase III study of enzalutamide versus placebo in patients with metastatic prostate cancer.[17] Postprogression AEs were sourced from pivotal trial publications for the corresponding subsequent therapies available in the model.[18-23] A per-cycle disutility was applied based on the type, frequency, and duration of AE for each treatment. The disutility values were derived from the literature and the duration was informed by expert opinion solicited by the sponsor.[24-27] Costs associated with AEs were obtained from the Ontario Case Costing Initiative Analysis Tool.[28] Preprogression AE costs were applied as a 1-time cost in the first cycle, and postprogression AE costs were applied as a 1-time cost at the time of disease progression.

In the submitted model, patients could receive up to 3 lines of subsequent therapy in the PD health state, which were dependent on the first-line treatment received. Subsequent treatments were modelled as a mix of treatments and costs were estimated using median treatment durations and completion rates, which were applied as a lump sum during the first incident cycle in the PD health state. Only costs related to subsequent therapies were captured in the submitted model, and not postprogression survival benefits.

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically (1,000 iterations for the base case and scenario analyses). The deterministic and probabilistic results were similar. The probabilistic findings are presented as follows.

Base-Case Results

In the sponsor's base-case analysis, compared with abiraterone acetate with prednisone, treatment with niraparib and abiraterone acetate with prednisone was associated with an incremental QALY gain of 0.92 and an incremental cost of $136,932, resulting in an ICER of $149,066 per QALY gained. Compared with enzalutamide, niraparib and abiraterone acetate with prednisone was associated with an incremental QALY gain of 0.87 and an incremental cost of $114,894, resulting in an ICER of $131,972 per QALY gained (Table 3). The probability of niraparib and abiraterone acetate with prednisone being cost-effective at a $50,000 per QALY gained threshold compared to abiraterone acetate with prednisone and enzalutamide was 0% for both comparisons. In the niraparib and abiraterone acetate with prednisone arm of the model, 2% of patients were alive at the end of the 10-year time horizon. Approximately 27% of the incremental QALYs in the sponsor's base case were accrued beyond 36.8 months, the median follow-up time in the MAGNITUDE trial.

The sponsor's model predicted that treatment with niraparib and abiraterone acetate with prednisone would result in a longer duration of life (i.e., LYs) compared to abiraterone acetate with prednisone and enzalutamide by 1.01 years and 0.84 years, respectively.

Table 3: Summary of the Sponsor's Economic Evaluation Results, Pairwise

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER ($/QALY)
Niraparib and abiraterone acetate with prednisone vs. abiraterone acetate with prednisone					
Abiraterone acetate with prednisone	80,362	Reference	1.47	Reference	Reference
Niraparib and abiraterone acetate with prednisone	217,294	136,932	2.39	0.92	149,066
Niraparib and abiraterone acetate with prednisone vs. enzalutamide					
Enzalutamide	102,400	Reference	1.52	Reference	Reference
Niraparib and abiraterone acetate with prednisone	217,294	114,894	2.39	0.87	131,972

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments.

Source: Sponsor's pharmacoeconomic submission.[1]

Sensitivity and Scenario Analysis Results

The sponsor conducted several scenario and sensitivity analyses testing alternative parameter values and assumptions. These included alternative parametric distributions for rPFS, OS, and TTTD, subsequent treatment assumptions, and alternative utility values. The sponsor's base case was most influenced by assumptions relating to the OS parametric distributions, with the ICER for niraparib and abiraterone acetate with prednisone compared to abiraterone acetate with prednisone ranging from $101,367 to $662,526 per QALY gained, depending on what distributions were individually fit to the treatment groups (with the other remaining as the base-case selection).

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis.

- **The submitted model does not align with the indicated population.** The approved indication for niraparib and abiraterone acetate with prednisone is for all adult patients with *BRCA*-deficient mCRPC, irrespective of the line of treatment. The MAGNITUDE trial was restricted to patients receiving their first line of treatment. As a result, there is no direct comparative evidence for the use of niraparib and abiraterone acetate in the second-line, third-line, and later-line settings. Clinical experts consulted by CADTH indicated that niraparib and abiraterone acetate with prednisone may be used in subsequent treatment lines due to the decreasing number of patients who are androgen receptor pathway inhibitor (ARPi)–naive (i.e., have received treatment with abiraterone acetate with prednisone, or enzalutamide).
    - CADTH was unable to address this limitation within the submitted model. As the trial only included patients receiving first-line mCRPC treatment, CADTH notes that the cost-effectiveness of niraparib and abiraterone acetate with prednisone used as a subsequent line of therapy is unknown.
- **Unclear definition of chemotherapy eligibility in clinical practice.** The indication for niraparib and abiraterone acetate with prednisone specifies that it is for use in patients "in whom chemotherapy is not clinically indicated." However, there is uncertainty regarding how chemotherapy eligibility would be defined in clinical practice. Clinical experts consulted by CADTH noted that any patient with mCRPC fit enough for cytotoxic chemotherapy should be considered eligible for it, and that any decision that a patient is not indicated for chemotherapy is therefore based on the judgment of the treating physician rather than on consistent clinical criteria. Clinical experts consulted by CADTH indicated that there are 2 groups of patients that may be deemed ineligible for chemotherapy. The first group is patients who are too sick for chemotherapy, who clinical experts consulted by CADTH also indicated may mean they are not well enough for treatment with niraparib and abiraterone acetate with prednisone. The second group is patients who are considered too well for chemotherapy; these patients may express a preference to delay chemotherapy and avoid the associated AEs. It is uncertain how these groups of ineligible patients are distributed in the Canadian context, and evidence from the MAGNITUDE trial does not provide comparative evidence for niraparib and abiraterone acetate with prednisone in those subgroups.
    - CADTH notes that given this uncertainty, the cost-effectiveness results may not be generalizable to the patient population that is most likely to receive niraparib and abiraterone acetate with prednisone in Canada.
- **The extrapolation of OS is uncertain**. The submitted model predicted a gain in LYs such that treatment with niraparib and abiraterone acetate with prednisone would result in a longer duration of life compared to abiraterone acetate with prednisone and enzalutamide by 1.01 years and 0.84 years, respectively, despite finding no significant difference in OS during the trial period. At the time of the second interim analysis (with a data cut-off date of June 17, 2022) of the MAGNITUDE

trial, the median OS was estimated to have a between-group HR of 0.88; however, the 95% CI was found to cross 1 (95% CI, 0.58 to 1.33). When fitting parametric distributions to support the long-term extrapolation of OS data, the sponsor selected parametric distributions based primarily on goodness-of-fit criteria and clinical plausibility. The sponsor chose different distributions for niraparib and abiraterone acetate with prednisone and abiraterone acetate with prednisone, selecting the gamma and Gompertz distributions, respectively. However, in the case where separate parametric models are fitted to individual treatment groups, it is best practice to select the same type of model unless substantial justification is provided, allowing the treatment effect to act on both the shape and scale parameters of the distribution.[29] While CADTH acknowledges that the sponsor chose OS models largely based on best fit statistics, it is important to consider that these tests assess the internal validity of the fitted models, but not the extrapolated time period. In light of this, CADTH had clinical experts assess the survival estimates predicted by several parametric distributions for each treatment strategy at specified time points over the modelled time horizon to validate survival curves in accordance with biological plausibility, with particular consideration of the extrapolated period.

  - The CADTH reanalysis used the gamma distribution for both niraparib and abiraterone acetate with prednisone and abiraterone acetate with prednisone, based on advice from clinical experts consulted by CADTH.
  - CADTH conducted a scenario analysis assuming equivalent OS for niraparib and abiraterone acetate with prednisone and abiraterone acetate with prednisone.

- **The comparative efficacy of niraparib and abiraterone acetate with prednisone versus enzalutamide is highly uncertain.** In the absence of head-to-head evidence for niraparib and abiraterone acetate with prednisone versus enzalutamide, the sponsor estimated comparative effectiveness using an ITC. CADTH's clinical review team noted several methodological limitations with the ITC, including that the patient cohorts in the CAPTURE study and MAGNITUDE trial were not comparable, the PHs assumption for OS had been violated, there was uncertainty with regard to the definitions of disease progression, and the temporal relevance of data from CAPTURE was in question. Given the use of HRs derived from this ITC to inform the clinical efficacy of enzalutamide relative to niraparib and abiraterone acetate with prednisone, substantial uncertainty exists in the pairwise comparison between these treatments.
  - Given the inability to draw conclusions from the ITC, CADTH presented the pairwise comparison of niraparib and abiraterone acetate with prednisone versus enzalutamide as a scenario analysis.
- **The health state utility values are uncertain and lack face validity.** Clinical experts consulted by CADTH agreed that the utility values used in the sponsor's submission lack face validity. Based on the Canadian utility norms from the 2013 Canadian Community Health Survey, the reported utility for those age 60 years to 70 years is 0.842.[30] The sponsor applied a baseline utility value of 0.929 to patients in the progression-free health state, implying that people with mCRPC have a higher level of well-being than the Canadian norm for people of a similar age to the modelled population. This utility value was derived from the MAGNITUDE trial data, collected using the EQ-5D-5L instrument. The health state utility value for the PD health state is derived from the literature: an observational

study of patients with mCRPC in Germany and utilities that were derived using the EQ-5D-3L instrument. Based on this study, the sponsor applied a utility of 0.60 for the PD health state, which reflects patients with mCRPC who were post–chemotherapy treatment. CADTH recommends that all utilities used to populate models be derived from 1 source — that is, from the same population, assessed using the same instrument, and valued with the same preference weights.[31] While clinical experts consulted by CADTH indicated that there would be a decline in quality of life for each line of subsequent therapy, it is unclear if the population included by Diels et al. (2015)[6] appropriately captures all patients in the PD health state. Additional uncertainty arises with regard to the treatment landscape over time and across jurisdictions, which may not be reflective of Canadians with mCRPC.

  - To address the use of different instruments to estimate utility values for health states, the CADTH reanalysis used utility estimates derived from the EQ-5D-3L analysis of the MAGNITUDE trial data for the progression-free health state.
  - CADTH maintained the sponsor's utility estimate for the PD health state; however, CADTH notes that there is a high degree of uncertainty with regard to the patient population included in the post–chemotherapy treatment group and timing of disease. Given that the progressed disease health state is made up of patients on multiple lines of treatment who clinical experts consulted by CADTH indicated would have different utility values, significant uncertainty remains with regard to a utility value that is representative of patients in this health state.

- **TTTD was modelled inconsistently.** In the submitted model, the sponsor fitted distributions to TTTD data from the MAGNITUDE trial to model time on treatment for niraparib and abiraterone acetate with prednisone and abiraterone acetate with prednisone, and assumed that treatment with enzalutamide would continue until disease progression. The sponsor capped time on treatment at progression-free survival such that patients would stop treatment at the time of disease progression regardless of the estimate of the TTTD curve. The TTTD data were not included as part of CADTH's clinical review and thus have not been appraised. Further, clinical experts consulted by CADTH indicated that, with the exception of ADT (which is continued throughout the entire disease trajectory), oral treatments are typically discontinued at the time of disease progression, or when the next line of treatment is being initiated. In the sponsor's base-case analysis, the selected distribution for abiraterone acetate with prednisone resulted in patients being treated until progression; however, niraparib and abiraterone acetate with prednisone was discontinued before progression, resulting in patients accruing health outcomes in the progression-free health state with no treatment cost. The inconsistent discontinuation timing as modelled does not align with the expectations of clinical experts who indicated that treatment-free intervals are not standard practice in the mCRPC setting.
  - CADTH assumed that all treatments were continued until the time of disease progression.
- **The use of RDI underestimated drug acquisition costs**. In the sponsor's base-case analysis, the mean RDI observed in the MAGNITUDE trial was used to derive the drug acquisition cost (i.e., expected versus observed doses). The inclusion of RDI may underestimate the total treatment costs in real-world clinical practice as the dose received by patients may be different from the planned dose for several reasons. For oral therapies, Canadian pharmacies are likely to fill and dispense prescriptions

in full. Therefore, it is unlikely that any unused tablets would result in lower prescription costs as unused tablets are unlikely to be recuperated.

  - In the CADTH reanalysis, RDI was assumed to be 100% for all treatments.

- **Companion diagnostic tests were modelled inappropriately.** The sponsor assumed that all patients in the submitted model accrued the cost of 1 diagnostic test. However, of the modelled treatments, only niraparib and abiraterone acetate with prednisone is reliant upon the results of the diagnostic test; therefore, the sponsor's approach did not adequately capture the difference in costs associated with requiring germline-confirmed and/or somatically confirmed *BRCA* mutation for treatment with niraparib and abiraterone acetate with prednisone. In fact, it is likely that for each *BRCA* mutation identified, multiple patients had to be tested, which increases the potential costs associated with niraparib and abiraterone acetate with prednisone without accruing any health benefit since those patients would go on to be treated with a comparator treatment. Further, the sponsor's approach did not incorporate relevant diagnostic test parameters, including test sensitivity and specificity. By not accounting for the possibility of false-positive results, the efficacy of niraparib and abiraterone acetate with prednisone may be overestimated if it is being used for patients without a *BRCA* mutation. The Specific Guidance for Treatments With Companion Diagnostics appendix of CADTH's *Guidelines for the Economic Evaluation of Health Technologies* indicates that "the consequences of a false-positive companion diagnostic result should be fully modelled" due to the potential reduction in treatment effectiveness, harm from treatment, and associated resource consumption.[32]
  - With the sponsor's assertion that 10% of patients with mCRPC have either germline-confirmed or somatically confirmed *BRCA* mutation,[33] CADTH conducted a scenario analysis that assumed each modelled patient being treated with niraparib and abiraterone acetate accrued the cost of 10 diagnostic tests (i.e., approximately 10 tests conducted to identify 1 patient with a *BRCA* mutation).
- **Poor modelling practices were employed**. The sponsor's submitted model included numerous IFERROR statements, which lead to situations in which the parameter value is overwritten with an alternative value without alerting the user to the automated overwriting. The systematic use of IFERROR statements makes thorough auditing of the sponsor's model impractical and it remains unclear whether the model is running inappropriately by overriding errors.
  - CADTH was unable to address this limitation and notes that a thorough validation of the sponsor's model was not possible.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (refer to Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
The costs of ADT were excluded.	ADT is often administered concurrently for patients receiving abiraterone acetate. While this cost is relevant to the analysis, the impact of this assumption on the model results is small.
The duration of subsequent treatment lines was assumed to be the same regardless of the initial mCRPC treatment received and were derived from historical clinical trials.	While it is uncertain whether the historical clinical trial data and subsequent treatment patterns will be the same for patients who receive different initial mCRPC treatments, assumptions regarding subsequent therapies in the model have a minimal impact on the cost-effectiveness results.

ADT = androgen deprivation therapy; mCRPC = metastatic castration-resistant prostate cancer.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

The CADTH base case was derived by making changes in model parameter values and assumptions in consultation with clinical experts. These changes, summarized in Table 5, included using alternative OS extrapolations, changing the utility value in the progression-free health state, assuming that patients were treated until progression, and removing RDI assumptions. The reanalysis is based on publicly available prices of the comparator treatments.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Price of abiraterone acetate	RAMQ price: $15.3125 per tablet	Ontario price: $52.0625 per tablet
Changes to derive the CADTH base case		
1. Aligned OS extrapolation function	Niraparib and abiraterone acetate with prednisone modelled with the gamma distribution Abiraterone acetate with prednisone modelled with the Gompertz distribution	Niraparib and abiraterone acetate with prednisone and abiraterone acetate with prednisone, both modelled with the gamma distribution
2. Utility values	Progression-free health state: 0.93	Progression-free health state: 0.77
3. TTTD	TTTD distributions used for niraparib and abiraterone acetate with prednisone and abiraterone acetate with prednisone Treat to progression for enzalutamide	Treat to progression for all treatments
4. Use of RDI	Niraparib and abiraterone acetate with prednisone: 87.5% Abiraterone acetate with prednisone: 96.0% Enzalutamide: 87.5%	Niraparib and abiraterone acetate with prednisone: 100% Abiraterone acetate with prednisone: 100% Enzalutamide: 100%
CADTH base case	—	1 + 2 + 3 + 4

OS = overall survival; RDI = relative dose intensity; TTTD = time to treatment discontinuation; RAMQ = Régie de l'assurance maladie du Québec.

The CADTH base case focuses on the comparison of niraparib and abiraterone acetate with prednisone versus abiraterone acetate with prednisone, the only comparison for which head-to-head trial data were available. The CADTH base case resulted in an ICER of $271,803 per QALY gained for niraparib and abiraterone acetate with prednisone versus abiraterone acetate with prednisone (incremental cost = $133,835; incremental QALYs = 0.49) with a 0% probability of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. Cost-effectiveness was driven by the higher treatment cost of niraparib and abiraterone acetate with prednisone compared to abiraterone acetate with prednisone and longer progression-free survival, leading to patients remaining on therapy longer. The results of the stepped analysis are presented in Table 6.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results (Deterministic)

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Sponsor's base case	Abiraterone acetate with prednisone	79,983	1.46	Reference
	Niraparib and abiraterone acetate with prednisone	222,215	2.39	153,187
Sponsor's base case (corrected)	Abiraterone acetate with prednisone	106,858	1.46	Reference
	Niraparib and abiraterone acetate with prednisone	222,215	2.39	124,243
CADTH reanalysis 1	Abiraterone acetate with prednisone	108,569	1.73	Reference
	Niraparib and abiraterone acetate with prednisone	222,215	2.39	173,437
CADTH reanalysis 2	Abiraterone acetate with prednisone	106,858	1.29	Reference
	Niraparib and abiraterone acetate with prednisone	222,215	2.06	150,089
CADTH reanalysis 3	Abiraterone acetate with prednisone	106,858	1.46	Reference
	Niraparib and abiraterone acetate with prednisone	241,911	2.39	145,457
CADTH reanalysis 4	Abiraterone acetate with prednisone	108,445	1.46	Reference
	Niraparib and abiraterone acetate with prednisone	246,737	2.39	148,945
CADTH base case (1 + 2 + 3 + 4)	Abiraterone acetate with prednisone	110,182	1.56	Reference
	Niraparib and abiraterone acetate with prednisone	269,248	2.06	319,357

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
CADTH base case (probabilistic; 1 + 2 + 3 + 4)	Abiraterone acetate with prednisone	111,875	1.57	Reference
	Niraparib and abiraterone acetate with prednisone	245,710	2.06	271,803

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Given the magnitude of uncertainty surrounding the sponsor's ITC and the long-term extrapolation of clinical benefits, CADTH was unable to derive a robust base-case estimate of the cost-effectiveness of niraparib and abiraterone acetate with prednisone versus enzalutamide. CADTH conducted an additional scenario analysis to estimate the cost-effectiveness versus enzalutamide (Appendix 4).

Scenario Analysis Results

A price reduction analysis based on the CADTH base case indicated that, at a willingness-to-pay threshold of $50,000 per QALY gained, niraparib and abiraterone acetate with prednisone would be considered cost-effective compared to abiraterone acetate with prednisone with a 61% price reduction (Table 7).

Table 7: CADTH Price Reduction Analyses

Analysis	ICERs for niraparib and abiraterone acetate with prednisone vs. abiraterone acetate with prednisone ($/QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	$153,187	$319,357
10%	$134,701	$275,453
20%	$116,214	$231,550
30%	$97,728	$187,647
40%	$79,242	$143,743
50%	$60,755	$99,840
60%	$42,269	$55,937
70%	$23,782	$12,033
80%	$5,296	Dominant
90%	Dominant	Dominant

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Additionally, CADTH conducted scenario analyses to determine the impact of alternative assumptions on the cost-effectiveness of niraparib and abiraterone acetate with prednisone. In the scenario assuming that OS is equivalent between niraparib and abiraterone acetate with prednisone and abiraterone acetate with prednisone, the ICER increased to $1,033,787 per QALY gained. Including the higher companion diagnostic tests for niraparib and abiraterone acetate with prednisone resulted in an ICER of $345,453 per QALY gained for niraparib and abiraterone with prednisone compared to abiraterone acetate with prednisone.

Issues for Consideration

- Drug plan input and feedback received from clinical experts consulted by CADTH noted changes in the treatment landscape for patients with prostate cancer in recent years. In many Canadian treatment settings, patients with mCSPC are receiving treatment intensification such that they are being treated with ARPis, including abiraterone acetate and enzalutamide. As a result, patients who progress to mCRPC have largely already received ARPi treatment and are unlikely to be treated with them again. For these patients, the most common approach to first-line mCRPC treatment is taxane-based chemotherapy (i.e., docetaxel). Both Health Canada and the clinical experts consulted by CADTH noted that determining chemotherapy eligibility is based on clinical judgment. The clinical experts consulted by CADTH indicated that, technically, all patients with mCRPC have an indication for chemotherapy and that it may be difficult to exclude patients in whom chemotherapy is not clinically indicated from treatment with niraparib and abiraterone acetate with prednisone. Given this, it is important to note that there is no direct comparative efficacy data for niraparib and abiraterone acetate with prednisone compared to docetaxel, and the cost-effectiveness and budgetary impact is unknown.
- At the time of writing this report, olaparib (Lynparza) in combination with abiraterone acetate and prednisone is under review for the first-line treatment of adult patients with deleterious or suspected deleterious germline and/or somatic *BRCA*-mutated mCRPC, for whom chemotherapy is not clinically indicated.[34] Given that this indication significantly overlaps with that being reviewed for niraparib and abiraterone acetate, olaparib may be a relevant comparator that could not be included in the present analysis. The cost-effectiveness of niraparib and abiraterone acetate with prednisone compared to olaparib with abiraterone acetate and prednisone is unknown. Additionally, it is uncertain how the introduction of olaparib with abiraterone acetate and prednisone would impact market share expectations and, subsequently, the estimated 3-year budget impact.
- To receive treatment with niraparib and abiraterone acetate with prednisone, patients must have a germline-confirmed or somatically confirmed *BRCA* mutation. As this will be the first first-line treatment for mCRPC that is dependent on genetic testing results, it is anticipated that there will be an increase in the overall number of genetic tests in patients with prostate cancer. Drug plan input noted that while some provinces may already test for *BRCA* mutations to treat with olaparib monotherapy as a subsequent therapy, genetic testing at diagnosis (i.e., before first-line treatment) is not standard practice in all CADTH-participating jurisdictions. The increase in genetic testing of patients with prostate cancer represents an added cost to the health care system. Further, the actual cost of companion diagnostic tests is uncertain due to the use of different platforms and testing methods (e.g., multipanel somatic gene testing, next-generation sequencing).
- The pan-Canadian Pharmaceutical Alliance concluded negotiations with a letter of intent for enzalutamide for multiple indications: mCSPC, nonmetastatic castrate-resistant prostate cancer, and first-line and subsequent-line mCRPC.[35-38] As such, enzalutamide has a confidential negotiated price and is currently funded by jurisdictional cancer formularies.[39,40] The CADTH reanalyses are based on

the publicly available price of enzalutamide, which may be different than the confidential price and may influence the results of the cost-effectiveness and budget impact analyses (BIAs).

- The pan-Canadian Pharmaceutical Alliance concluded negotiations with a letter of intent for abiraterone acetate for the treatment of mCRPC and as such, abiraterone acetate has a confidential negotiated price and is currently funded by jurisdictional cancer formularies.[39-41] The CADTH reanalyses are based on the publicly available price of abiraterone acetate, which may be different than the confidential price and may influence the results of the cost-effectiveness and BIAs.

Overall Conclusions

Based on the CADTH clinical review of the MAGNITUDE trial, moderate certainty of evidence shows niraparib and abiraterone acetate with prednisone resulted in little improvement in rPFS when compared with abiraterone acetate with prednisone, although the findings are slightly below the clinically important threshold of a 25% difference suggested by clinical experts consulted by CADTH. CADTH's clinical review reported that treatment with niraparib and abiraterone acetate with prednisone did not demonstrate a benefit in OS compared to abiraterone acetate with prednisone. Given the lack of direct comparative evidence, the sponsor submitted an ITC using data from the CAPTURE study to estimate the relative clinical efficacy of niraparib and abiraterone acetate with prednisone versus enzalutamide. The CADTH clinical review reported that the results of this analysis were highly uncertain due to several major limitations, including patient comparability across studies, a violation of the PHs assumption, outcome definitions, and the temporal relevance of the CAPTURE study.

In addition to these limitations, CADTH identified several limitations with the sponsor's economic submission that could be addressed through reanalysis. For the CADTH base-case analysis, CADTH revised the assumptions about OS, which led to more plausible estimates of survival benefit; applied a more realistic health state utility value in the progression-free health state; assumed that patients were treated until progression for all treatments; and removed RDI assumptions. In CADTH's base-case analysis, the ICER of niraparib and abiraterone acetate with prednisone compared to abiraterone acetate with prednisone was $271,803 per QALY gained (incremental costs = $133,835; incremental QALYs = 0.49). The probability of being cost-effective at a $50,000 per QALY gained threshold was 0%. Based on CADTH's base-case analysis, for niraparib and abiraterone acetate with prednisone to be considered cost-effective at a $50,000 per QALY gained threshold compared to abiraterone acetate with prednisone, the price of niraparib and abiraterone acetate would need to be $3,213 per 28-day cycle, reflecting a price reduction of 61%. Given the limitations in the comparative clinical efficacy data for enzalutamide, a high degree of uncertainty remained in estimating the cost-effectiveness of niraparib and abiraterone acetate with prednisone versus enzalutamide; this comparison was explored through scenario analysis only.

CADTH identified key considerations regarding the alignment of the trial population, the reimbursement request, and the indicated population. First, the evidence generated by the MAGNITUDE trial was in patients receiving first-line treatment for mCRPC, whereas the Health Canada indication does not specify a treatment line. Clinical experts consulted by CADTH also indicated that a limited number of patients would meet the

MAGNITUDE trial's inclusion criteria, as they would have experienced prior exposure to abiraterone acetate with prednisone and enzalutamide in the castration-sensitive stage of their disease.

In addition to the limitations in trial population alignment, there remained uncertainty regarding how "in whom chemotherapy is not clinically indicated" would be defined in clinical practice. Clinical experts consulted by CADTH noted that any patient with mCRPC fit enough for cytotoxic chemotherapy should be considered eligible for it, and that any decision that a patient is not indicated for chemotherapy is therefore based on the judgment of the treating physician rather than on consistent clinical criteria. Consequently, CADTH was unable to estimate the cost-effectiveness of niraparib and abiraterone acetate with prednisone for the full population in which the treatment is likely to be used. CADTH's estimates of the ICER and the price reduction needed to reach cost-effectiveness at a given willingness-to-pay threshold only apply to the narrow subset of patients meeting the MAGNITUDE trial's inclusion criteria (i.e., patients without prior exposure to abiraterone or enzalutamide, and who had not been previously treated with chemotherapy in the mCRPC setting). The cost-effectiveness of niraparib and abiraterone acetate with prednisone as a subsequent therapy or in patients for whom chemotherapy is clinically indicated remains unknown.

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Appendix 1: Cost Comparison Table

Note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts and CADTH-participating drug plans. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Treatment of mCRPC

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	Average 28-day cost ($)
Niraparib and abiraterone acetate (Akeega)	100 mg niraparib / 500 mg abiraterone acetate 50 mg niraparib / 500 mg abiraterone acetate	Tablet	147.1000[a]	200 mg niraparib and 1,000 mg abiraterone acetate Reduced dose 100 mg niraparib and 1,000 mg abiraterone acetate	294.2000	8,238
Prednisone (generic)	5 mg	Tablet	0.0220	10 mg daily	0.0440	1
Niraparib and abiraterone acetate, with prednisone					294.2440	8,239
Androgen receptor-axis-targeted therapy						
Abiraterone (generic)	250 mg 500 mg	Tablet	26.0313 52.0625	1,000 mg daily	104.1252	2,916
Prednisone (generic)	5 mg	Tablet	0.0220	10 mg daily	0.0440	1
Abiraterone, taken with prednisone					104.1692	2,917
Enzalutamide (Xtandi)	40 mg	Tablet	29.1954	160 mg daily	116.7816	3,270

Note: All prices are wholesale from IQVIA DeltaPA (accessed June 2023), unless otherwise indicated, and do not include dispensing fees.

[a]Sponsor's submitted price.[1]

Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

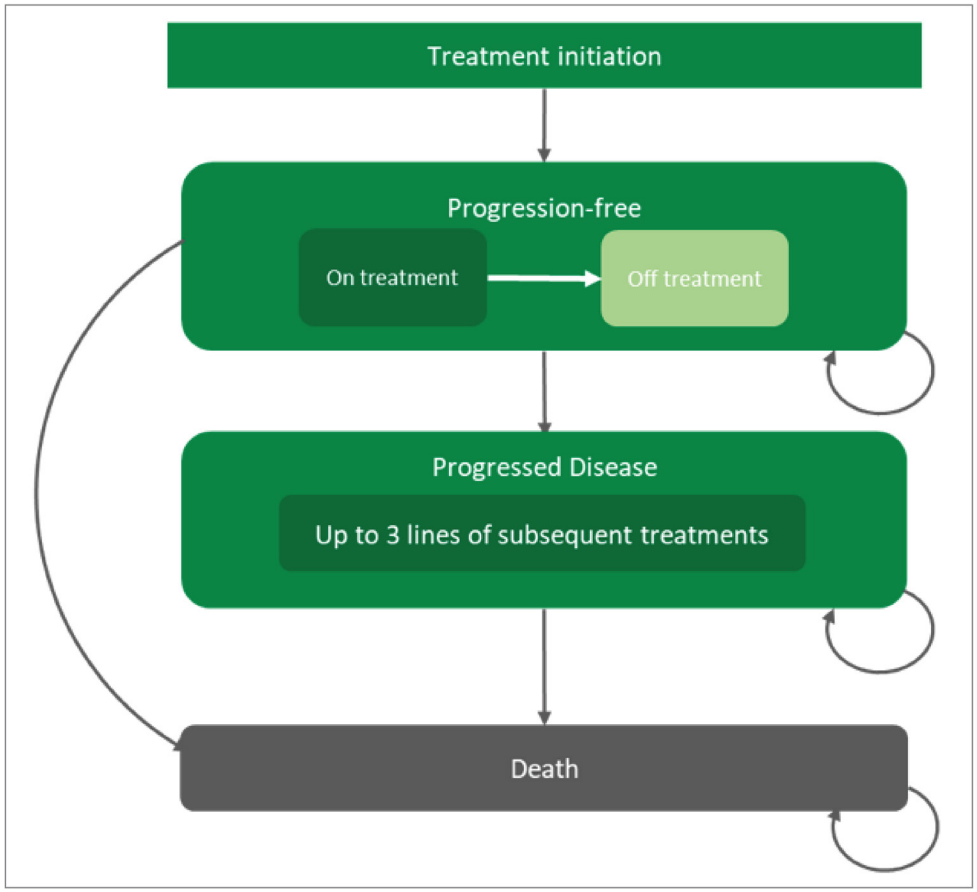
Table 9: Submission Quality

Description	Yes/no	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	Yes	The population included in the trial was restricted to first-line use of niraparib and abiraterone acetate with prednisone. Subsequent therapy was not included in the model. The model also has generalizability concerns given the uncertainty around defining eligibility.
Model has been adequately programmed and has sufficient face validity	No	Refer to limitations: The health state utility values are uncertain and lack face validity; time to treatment discontinuation was modelled inconsistently; and companion diagnostic tests were modelled inappropriately.
Model structure is adequate for decision problem	Yes	No comment.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	No	Refer to limitation: Poor modelling practices were employed.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	Yes	No comment.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	Yes	No comment.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note that this appendix has not been copy-edited.

Figure 1: Model Structure



Source: Sponsor's pharmacoeconomic submission.[1]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has not been copy-edited.

Detailed Results of CADTH Base Case

Table 10: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	Niraparib and abiraterone acetate with prednisone	Abiraterone acetate with prednisone	Incremental
Discounted LYs			
Total	2.94	2.38	0.56
By health state			
Preprogression	2.02	1.06	0.95
Postprogression	0.93	1.31	−0.39
Discounted QALYs			
Total	2.06	1.57	0.49
By health state			
Preprogression	1.55	0.82	0.73
Preprogression AEs	0.00	0.00	0.00
Postprogression	0.56	0.79	−0.23
Postprogression AEs	−0.05	−0.04	−0.01
Discounted costs ($)			
Total	245,710	111,875	133,835
Acquisition	195,147	40,435	154,712
Diagnostic	1,300	1,300	0
Preprogression medical resources	5,978	3,149	2,829
Preprogression AE	869	409	460
Subsequent treatment	11,140	33,912	−22,772
Postprogression medical resources	439	1,225	−786
Postprogression AE	1,724	1,581	143
End-of-life	29,113	29,864	−751
ICER ($/QALY)	271,803		

AE = adverse event; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

Scenario Analyses

Table 11: Summary of CADTH's Scenario Analysis Results

Scenario analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
CADTH scenario analysis: pairwise comparison with enzalutamide (probabilistic)	Enzalutamide	106,768	1.37	Reference
	Niraparib and abiraterone acetate with prednisone	245,710	2.06	202,444
CADTH scenario analysis: Equivalent OS (deterministic)	Abiraterone acetate with prednisone	109,506	1.91	Reference
	Niraparib and abiraterone acetate with prednisone	269,248	2.06	1,033,787
CADTH scenario analysis: Companion diagnostics (deterministic)	Abiraterone acetate with prednisone	108,882	1.56	Reference
	Niraparib and abiraterone acetate with prednisone	280,946	2.06	345,453

Appendix 5: Submitted BIAs and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 12: Summary of Key Take-Aways

Key take-aways of the BIA

• CADTH identified the following key limitations with the sponsor's analysis:
  ◦ The submitted model does not align with the reimbursement request.
  ◦ The eligible population is highly uncertain.
  ◦ The inclusion of docetaxel in the market share estimates was inappropriate.
  ◦ Public drug coverage was underestimated.
  ◦ Treatment duration was inappropriately estimated.
  ◦ The inclusion of genetic testing costs does not align with the perspective of analysis.
• The CADTH reanalysis included: adjusting the proportion of patients in whom chemotherapy is not clinically indicated, removing docetaxel as a comparator, modifying the public drug coverage rate, aligning the time on treatment with rPFS, and excluding diagnostic testing costs.
• Based on the CADTH reanalysis, the 3-year budget impact to the public drug plans of introducing niraparib and abiraterone acetate with prednisone for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated (germline and/or somatic) mCRPC, who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated is expected to be $9,085,054 (year 1: $1,581,059; year 2: $3,553,202; year 3: $3,950,792).

Summary of Sponsor's BIA

The sponsor submitted a BIA estimating the incremental budget impact of reimbursing niraparib and abiraterone acetate with prednisone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (germline and/or somatic) mCRPC, who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated. The analysis was undertaken using an epidemiologic approach from the perspective of the CADTH-participating public drug plans over a 3-year time horizon (2023 to 2025). The sponsor compared a reference scenario where niraparib and abiraterone acetate with prednisone was not reimbursed with a new drug scenario where it was reimbursed, as per its Health Canada indication. The reference scenario included abiraterone acetate with prednisone, and enzalutamide as comparators. Key inputs to the BIA are documented in Table 13. Data informing the model were obtained from various sources including the MAGNITUDE trial, Canadian Cancer Society, real-world evidence,[42,43] sponsor internal data, and clinical expert opinion.

The sponsor's BIA included the following key assumptions:

- The submitted model accounts for the duration of therapy in 30-day cycles, which was estimated to be 17.9 cycles for niraparib and abiraterone acetate with prednisone, 15.2 cycles for abiraterone acetate with prednisone, 16.2 cycles for enzalutamide, and 9.5 cycles for docetaxel, based on their respective clinical trial (i.e., the MAGNITUDE, PREVAIL, and TAX 327 trials).[17,21,44]
- Docetaxel with prednisone was included in the market share estimates but is not considered an appropriate drug comparator and so none of the market share is displaced by the introduction of

niraparib and abiraterone acetate with prednisone. The cost of docetaxel is not included in the estimated annual costs.

Table 13: Summary of Key Model Parameter

Parameter	Sponsor's estimate (reported as year 1/year 2/year 3 if appropriate)
Target population	
Pan-Canadian male population aged 18+ (excluding Quebec) in base year	19,357,704
Annual population growth rate	3.02% / 2.93% / 2.84%
Prevalence of prostate cancer	993.66 per 100,000[45]
Prevalence of mCRPC	1.65%[42]
Percentage of patients with mCRPC in whom chemotherapy is not clinically indicated	72%[43]
Percentage of patients with mCRPC with biomarker screening	84%[a]
Percentage of mCRPC with *BRCA* alterations	10%[33]
Percentage of patients with public coverage	84%[b]
Number of patients eligible for drug under review	129 / 133 / 136
Market uptake (3 years)	
Uptake (reference scenario) Abiraterone acetate with prednisone Enzalutamide Docetaxel	[redacted]
Uptake (new drug scenario) Niraparib and abiraterone acetate with prednisone Abiraterone acetate with prednisone Enzalutamide Docetaxel	[redacted]
Cost of treatment (per patient)	
Cost of treatment over 28 days Niraparib and abiraterone acetate with prednisone Abiraterone acetate with prednisone Enzalutamide Docetaxel	 $8,238.83 $858.73 $3,269.88 $1,603.79

mCRPC = metastatic castration-resistant prostate cancer.

[a]Estimate based on Janssen data on file.

[b]Estimate based on age-based prostate cancer prevalence from Canadian Cancer Society data.[45]

Summary of the Sponsor's BIA Results

The sponsor estimated the net budget impact of funding niraparib and abiraterone acetate with prednisone for the indicated population will be $6,671,001 in year 1, $11,986,811 in year 2, and $13,326,201 in year 3, for a 3-year total budget impact of $31,984,013.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **The submitted model does not align with the indicated population.** The approved indication for niraparib and abiraterone acetate with prednisone is for all adult patients with *BRCA*-deficient mCRPC, irrespective of line of treatment. The MAGNITUDE trial was restricted to patients receiving their first line of treatment. Clinical experts consulted by CADTH indicated that niraparib and abiraterone acetate with prednisone may be used in subsequent treatment lines due to the decreasing number of patients who are ARPi-naive (i.e., have received treatment with abiraterone acetate with prednisone, or enzalutamide).
    - CADTH was unable to address this limitation within the submitted model. CADTH notes that the budgetary impact of niraparib and abiraterone acetate with prednisone used as a subsequent line of therapy is unknown.
- **The eligible population is uncertain.** Drug plan input and feedback received from clinical experts consulted by CADTH noted changes in the treatment landscape for patients with prostate cancer in recent years. In many Canadian treatment settings, patients with mCSPC are receiving treatment intensification such that they are being treated with ARPis including abiraterone acetate and enzalutamide. As a result, patients who progress to mCRPC have largely already received ARPi treatment and are unlikely to be treated with them again. For these patients, the most common approach to first-line mCRPC treatment is taxane-based chemotherapy (i.e., docetaxel). Clinical experts consulted by CADTH indicated that given that chemotherapy eligibility is based on clinical judgment, and that most patient would be considered eligible for chemotherapy in the mCRPC setting, that approximately 20% of patients might be deemed ineligible. These patients may have not received treatment intensification with ARPis in the mCSPC setting, might have a preference not to start chemotherapy, or might be considered too sick or too well for chemotherapy.
    - CADTH assumed that 20% of patients with mCRPC would be considered ineligible for chemotherapy.
- **Inclusion of an inappropriate comparator.** The sponsor included docetaxel in their market share estimates, however, included no cost associated with treatment. Given that the indication of niraparib and abiraterone acetate with prednisone, and the modelled population, is patients that are not clinically indicated for chemotherapy assigning market share to docetaxel was inappropriate.

- The CADTH reanalysis excluded docetaxel as a comparator in the market share estimates and reassigned the docetaxel market share evenly between the 2 remaining comparators (i.e., abiraterone acetate with prednisone, and enzalutamide).

- **Public drug coverage was estimated inappropriately.** The sponsor based their estimate of public drug coverage on the proportion of prevalent patients with prostate cancer in Canada who are age 65 years and older using data reported by the Canadian Cancer Society.[45] The sponsor did not provide justification as to why they applied the prevalence of prostate cancer in adults age 65 years and older as a proxy for public drug coverage for all CADTH-participating jurisdictions.

  Niraparib and abiraterone acetate with prednisone is a take home cancer drug, which is a type of medication that is 100% publicly funded in several Canadian jurisdictions (i.e., Alberta, British Columbia, Manitoba, and Saskatchewan).[46] The remaining jurisdictions have varying public drug coverage programs that may be relevant to the public coverage of niraparib and abiraterone acetate, including Ontario's Ontario Drug Benefit program that reimburses drug costs for adults age 65 years and older.[47] Other relevant jurisdictional programs (e.g., Nova Scotia's Take Home Cancer Drug Fund, Prince Edward Island's Catastrophic Drug Program) cap out-of-pocket drug costs by a percentage of household income at which point the drug is publicly reimbursed.[48,49]

  - CADTH estimated that the weighted national (excluding Quebec) drug coverage would be 90%. This estimation assumed that there is 100% public drug coverage for patients in Alberta, British Columbia, Manitoba, and Saskatchewan based on provincial policies for take come cancer medication.[46] CADTH then assumed, based on the Canadian Cancer Society's reported prostate cancer prevalence by age group,[45] that 84% of patients would be eligible for public drug coverage in the remaining jurisdictions. This estimate does not take into account that many jurisdictions also have public funding programs that take effect for high-cost drugs for those with low incomes that may increase public funding for niraparib and abiraterone acetate in jurisdictions without 100% coverage for take home cancer drugs.[46]

- **Treatment duration was estimated inappropriately.** As the pharmacoeconomic evaluation described in the main body of this report, clinical experts consulted by CADTH indicated that, with the exception of ADT (which is continued throughout the entire disease trajectory), oral treatments are typically discontinued at the time of disease progression, or when the next line of treatment is being initiated. The sponsor's BIA model used median TTTD derived from clinical trials to estimate treatment duration to calculate therapy costs, however, these estimates did not align with the assumption that patients would be treated until disease progression.

  - To align with CADTH's CUA, the CADTH reanalysis assumed that treatment duration for niraparib and abiraterone acetate with prednisone, and abiraterone acetate with prednisone, was the median rPFS observed in the MAGNITUDE trial: 19.52 and 10.87 months, respectively. As there was no similar evidence for enzalutamide, CADTH maintained the sponsor's assumption of 16.6 months of treatment, however, notes that this may overestimate enzalutamide treatment costs (e.g., the sponsor-submitted ITC reported median rPFS for

patients being treated with enzalutamide from the CAPTURE study to be 7.4 months), and thus underestimate the budgetary impact of niraparib and abiraterone acetate with prednisone.

- **The inclusion of diagnostic costs in the BIA was inappropriate.** The sponsor included a 1-time diagnostic cost for the entire population included in the BIA in the reference case analysis. The cost assumed that there would be an average of 10 tests performed per treated patient, based on the assumed prevalence rate of *BRCA* mutations of 10%. Given that the perspective of analysis is the CADTH-participating Canadian public drug plans, these costs are ineligible for inclusion.
  - The CADTH base-case analysis excluded costs associated with diagnostic tests.
  - CADTH conducted a scenario analysis applying the cost of 10 genetic tests per patient being treated with niraparib and abiraterone acetate with prednisone and no genetic testing costs for the comparators, as aligned with the CUA scenario analysis.

CADTH Reanalyses of the BIA

CADTH revised the sponsor's submitted analysis by adjusting the proportion of patients in whom chemotherapy is not clinically indicated, removing docetaxel as a comparator, modifying the public drug coverage rate, aligning the time on treatment with rPFS, and excluding diagnostic testing costs. The changes applied to derive the CADTH base case are described in Table 14.

Table 14: CADTH Revisions to the Submitted BIA

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Price of abiraterone acetate	RAMQ price: 15.3125 per tablet	Ontario price: 52.0625 per tablet
Changes to derive the CADTH base case		
1. Not eligible for chemotherapy	72%	20%
2. Docetaxel as comparator	Assigned market share	Not assigned market share
3. Public drug coverage	84%	90%
4. Time on treatment	Niraparib and abiraterone acetate with prednisone: 17.9 months Abiraterone acetate with prednisone: 15.2 months Enzalutamide: 16.6 months	Niraparib and abiraterone acetate with prednisone: 19.52 months Abiraterone acetate with prednisone: 10.87 months Enzalutamide: 16.6 months
5. Companion diagnostics	Included	Excluded
CADTH base case	1 + 2 + 3 + 4 + 5	

BIA = budget impact analysis.

The results of the CADTH step-wise reanalysis are presented in summary format in Table 15 and a more detailed breakdown is presented in Table 16. The CADTH reanalysis suggests that reimbursing niraparib and abiraterone acetate with prednisone would be associated with an incremental cost of $1,581,059 in year 1, $3,553,202 in year 2, and $3,950,792 in year 3, for a 3-year budgetary impact of $9,085,054.

Table 15: Summary of the CADTH Reanalyses of the BIA

Stepped analysis	3-year total
Submitted base case	$31,984,013
Submitted base case (corrected)	$26,795,207
CADTH reanalysis 1	$7,449,743
CADTH reanalysis 2	$26,781,643
CADTH reanalysis 3	$28,724,259
CADTH reanalysis 4	$30,570,130
CADTH reanalysis 5	$26,795,207
CADTH base case	$9,085,054

BIA = budget impact analysis.

CADTH conducted additional scenario analyses to address remaining uncertainty, using the CADTH base case. Results are provided in Table 16.

1. Price reduction of 61% to assess the budget impact if the price of the drug under review reflected the price in which the ICER would be at $50,000 per QALY gained in CADTH's base-case CUA.
2. Included the cost of 10 diagnostic tests per patient that receives treatment with niraparib and abiraterone acetate with prednisone, as aligned with the CADTH CUA scenario analysis.

Results of CADTH's scenario analyses demonstrate that the estimated budget impact is sensitive to changes in drug cost, with the 3-year total budgetary impact declining to $1,064,567. Including diagnostic testing costs for patients treated with niraparib and abiraterone acetate with prednisone resulted in a 13% increase in the budgetary impact.

Table 16: Detailed Breakdown of the CADTH Scenario Analyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	3-year total
Submitted base case	Reference	$4,669,457	$5,828,300	$5,999,203	$6,167,243	$17,994,746
	New drug	$4,669,457	$12,499,301	$17,986,014	$19,493,444	$49,978,759
	Budget impact	$0	$6,671,001	$11,986,811	$13,326,201	$31,984,013
Submitted base case (corrected)	Reference	$6,402,587	$8,076,518	$8,311,807	$8,546,173	$24,934,499
	New Drug	$6,402,587	$13,405,997	$18,464,411	$19,859,297	$51,729,706
	Budget Impact	$0	$5,329,479	$10,152,604	$11,313,124	$26,795,207
CADTH base case	Reference	$1,469,950	$1,783,133	$1,834,712	$1,882,087	$5,499,932
	New drug	$1,469,950	$3,364,192	$5,387,914	$5,832,880	$14,584,986
	Budget impact	$0	$1,581,059	$3,553,202	$3,950,792	$9,085,054

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	3-year total
CADTH scenario analysis: 61% price reduction	Reference	$1,469,950	$1,783,133	$1,834,712	$1,882,087	$5,499,932
	New drug	$1,469,950	$1,632,743	$2,390,526	$2,541,231	$6,564,499
	Budget impact	$0	–$150,390	$555,814	$659,143	$1,064,567
CADTH sensitivity analysis: diagnostic testing costs	Reference	$1,469,950	$1,783,133	$1,834,712	$1,882,087	$5,499,932
	New drug	$1,469,950	$3,712,893	$5,772,460	$6,254,729	$15,740,082
	Budget impact	$0	$1,929,760	$3,937,748	$4,372,642	$10,240,150

BIA = budget impact analysis.

Stakeholder Input

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Patient Input

Canadian Cancer Survivor Network

About Canadian Cancer Survivor Network

The Canadian Cancer Survivor Network (CCSN) is a national network of patients, families, survivors, friends, community partners, funders, and sponsors who have come together to take action to promote the very best standard of care, whether it be it be early diagnosis, timely treatment and follow-up care, support for cancer patients, or issues related to survivorship or quality of end-of-life care. https://survivornet.ca/

Information Gathering

The Canadian Cancer Survivor Network utilized SurveyMonkey to create and collect all data for the survey on Niraparib. We then utilized our newsletter as well as our social media platforms to disseminate the survey to collect responses. The survey was conducted from June 2, 2023, to June 19, 2023, to obtain responses. Six of the eight respondents are from Canada, one from the United States, and one from Mauritius. All seven respondents to the survey are patients. All the respondents to the survey are male. When the survey data was analyzed, it was clear that one of the eight patients (1 of 8) had experience with Niraparib, and seven of eight patients (7 of 8) do not have experience with Niraparib.

Disease Experience

When asked what stage of prostate cancer they had been diagnosed with, the following responses were received from the respondents:

- Early Stage (1): 1
- Middle Stage (2 or 3): 2
- Late Stage (4) or metastatic: 5

Current treatments that were identified include:

- Radiation: 5
- Surgical Therapy: 5
- ADT: 5
- Chemotherapy: 2
- ADT+Chemotherapy: 1
- Other: 3 (1 PSA blood test and PET CT SCAN & Tranfusion for stimulating my bone marrows, 1 Hormone Therapy, 1 ADT)

When asked if there was an aspect of their disease that is most important to them to control, seven respondents replied:

> “Find the cause.”
>
> “Constipation and temper and mental affliction as to whether I can one day be cured????”
>
> “I wish to avoid metabolic syndrome.”

"For the prostate cancer cell to become metastatic."

"Metastases progression to other body locations."

"Would very much like to prevent or mitigate spread of cancer in my bones."

"ED for intimacy. Incontinence."

Respondents were asked if they have had any issues accessing any therapies. The following issues were highlighted by their responses:

- Limited availability in my community: 2
- Financial hardship due to cost: 1
- Travel costs associated with accessing therapy/treatment: 1
- Supplies or issues with administration: 2
- I haven't had any issues accessing therapy: 5
- Other: 1 (1 The way to find a general practitioner to support my treatment especially with the Zoladex Injection)

When asked if there was anything that they would like to share about their cancer journey, four respondents shared these comments:

"There are MANY things that I would like to share but this survey does not have enough space."

"I am a soldier to combat this health problem inside me and trying to motivate myself not to accept any negative thoughts which could contribute to the destruction of my immune cells."

"Lots. I do research on the quality of life of PCa patients...as well as being a patient myself. I see some problems with the both the design of this questionnaire and the strategy CADTH is using to get useful responses to this survey (and similar survey's of the PCa community. I'd be happy to discuss with you hopefully easy ways to improve both."

"Anticipating advancements in cancer treatments to significantly prolong my life."

Experiences With Currently Available Treatments

With the use of currently available treatments, patients reported that the following symptoms affected their quality of life and day-to-day living:

- Frequency in urination: 5
- Difficulty urinating: 1
- Loss of appetite: 1
- Bone/Skeletal Pain: 2
- Indigestion: 1
- Weight Loss: 3
- Erectile Dysfunction: 6
- Loss of quality of life: 3

- Other: 2 (1 weight gain and fatigue, 1 lethargy and muscle loss)

When asked if any needs in their current therapy are not yet being met, seven patients said no and one patient responded that they are, “I'm on an off-label treatment following a clinical trial protocol.”

Respondents were asked to select what adverse effects they are currently dealing with while on their treatments. Eight respondents selected the following:

- Feeling very tired: 7
- Joint Pain: 3
- High Blood Pressure: 1
- Swelling in your legs or feet: 3
- Low blood potassium levels: 1
- Hot flushes:6
- Cough: 1
- Headache: 1
- High blood sugar levels: 1
- Fertility Problems: 2
- Other: 2 (1 Caused heart attack, 1 Weight Gain)

When asked if their adverse effects were tolerated, one said no, and six said yes with these responses on how they did:

> “By following in parallel Homopaedic medicines together with the normal ones.”
>
> “I went to an off-label treatment protocol currently being investigated in a large clinical trial in the UK.”
>
> “Mild side effects.”
>
> “Will power.”
>
> “Staying positive.”
>
> “Exercise.”

We asked respondents to respond with how they are managing on their current treatment as if they were talking to a friend and what they would tell them. These are their responses:

> “I am on ADT (Aberaterone and Dexamethazone) at this time, and they are working as planned.”
>
> “I am following what my Oncologist is asking me to me and to follow in parallel some natural substances that can contribute to that, stop having worries and negative thoughts and doing appropriate exercises and think of what you eat, and my motto is to starve the progression of cancer.”
>
> “I'd tell them to read the new edition of the book "Androgen Derivation Therapy" An essential guide for prostate cancer patients and their loved ones" formally endorsed by the Canadian Urological Association.”
>
> “I am on hormone therapy. I would recommend it to them.”

"ADT + AADT managing OK."

"On ADT. have manageable side effects."

"Enzalutamide is effective at lowering PSA."

Improved Outcomes

When asked about the following issues that they would hope to see a new drug address to manage their disease, eight respondents answered as follows:

- Maintain quality of life: 8
- Delay onset of symptoms: 2
- Access to a new option for treatment: 1
- Reduce side effects from current medications or treatments: 3
- Ease of use: 2
- Prolong life: 7
- Provide a cure: 5

Patients were asked to describe how much of an improvement would be needed from the new drug to make it better than the current treatment:

"Minimal."

"Total Healing."

"Since I am following a trial protocol, I can't say how well my current therapy is doing and thus can't compare alternative treatments to it."

"No side effects, eliminate and stop the cancer cells to metastasize."

"Significant and Predictable increase in time to loss of life from PC (Many months)."

"Reduce side effects; mitigate cancer spread in bones."

"Less fatigue. Recovery from ED. Less muscle attrition."

We then followed up with the question of how might their quality of life be different with those improvements:

"Improved energy levels."

"Mentally affected as I do not know what is going on inside my body as all are internally concentrated and it is only when doing tests that I am aware of the illness."

"High quality of life. Reduce mental stress."

"Enable continued participation in golf and curling; allow much longer enjoyment of life with my grandchildren."

"Much better."

We asked what considerations patients make when it comes to balancing the advantages and disadvantages of a treatment. Seven respondents shared these thoughts:

> "Life extension and cures."
>
> "If the treatment will bring about what I am expecting living a healthy life for long years ahead."
>
> "At this point in my life I mostly focus on quality of life."
>
> "The severity of the side effects. Reduce quality of life. High mental stress."
>
> "Effects on cancer control versus probable side effects."
>
> "The side effects; maintain QOL."
>
> "Effectiveness. Side effects."

Experience With Drug Under Review

The one patient who has taken Niraparib reported constipation and decreased appetite as adverse effects that were caused by taking Niraparib.

We asked respondents to rate on a scale of 1-5 how likely they would be to recommend that Niraparib be available to all patients who qualify for it. The one patient who has taken Niraparib responded with a level 4 in favour of recommending Niraparib.

When asked in comparison to other therapies how was their treatment experience with Niraparib in treating their prostate cancer, the respondent rated the following areas on a scale of much better, little or no difference, and much worse:

- Symptom management: Little or no difference
- Side effects: Little or no difference
- Ease of use: Little or no difference
- Disease progression: Much better
- Other (please specify): Much better

Companion Diagnostic Test

Not applicable.

Anything Else?

CCSN is aware of the limitations of this submission given the small number of respondents and with only one patient on Niraparib. However, it is clear in this submission, and from past submissions, that what this community is looking for is a treatment that will prevent further spread of their cancer and provide good quality of life while receiving their treatment. Another desire of these individuals is to see a treatment that can prolong life in a significant way to be able to spend as much time as they can with their friends, family, and other loved ones.

Conflict of Interest Declaration — Canadian Cancer Survivor Network

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission?

No.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures for Canadian Cancer Survivor Network

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Janssen (2022)	–	–	–	X
Janssen (2023)	–	–	–	X

Canadian Cancer Society

About Canadian Cancer Society

Our purpose: To unite and inspire all Canadians to take control of cancer.

Our mission: In trusted partnership with donors and volunteers, we improve the lives of all those affected by cancer through world-class research, transformative advocacy and compassionate support.

We set ourselves apart from other cancer charities by taking a comprehensive approach against cancer. We are also the only national charity that supports all Canadians living with all cancers across the country. We shared our survey to through relevant CCS communication channels and support programs as well as through patient panels.

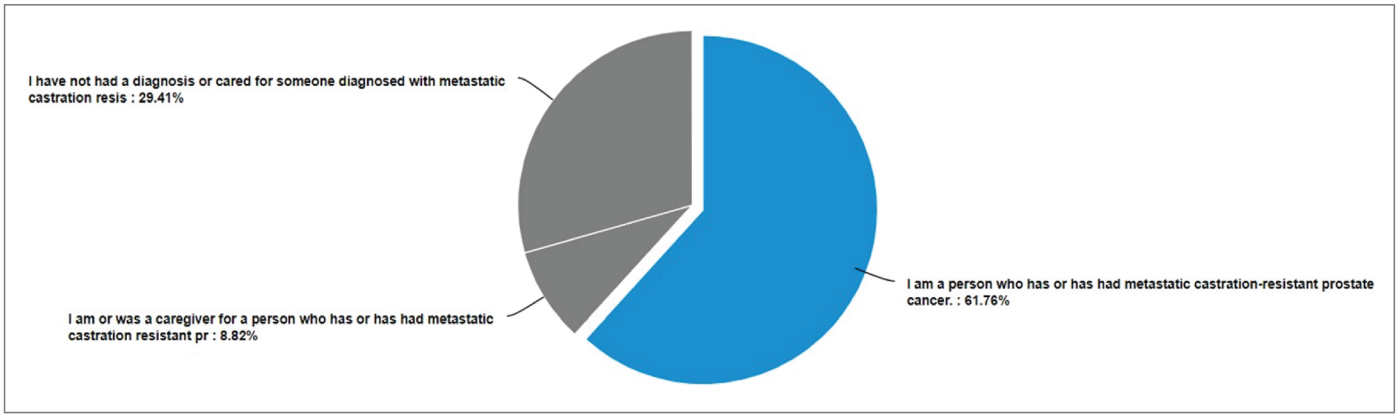
Website Link: https://cancer.ca/en

Information Gathering

The Canadian Cancer Society gathered perspectives through survey responses from patients and caregivers. The survey was open to people in Canada from April until May 18th for this submission. In total, we received 34 responses to our survey. 21 respondents (61.8%) identified as a person who has or has had metastatic castration-resistant prostate cancer [referred to as respondents with disease experience] and 3 respondents (8.8%) identified as a caregiver for a person who has or has had metastatic castration resistant prostate cancer [referred to as caregivers]. The remaining 10 respondents did not have a diagnosis and have

not cared for someone with a diagnosis — as such, these responses were omitted. 97% of respondents responded from Canada.

Figure 1: Patients and Caregivers Responses on Metastatic Castration Resistant Prostate Cancer



Disease Experience

How much of an impact have symptoms associated with metastatic castration resistant prostate cancer had on your day-to-day activities and quality of life?

Please refer to Table 2 for more details. Out of a total of 21 respondents with disease experience, the ability to engage in sexual activity was most affected with 14 (67%) reporting moderate to significant impact. The second most affected ability was the ability to work, with 9 (43.1%) respondents with disease experience reporting moderate to significant impact. The ability to exercise and the ability to maintain positive mental health were the next most affected with 8 respondents in each category reporting a moderate to significant impact.

Specify any other areas of your life that have been impacted and how significant the impact has been?

One respondent with disease experience stated that “headaches and joint pain have become debilitating”. Another respondent with disease experience elaborated on the impact their disease had on exercise, sharing that “cycling is painful”. Two respondents noted significant impact on sleep, with one saying “… I have bouts of sleepless nights and am being treated for constant daily crying.”

Of the caregiver respondents, all 3 (100%) indicated that the disease had a significant impact ability to work for the person that they were caring for.

Experiences With Currently Available Treatments

Which of the following barriers have you faced when receiving treatment for your cancer?

Please refer to Figure 1 for more details. Respondents with disease experience identified 31 barriers from all barriers listed on the survey. Of these barriers, transportation costs associated with appointments was the

largest barrier to care (26%), followed by lack of familiarity with navigating the health care system and long wait times to receive tests or treatments, each with 13% of respondents identifying those barriers.

How many lines of treatment have you undergone since your initial diagnosis of prostate cancer?

A description of what a line of treatment entails was provided. The majority of respondents with disease experience indicated they had undergone 3 or more lines of therapy (62%). 14% of respondents were unsure.

Since your initial diagnosis of prostate cancer, which treatments have you tried?

For more details, please refer to Figure 2. Respondents were able to select from 14 options including a variety of treatments, watchful waiting and options to indicate they were unsure, or to provide additional information. The largest percentage of respondents with disease experience indicated that they used luteinizing hormone-releasing hormone (LHRH) agonists (23%), followed by external beam radiation (20%), followed by anti-androgen drugs (15%) and surgery (14%).

How much of an impact do the following cancer treatment side effects have on your daily life?

Please refer to Table 3 for more details. Respondent with disease experience were given a total of 31 different side-effects to rank as having no impact, small impact, moderate impact, severe impact or as N/A. Reported changes in libido, sexual function or fertility stood out as having the most significant impact for respondents experiencing these side effects compared to other side effects listed, with 62% indicating a significant impact. This was followed by hot flushes as well as fatigue and low energy being reported as having a moderate to significant impact on daily life by 62% and 48% of respondents respectively.

Of caregiver respondents, fatigue and low energy was the most significant side effect reported for the person they were caring. All 3 caregiver respondents reported that this had a significant impact on the person that they were caring for.

How willing would you be to tolerate new side effects from therapies if they could offer better control of disease progression?

Respondents were asked to rank willingness on a scale of 1 (will not tolerate side effects at all) to 5 (will tolerate significant side effects). Thirty-three percent of respondents with disease experience ranked their willingness as a "5", followed by 29% ranking "4" and 23% ranking "3".

Improved Outcomes

What improvements would you like to see in new treatments that are not achieved in currently available treatments?

One respondent with disease experience commented on difficulty travelling to access treatment, saying they were "…not able to navigate larger cities (only have one working eye)" and that they were "…not able to contend with traffic…". They also commented on the costs associated with travelling to appointments, saying "being retired I have to watch my budget." Other respondents noted the difficulty of managing side effects, with one respondent stating they wanted to see "fewer or less severe side effects," and another mentioning the need to discuss "ways to mitigate side effects whenever possible."

Caregiver responses focused primarily on improving access to health human resources, affordability and availability of treatments.

Experience With Drug Under Review

No respondents had experience with the drug under review. As such, our submission focuses on respondents with disease experience and caregivers of people with disease experience.

Table 2: Symptoms of Metastatic Castration Resistant Prostate Cancer and Impact on Quality of Life Reported by People With Disease Experience

Statement	No impact	Small impact	Moderate impact	Significant impact	Not sure	Not applicable	Overall
Ability to work	6	4	4	5	0	2	21
	28.57%	19.05%	19.05%	23.81%	0%	9.52%	100%
Ability to travel	11	2	3	4	1	0	21
	52.38%	9.52%	14.29%	19.05%	4.76%	0%	100%
Ability to exercise	8	5	6	2	0	0	21
	38.1%	23.81%	28.57%	9.52%	0%	0%	100%
Ability to conduct household chores	10	5	4	1	1	0	21
	47.62%	23.81%	19.05%	4.76%	4.76%	0%	100%
Ability to fulfill family obligations	11	5	0	3	1	1	21
	52.38%	23.81%	0%	14.29%	4.76%	4.76%	100%
Ability to spend time with family and friends	14	3	2	2	0	0	21
	66.67%	14.29%	9.52%	9.52%	0%	0%	100%
Ability to concentrate	12	1	2	5	1	0	21
	57.14%	4.76%	9.52%	23.81%	4.76%	0%	100%
Ability to fulfill practical needs (dressing, bathing, preparing meals)	16	2	2	1	0	0	21
	76.19%	9.52%	9.52%	4.76%	0%	0%	100%
Ability to maintain positive mental health	9	3	3	5	1	0	21
	42.86%	14.29%	14.29%	23.81%	4.76%	0%	100%
Engage in sexual activity	2	1	1	13	1	3	21
	9.52%	4.76%	4.76%	61.9%	4.76%	14.29%	100%

Table provides a breakdown of respondents with disease experience stated symptoms and impact on quality of life, ranging from no impact to significant impact.

Figure 2: Respondents With Disease Experience Barriers to Receiving Treatment

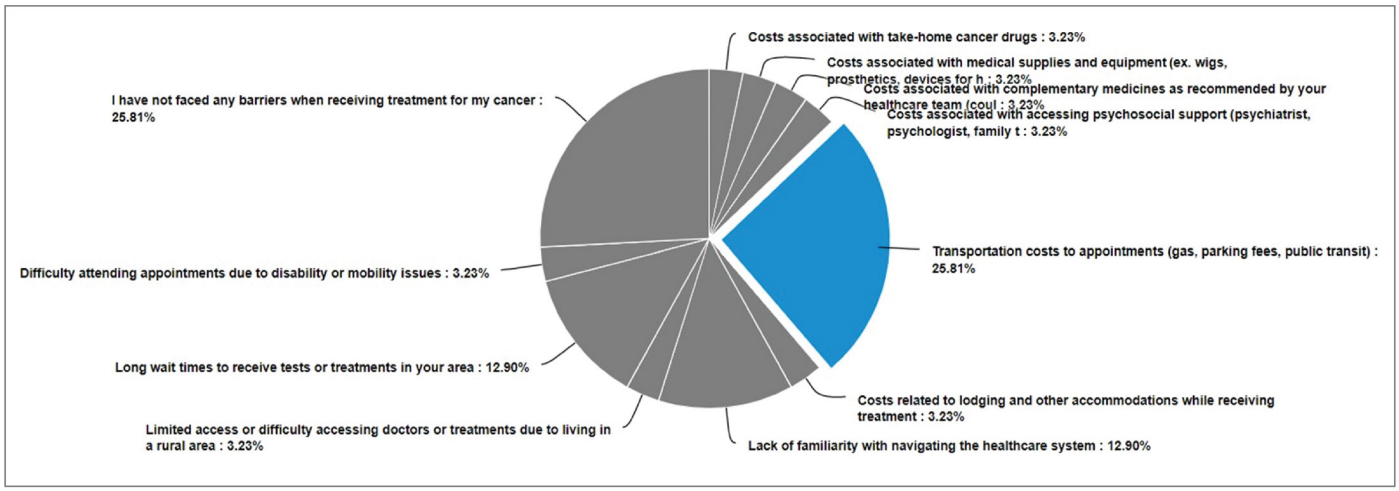


Figure 3: Treatments Tried by Respondents With Disease Experience Since Initial Diagnosis

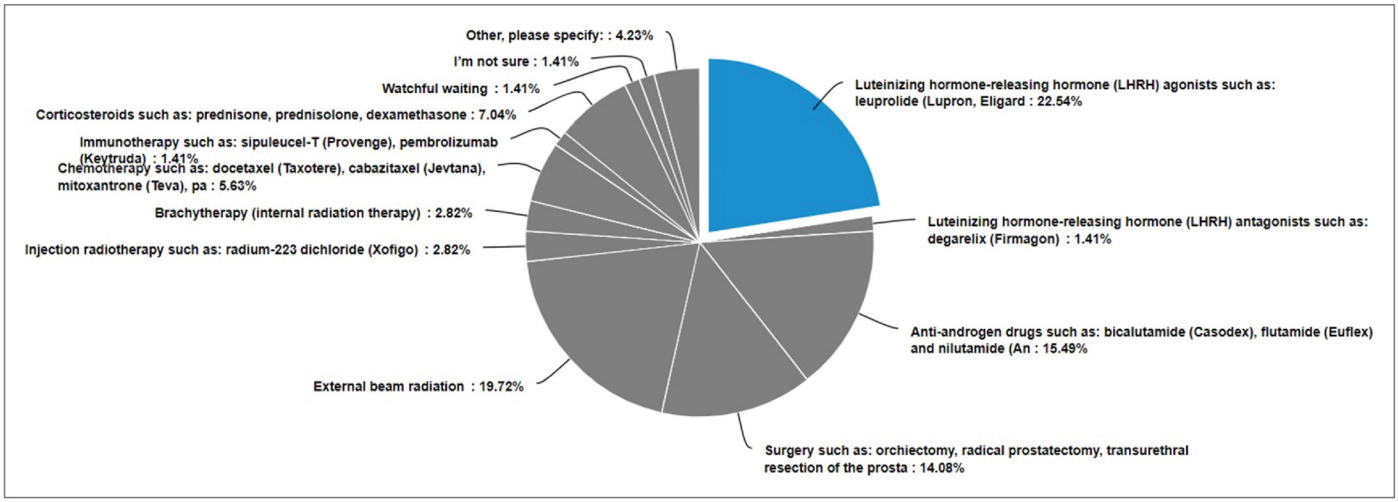


Table 3: Side-Effects Reported by Respondents With Disease Experience

Statement	No impact	Small impact	Moderate impact	Significant impact	Not sure	Not applicable	Overall
Loss of bone density or osteoporosis	5	10	2	0	4	0	21
	23.81%	47.62%	9.52%	0%	19.05%	0%	100%
Breast swelling and/ or discharge	10	5	2	0	0	4	21
	47.62%	23.81%	9.52%	0%	0%	19.05%	100%
Loss of muscle mass or muscle weakness	3	7	7	3	1	0	21
	14.29%	33.33%	33.33%	14.29%	4.76%	0%	100%
Abnormal electrolytes (Low blood potassium levels)	12	2	0	2	4	1	21
	57.14%	9.52%	0%	9.52%	19.05%	4.76%	100%
Hot flushes	1	6	9	4	1	0	21
	4.76%	28.57%	42.86%	19.05%	4.76%	0%	100%
Fluid retention (e.g. swollen legs)	10	5	4	0	1	1	21
	47.62%	23.81%	19.05%	0%	4.76%	4.76%	100%
Changes in blood sugar levels or diabetes	13	1	3	1	1	2	21
	61.9%	4.76%	14.29%	4.76%	4.76%	9.52%	100%
Fatigue or low energy	4	5	4	6	2	0	21
	19.05%	23.81%	19.05%	28.57%	9.52%	0%	100%
Hair loss	12	6	2	1	0	0	21
	57.14%	28.57%	9.52%	4.76%	0%	0%	100%
Anemia (easy bruising and bleeding)	11	4	3	1	2	0	21
	52.38%	19.05%	14.29%	4.76%	9.52%	0%	100%
Issues with memory or concentration	9	6	2	3	1	0	21
	42.86%	28.57%	9.52%	14.29%	4.76%	0%	100%
Increase in cholesterol levels	9	6	3	1	1	1	21
	42.86%	28.57%	14.29%	4.76%	4.76%	4.76%	100%

Statement	No impact	Small impact	Moderate impact	Significant impact	Not sure	Not applicable	Overall
Frequent infections (low white blood cell counts)	14	3	1	0	2	1	21
	66.67%	14.29%	4.76%	0%	9.52%	4.76%	100%
Nausea and/or vomiting	18	1	1	1	0	0	21
	85.71%	4.76%	4.76%	4.76%	0%	0%	100%
Appetite changes	13	4	2	2	0	0	21
	61.9%	19.05%	9.52%	9.52%	0%	0%	100%
Bowel problems (constipation or diarrhea)	8	5	5	3	0	0	21
	38.1%	23.81%	23.81%	14.29%	0%	0%	100%
Peripheral neuropathy (numbness, tingling and pain in the nerves in the hands and feet)	7	5	4	3	2	0	21
	33.33%	23.81%	19.05%	14.29%	9.52%	0%	100%
Kidney problems	16	2	0	1	2	0	21
	76.19%	9.52%	0%	4.76%	9.52%	0%	100%
Weight changes	7	4	6	3	1	0	21
	33.33%	19.05%	28.57%	14.29%	4.76%	0%	100%
Changes in libido, sexual function or fertility	3	2	0	13	0	3	21
	14.29%	9.52%	0%	61.9%	0%	14.29%	100%
Pain	7	7	3	3	1	0	21
	33.33%	33.33%	14.29%	14.29%	4.76%	0%	100%
Mouth, tongue, and throat problems such as sores and pain with swallowing	17	3	0	0	1	0	21
	80.95%	14.29%	0%	0%	4.76%	0%	100%
Blood pressure changes	11	6	1	1	2	0	21
	52.38%	28.57%	4.76%	4.76%	9.52%	0%	100%
Irregular heartbeats (palpitations) or chest pain	13	5	1	1	1	0	21

Statement	No impact	Small impact	Moderate impact	Significant impact	Not sure	Not applicable	Overall
	61.9%	23.81%	4.76%	4.76%	4.76%	0%	100%
Slow breathing or difficulty breathing	10	4	4	2	1	0	21
	47.62%	19.05%	19.05%	9.52%	4.76%	0%	100%
Difficulties with urination (Incontinence, frequent or urgent need for urination, painful urination)	6	8	3	3	1	0	21
	28.57%	38.1%	14.29%	14.29%	4.76%	0%	100%
Headaches or pounding in the neck or ears	13	4	2	1	1	0	21
	61.9%	19.05%	9.52%	4.76%	4.76%	0%	100%
Blurred vision	13	3	3	1	1	0	21
	61.9%	14.29%	14.29%	4.76%	4.76%	0%	100%
Liver problems or abnormal liver function tests	15	1	1	0	4	0	21
	71.43%	4.76%	4.76%	0%	19.05%	0%	100%
Dizziness or feeling lightheaded	7	6	3	4	1	0	21
	33.33%	28.57%	14.29%	19.05%	4.76%	0%	100%
Dry mouth	9	3	6	2	1	0	21
	42.86%	14.29%	28.57%	9.52%	4.76%	0%	100%

Table provides breakdown of respondents with disease experience listed treatment showcasing side effects causing moderate to severe impact on daily life.

Conflict of Interest Declaration — Canadian Cancer Society

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Did you receive help from outside your patient group to complete this submission?

No.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 4: Financial Disclosures for Canadian Cancer Society

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Janssen Inc (2022)	–	–	X	–
Janssen Inc (2021)	–	–	X	–

Clinician Input

Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee (GU DAC)

About Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee (GU DAC)

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

Information Gathering

Information was gathered via videoconferencing and email.

Current Treatments and Treatment Goals

In the mCRPC setting, therapy is aimed at prolonging life. There currently remains no cure for these patients. Treatments should also aim to maximize QOL. The current treatment landscape options include: abiraterone OR enzalutamide OR Docetaxel OR Radium-223 (in docetaxel ineligible patients) all given concurrently with ADT. Cabazitaxel is another option after docetaxel intensification in the mCSPC setting.

Treatment Gaps (Unmet Needs)

Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

As there are no cures currently available in the 1L mCRPC setting, therapies that can prolong life are needed. Niraparib with Abiraterone Acetate/Prednisone (AAP) adds to a current SOC therapy (AAP) with improved PFS in HRR mutated prostate cancer and thus addresses the goal of prolonged life. Currently there are no targeted treatments available in 1L mCRPC patients.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

As per the MAGNITUDE trial, in treatment naïve mCRPC patients with HRR mutations, niraparib and AAP would become a standard of care.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

The combination of niraparib and AAP should be reserved for patients in the mCRPC setting. As per the MAGNITUDE trial, treatment with chemotherapy or ARPI in the mCSPC or nmCRPC setting should not preclude niraparib + AAP in the 1L mCRPC setting.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

PSA will be used as a burden of disease and to monitor response to therapy. Serial radiographic imaging will also be used for response and to determine progression as per standard of care. Other markers of disease burden can also be used such as LDH and ALP in select individuals.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Significant side effects and progression of disease on imaging.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Niraparib + AAP therapy should be administered by oncologists with experience using PARP inhibitors. These individuals can be urologic oncologists, medical oncologists, or radiation oncologists. Expertise in management of PARPi side effects is required.

Additional Information

There currently is no other combination therapy available for 1L mCRPC patients in this setting. Therapies specific to HRR+ patients are not present in the 1L mCRPC setting. This is a novel combination of therapies that will benefit a targeted population of prostate cancer patients.

Conflict of Interest Declarations — Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee (GU DAC)

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

OH-CCO provided secretariat function to the group.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. Please note that this is required for *each clinician* who contributed to the input.

Declaration for Clinician 1
Name: Dr. Girish Kulkarni

Position: Lead, Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee (GU DAC)

Date: 01-06-2023

Table 5: COI Declaration for OH-CCO Genitourinary Cancer Drug Advisory Committee — Clinician 1

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 2
Name: Dr. Sebastian Hotte

Position: Member, Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee (GU DAC)

Date: 14-06-2023

Table 6: COI Declaration for OH-CCO Genitourinary Cancer Drug Advisory Committee — Clinician 2

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Janssen	X	–	–	–

Declaration for Clinician 3
Name: Dr. Aly-Khan Lalani

Position: Member, Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee (GU DAC)

Date: 14-06-2023

Table 7: COI Declaration for OH-CCO Genitourinary Cancer Drug Advisory Committee — Clinician 3

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Janssen	X	–	–	–

Declaration for Clinician 4
Name: Dr. Urban Emmenegger

Position: Member, Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee (GU DAC)

Date: 14-06-2023

Table 8: COI Declaration for OH-CCO Genitourinary Cancer Drug Advisory Committee — Clinician 4

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Janssen	–	X	–	–

Declaration for Clinician 5
Name: Dr. Christina Canil

Position: Member, Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee (GU DAC)

Date: 14-06-2023

Table 9: COI Declaration for OH-CCO Genitourinary Cancer Drug Advisory Committee — Clinician 5

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Janssen	X	–	–	–

Declaration for Clinician 6
Name: Dr. Chris Morash

Position: Member, Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee (GU DAC)

Date: 14-06-2023

Table 10: COI Declaration for OH-CCO Genitourinary Cancer Drug Advisory Committee — Clinician 6

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Janssen	X	–	–	–

Declaration for Clinician 7
Name: Dr. Reeta Barua

Position: Member, Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee (GU DAC)

Date: 14-06-2023

Table 11: COI Declaration for OH-CCO Genitourinary Cancer Drug Advisory Committee — Clinician 7

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Janssen	X	–	–	–

Declaration for Clinician 8

Name: Dr. Akmal Ghafoor

Position: Member, Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee (GU DAC)

Date: 14-06-2023

Table 12: COI Declaration for OH-CCO Genitourinary Cancer Drug Advisory Committee — Clinician 8

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

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