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CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

OLAPARIB (LYNPARZA)

(AstraZeneca Canada Inc.)

Indication: As monotherapy for the treatment of adult patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who have progressed following prior treatment with a NHA.

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Abbreviations

ADT	androgen deprivation therapy
AE	adverse event
ARAT	Androgen receptor-axis-targeted therapies
ATM	A-T mutated
BICR	blinded independent central review
BPI-SF	Brief Pain Inventory (Short Form)
BRCA	BReast CAncer gene
CCO	Cancer Care Ontario
CCSN	Canadian Cancer Survivor Network
CGP	Clinical Guidance Panel
CI	confidence interval
CPSA	College of Physicians and Surgeons of Alberta
CRPC	castration-resistant prostate cancer
CSPC	castration-sensitive prostate cancer
CTA	clinical trial assay
CTCAE	common terminology criteria for adverse events
CLIA	Clinical Trial Improvement Amendments
ECOG	Eastern Cooperative Oncology Group
EQ-5D-5L	5-level 5-dimension EuroQol questionnaire
FAPSI-6	FACT Advanced Prostate Symptom Index 6
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FWB	functional well-being
GCSF	granulocyte colony-stimulating factor
HR	hazard ratio
HRQoL	health-related quality of life
HRR	homologous recombination repair
IQR	Interquartile range
ITC	indirect treatment comparison
ITT	intention-to-treat

LHRH	Luteinizing hormone-releasing hormone
MAIC	matched adjusted indirect comparison
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
mHSPC	metastatic hormone-sensitive prostate cancer
NGS	next-generation sequence
NHA	new hormonal agent
nmCRPC	non-metastatic castration-resistant prostate cancer
NMA	network meta-analysis
OR	odds ratio
ORR	objective response rate
OS	overall survival
PARP	poly(adenosine diphosphate)-ribose polymerase
pCODR	pan-Canadian Oncology Drug Review
PCS	Prostate Subscale
PCWG3	Prostate Cancer Clinical Trials Working Group
PFS2	Time to second progression by investigator assessment of radiological or clinical progression
PRO	patient reported outcome
PSA	prostate serum antigen
PWB	physical well-being
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
rPFS	radiographic progression-free survival
RPSFT	rank preserving structural failure time
SAE	serious adverse event
SLR	systematic literature review
SSRE	symptomatic skeletal-related event
SWB	social/family well-being

1 Guidance In Brief

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding olaparib (Lynparza) for metastatic castration-resistant prostate cancer (mCRPC). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of olaparib as a monotherapy for the treatment of adult patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in homologous recombination repair (HRR) genes BRCA or ATM who have progressed following prior treatment with a new hormonal agent (NHA).

Olaparib is a potent oral human polyadenosine 5'diphosphoribose polymerisation (PARP) inhibitor (PARP-1, PARP-2, and PARP-3) that exploits deficiencies in DNA repair pathways to preferentially kill cancer cells with these deficits compared to normal cells. Health Canada has issued market authorization, without conditions, for olaparib monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline and/or somatic BRCA or ATM mutated mCRPC who have progressed following prior treatment with a new hormonal agent. BRCA or ATM mutations must be confirmed before LYNPARZA treatment is initiated.

Note that the Health Canada indication aligns with the CADTH reimbursement criteria.

The recommended dosing of olaparib is 600 mg (2 x 150 mg tablets taken orally twice daily). The 100 mg tablet is available for dose reduction. Treatment should continue until progression of the underlying disease or unacceptable toxicity. Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Study Design

The pCODR systematic review included one multinational, open-label, randomized phase III trial, the PROfound trial,[1,2] that assessed the efficacy and safety of olaparib versus investigator's choice (i.e., enzalutamide or abiraterone acetate) for adult patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in HRR genes BRCA or ATM who have progressed following prior treatment with a NHA.

Patients were included in the trial if they met the following criteria: males ages 18 years and older with a histologically confirmed diagnosis of prostate cancer; progressed on prior NHA (e.g., abiraterone acetate and/or enzalutamide) for the treatment of metastatic prostate cancer and/or castration-resistant prostate cancer (CRPC); radiographic progression while on androgen deprivation therapy (ADT) or after bilateral orchiectomy; qualifying HRR mutation in tumor tissue by the FMI CLIA HRR (Lynparza HRR) CTA Assay; normal organ and bone marrow function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.[1] Patients were permitted in the trial if they had previous taxane chemotherapy.[1] Further details on the inclusion criteria and exclusion criteria are provided in Table 6.

Patients who had qualifying HRR mutations using the FMI Lynparza HRR Assay were divided into two cohorts. Patients were included in Cohort A if they had a BRCA1, BRCA2 or ATM mutation while those in Cohort B had a mutation in 12 other genes involved in HRR (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and RAD54L).[1] This review will present the efficacy results from cohort A, however, will not present the efficacy results from cohort B because cohort B was not part of the CADTH requested reimbursement criteria and is therefore beyond the scope of this review. However, the results from the PROfound trial were also analyzed and reported for the overall trial population (cohort A+B) and will be presented in this review as well.

Patients in both Cohort A and B were randomized in a 2:1 ratio to receive either olaparib (300 mg twice daily) or investigator's choice (enzalutamide [160 mg/daily] or abiraterone acetate [1000 mg/daily with 5 mg of prednisone twice daily]). Randomization was stratified by previous taxane chemotherapy (yes, no) and measurable disease at baseline (yes, no).[1]

The primary endpoint in the PROfound trial was radiographic progression-free survival (rPFS) by BICR using Response Evaluation Criteria in Solid Tumors (RECIST 1.1 soft tissue) and Prostate Cancer Working Group 3 (PCWG3 bone) criteria in Cohort A.[1] Secondary outcomes were confirmed overall response rate (ORR) by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria in Cohort A, rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria in Cohort A + B, pain progression based on Brief Pain Inventory Short Form (BPI-SF) item 3 "worst pain in 24 hours" and opiate analgesic use (AQA score) in Cohort A and overall survival (OS) in Cohort A. Other secondary outcomes in Cohort A include time from randomization to the first symptomatic skeletal-related event (SSRE), duration of response, time to opiate use for cancer-related pain, soft tissue response, proportion of patients achieving a ≥ 50% decrease in prostate specific antigen (PSA), circulating tumor cells (CTC) conversion, time to second progression by investigator assessment of radiological or clinical progression or death (PFS2) and health-related quality of life (HRQoL). Safety outcomes were assessed in Cohort A+B.

The trial was designed to have 95% power to detect a HR of 0.53 for rPFS events with a two-sided significance level (α) of 0.05.[1] The trial requires a sample size of 240 patients in Cohort A and 143 rPFS events (60% maturity) for the primary analysis.[1] The sample size required for Cohort B is 100 patients.

Patients in the control group who had radiographic progression by BICR were eligible to crossover and receive olaparib but patients who had radiographic progression as assessed by the investigator were not permitted to crossover until after the primary analysis. In addition, prior to switching to olaparib, patients were not receiving any intervening anticancer therapy following discontinuation of their randomized treatment and any unresolved toxicities from prior therapy should be controlled (and no greater than Common Terminology Criteria for Adverse Events [CTCAE] grade 1 at the time of starting olaparib therapy).[1] Patients who crossed over to receive olaparib may continue treatment until investigator's opinion and did not meet any other discontinuation criteria.

Patient Characteristics

Among those in Cohort A, the median age in the olaparib group was 68 years (range: 47 to 86) and 67 years (range: 49 to 86) in the control group, more than half of all patients had measurable disease at baseline (59% in olaparib and 55% in control) and the majority of patients received a previous taxane (65% in olaparib and 63% in control).[1] However, de Bono et al. (2020) reported that there was an imbalance in the patients with visceral metastases (28% in olaparib and 39 % in control), median baseline PSA concentration (62.2 [IQR: 21.9 to 280.4] in olaparib and 112.9 [IQR: 34.3 to 317.1] in control) and patients with an ATM alteration (37% in olaparib and 29% in control).[1] Similar results were observed for Cohort A+B. However, the Sponsor noted that these imbalances did not have an impact on efficacy endpoints. [redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Two hundred and forty-five patients were enrolled in Cohort A and 142 patients were enrolled in Cohort B. Among those in Cohort A, 162 patients were assigned to the olaparib treatment group and 83 were assigned to the control treatment (N=37 for enzalutamide and N=46 abiraterone).[1]

Patients randomized to the control group in Cohort A and B were allowed to cross-over and receive olaparib after the primary analysis. At the primary data-off date (June 4, 2019), 51/83 patients in Cohort A and 24/48 patients in Cohort B switched over to receive olaparib.[4] The Sponsor noted that three patients in the control group received olaparib at the time of the June 4, 2019 data cut-off without BICR confirmed progression (off-label commercial use) while all other patients had BICR confirmed progression prior to switching. At the final data cut-off date (March 20, 2020), patients were permitted to crossover and receive olaparib after investigator-assessed disease progression since rPFS by BICR was not collected beyond the primary analysis. At the March 20, 2020 cut-off, five additional patients in Cohort A (N=56/83) and six additional patients in Cohort B (N=30/48) crossed-over to receive olaparib.[4]

Limitations/Sources of Bias

The randomization method used in PROfound was adequate, and a stratified randomization procedure was used based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results. The efficacy analysis was conducted according to the ITT principal. However, there are a number of limitations and potential sources of bias, which include:

- The PROfound trial used an open-label study design. This study design has the potential to bias outcomes in favour of the treatment group, including: rPFS, PROs and safety. However, bias was minimized because the primary analyses of efficacy endpoints were based on radiographic progression assessments by BICR. For patient reported outcomes and safety, the investigators, patients, and sponsor were not blinded, which may have biased results in favour of olaparib. However, the CGP felt that there were no unexpected adverse events in the trial.
- All patients randomized to the control group were permitted to crossover and receive olaparib once they had objective radiological progression confirmed by a BICR or by the investigator after the date of the primary analysis. At the June 4, 2019 data cut-off, 51/83 (61%) patients in Cohort A and 24/48 (50%) patients in Cohort B switched over to receive olaparib.[4] Patient crossover could confound the results of the final OS and PFS2 analyses as well as the safety outcomes in favour of olaparib. However, RPSFT models were conducted for OS to try and reduce the potentially confounding effects of patient crossover and the results were similar to the unadjusted results.
- The control group may not be the most relevant comparator in Canadian clinical practice because patients were rechallenged with enzalutamide or abiraterone. The comparator in the trial was investigator's choice of NHA (i.e., enzalutamide or abiraterone). Sequencing of alternate NHAs upon progression (i.e., first line enzalutamide followed by second line abiraterone or vice versa) is rarely done in Canadian clinical practice and not funded in most provinces. However, the CGP felt that the PROfound trial results are generalizable to the Canadian clinical practice setting as it has been suggested that NHAs have similar efficacy compared to docetaxel in the post-NHA setting.[5] Furthermore, due to the COVID pandemic funding restrictions may be loosened in some places and Canadian clinicians may be encouraged to alternate NHAs upon progression to avoid having patients come to the hospital and avoid toxicity from taxane chemotherapy.
- [redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* The results of the subgroup analyses stratified by genotype carrier status suggested that olaparib had a protective effect for BRCA1 and/or BRCA2 carriers for rPFS and OS. However, subgroup analyses for BRCA1 carriers alone did not show a significant difference on efficacy outcomes, but this may be due to small sample sizes. There were no treatment differences observed for ATM carriers on rPFS and OS. Firm conclusions cannot be made on the basis the subgroup analyses because the trial was neither designed nor powered to reliably analyze the results in these subgroup analyses.

Efficacy Outcomes

Two data cut-offs were used for this analysis. The first data cut off was on June 4, 2019, which represents the date of the primary analysis and a median follow-up of 12.57 months (range: 1.87 to 23.89) in the olaparib group and 13.19 months (range: 0.95 to 23.23) in the control group for Cohort A.[4] The second data cut-off date was on March 20, 2020, which represents the date of the final

analysis and a median follow-up of 21.91 months (range: 1.87 to 33.41) in the olaparib group and 21.04 months (range: 0.95 to 32.76) in the control group for Cohort A.[4] Only the selected results from Cohort A and Cohort A+B will be presented in this section. Please refer to Section 6 for more details.

Primary Outcomes

Radiographic Progression Free Survival

rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria was defined as the time to objective disease progression (soft tissue or bone) or death (by any cause in the absence of progression). The BICR assessments using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria only apply to the results of the primary analysis, after this data-cut off, all assessments were performed by the investigator.[1]

Cohort A

rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria in Cohort A was the primary outcome of the trial. The primary analysis for rPFS occurred on June 4, 2019. At the data cut-off date, 71% of patients in Cohort A had progression as assessed by BICR or died (N=174). In the olaparib group 65.4% (N=106) had progressed or died as compared to 81.9% (N=68) of patients in the control group.[6] The median rPFS as assessed by BICR in the olaparib group was 7.39 months (95% CI: 6.24 to 9.33) and it was 3.55 months (95% CI: 1.91 to 3.71) in the control group.[6] de Bono et al. (2020) reported that treatment with olaparib was associated with statistically significant prolonged rPFS as assessed by BICR as compared to control (HR: 0.34, 95% CI: 0.25 to 0.47; P<0.001).[1] A prespecified sensitivity analysis of rPFS as assessed by the investigator showed similar results (HR: 0.24, 95% CI: 0.17 to 0.34).[1]

The effect of olaparib on rPFS as assessed by BIRC was compared to the control group and stratified by genotype carrier status in Cohort A+B. For BRCA1 and/or BRCA2 carriers, olaparib was associated with a longer rPFS as assessed by BICR as compared to control (HR: 0.22, 95% CI: 0.15 to 0.32) while there was no treatment difference on rPFS as assessed by BICR for ATM carriers. However, these results should be interpreted with caution because they are considered exploratory and not adjusted for multiplicity.

Objective Response Rate

Objective response rate by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria was defined as the proportion of patients with at least one visit response of complete response or partial response in their soft tissue and the absence of progression on bone scan.[1] Patients were only included in this analysis if they had measurable disease at baseline as assessed by BICR.[1]

Cohort A

Objective response rate by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria was a secondary outcome for Cohort A and 84 patients in the olaparib group and 43 patients in the control group were used in the analysis. At the June 4, 2019 data cut-off, 33% of patients in the olaparib group had confirmed ORR as compared to 2% in the control group.[1] A statistically significant difference in ORR was demonstrated with an OR of 20.86 (95% CI: 4.18 to 379.18; P<0.001).[1]

Time to Pain Progression

Time to pain progression in Cohort A was a secondary outcome in the trial and it was defined as the time to worsening pain. Worsening pain was based on the Brief Pain Inventory-short form (BPI-SF) item 3 “worst pain in 24 hours” and the opiate analgesic uses (AQA score). Time to pain progression was classified differently for asymptomatic and symptomatic patients.[1]

Cohort A

At the June 4, 2019 data cut-off date, 13% of patients in olaparib group (N=21) had pain progression as compared to 16.9% (N=14) of patients in the control group.[6] The median time to pain progression in the olaparib group was not reached (NR) while it was 9.92 months in the control group.[6] de Bono et al. (2020) reported that treatment with olaparib was associated with statistically significant prolonged time to pain progression as compared to control (HR: 0.44, 95% CI: 0.22 to 0.91; p=0.02).[1]

Overall Survival

Overall survival was a secondary outcome in the trial and it was defined as the time to death due to any cause regardless of whether the patient withdraws from their assigned therapy or received another anti-cancer therapy.[1] Two analyses were performed for OS: the interim analysis and the final analysis. The interim analysis occurred at the primary analysis of rPFS (June 4, 2019) and the final analysis occurred when 146 events had occurred (61% maturity) (March 20, 2020).[1]

Cohort A

The interim analysis for OS occurred at the primary analysis (June 4, 2019), [redacted].[3] [redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* Treatment with olaparib was associated with prolonged survival time as compared to control (HR: 0.62, 95% CI: 0.41 to 0.95; P=0.02).[1]

At the final analysis (March 20, 2020), 67% of patients in the control group of Cohort A had crossed over and received olaparib (N=56).[2] In the olaparib group, 56.2% of patients (N=91) had died as compared to 68.7% (N=57) of patients in the control group.[2] The median OS was 19.1 months (95% CI: 17.4 to 23.4) in the olaparib group and 14.7 months (95% CI: 11.9 to 18.8) months in the control group.[2] Treatment with olaparib was associated with statistically significant prolonged survival time as compared to control (HR: 0.69, 95% CI: 0.50 to 0.97; P=0.02).[2] Although these results may be confounded due to patient cross-over, the prespecified sensitivity analysis adjusting for patient cross-over showed a similar treatment effect (HR: 0.42, 95% CI: 0.19 to 0.91).[2]

Hussain et al. (2020) also performed subgroup analyses of OS stratifying by genotype carrier status in Cohort A+B.[2] At the March 20, 2020 data cut-off, 52% of BRCA1 and/or BRCA2 carriers treated with olaparib (N=53/102) had died as compared to 71% of those treated with control (N=41/58).[2] The median OS was 20.1 months (95% CI: 17.4 to 26.8) in the olaparib group and 14.4 months (95% CI: 10.7 to 18.9) months in the control group.[2] Treatment with olaparib was associated with a prolonged survival time as compared to control among BRCA1 and/or BRCA2 carriers (HR: 0.63, 95% CI: 0.42 to 0.95).[2] Similar estimates were observed for those who were single BRCA2 carriers, but the association was attenuated among single BRCA1 carriers.[2] In addition, there was no treatment difference between olaparib and the control group on OS for ATM carriers unadjusted and adjusted for cross-over. However, these results should be interpreted with caution due to small sample sizes and no adjustment for multiplicity or patient cross-over.

Quality of Life

The Functional Assessment of Cancer Therapy- Prostate Cancer

The FACT-P was used to assess HRQoL in Cohorts A and A+B. The baseline patient adherence rates for the FACT-P in Cohort A+B were 72% for patients receiving olaparib and 71% for patients receiving control while the overall rate was 64% for those who received olaparib (N=256) and 57% for those who received control (N=131).[7] In Cohort A, the baseline patient adherence rates for the FACT-P were 68% for patients receiving olaparib and 70% for patients receiving control while the overall rate was 60% for those who received olaparib (N=162) and 53% for those who received control (N=83).[7]

There was a clinically meaningful difference between the study groups in Cohort A+B for the adjusted mean change from week 32 to baseline in FACT-P total score, trial outcome index, physical well-being (PWB), and Prostate Subscale (PCS).[7]There was a clinically meaningful difference between the study groups in Cohort A for the adjusted mean change from baseline to week 32 in FACT-P total score, trial outcome index and PCS.[7]

EuroQoL 5-Dimension, 5-Level Health State Utility Index

The EQ-5D-5L was used to assess HRQoL in Cohort A and A+B. [redacted].[3] [redacted]

[redacted].[3]

[redacted].[3]

[redacted].[3] [redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Harms Outcomes

The safety set in the PROfound trial consisted of patients in Cohort A+B who had received at least one dose of the study treatment.[1] Patients were included in the safety switch analysis set if they were randomized to the control group and crossover to receive olaparib.[1]

There was a total of 386 patients in the safety set, with 256 patients in the olaparib group and 130 patients in the control group.[1] At the time of the final analysis, March 20, 2020, duration of treatment was 7.6 months (range: 0.03 to 28.9) in the olaparib group and it was 3.6 months (range: 0.6 to 29.1) in the control group.[2] Among the 83 patients in the control group who crossed over to receive olaparib, the median duration was 4.8 months (range: 0.2 to 28.9).[2]

Adverse Events

Hussain et al. (2020) reported that no new safety signals emerged after the later data-cut off.[2] Safety results reported for the final analysis (March 20, 2020) suggested that more patients in the olaparib group reported an AE and an AE of grade ≥ 3 as compared to those in the control group (96% vs 88% and 52% vs 40%, respectively).[2] More patients in the crossover group reported an AE of grade ≥ 3 (59%).[2] Twenty percent of patients in the olaparib group discontinued their assigned therapies due to an AE as compared to 8% in the control group.[2]

More patients in the olaparib group had a serious adverse event (SAE) as compared to the control group (37% vs 30%). More patients in the olaparib group have serious anemia relative to the control group (9% vs 0%).[2]

Overall, there were 19 AEs leading to death in the trial (olaparib = 4% [N=10] vs control = 5% [N=6] and cross-over = 4% [N=3]).[2]

Table 1: Highlights of Key Outcomes for Cohort A for the June 4, 2019 and March 20, 2020 data-cut off dates. Please refer to Section 6 of this review for more details.

	Cohort A	
	Olaparib (N=162)	Control (N=83)
Data cut-off date	**June 4, 2019**	
rPFS, N (%)	106 (65.4)	68 (81.9)
Median (95% CI), months	7.39 (6.24 to 9.33)	3.55 (1.91 to 3.71)
HR (95% CI)	0.34 (0.25 to 0.47)	
p-value	<0.001	
ORR, N (%)	84 (33)	43 (2)
OR (95%CI)	20.86 (4.18 to 379.18)	
p-value	<0.001	
Time to pain progression, N (%)	21 (13)	14 (16.9)
Median (95% CI), months	NR	9.92
HR (95% CI)	0.44 (0.22 to 0.91)	
p-value	0.02	
Data cut-off date	**March 20, 2020**	
OS, N (%)	91 (56.2)	57 (68.7)
Median (95% CI), months	19.1 (17.4 to 23.4)	14.7 (11.9 to 18.8)
HR (95% CI)	0.69 (0.50 to 0.97)	
p-value	0.02	

CI = confidence interval, HR = hazard ratio, OR = odds ratio, ORR = overall response rate, OS = overall survival; rPFS = radiographic progression-free survival

*HR < 1 favours [group]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One input was provided by the Canadian Cancer Survivor Network (CCSN) for the review of Olaparib (Lynparza) for mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who have progressed following prior treatment with a NHA.

The most common symptoms of prostate cancer reported by patients were fatigue and general loss of physical condition (63%), difficulty in getting an erection (52%), and problems with urination (37%). Twelve patient respondents indicated that the most important symptom to manage is fatigue and general loss of physical condition (63%). Seven respondents mentioned that urination problems were essential to manage. The caregiver respondents noted that patients were less energetic than pre-diagnosis, and that fatigue was a difficult symptom to manage. 17 of the 19 respondents (89%) received treatment for their prostate cancer. The most common type of treatment received by respondents was hormonal therapy (i.e. ADT, LHRH). Other reported treatments include chemotherapy, radiation therapy, enzalutamide, clinical trials, surgery, complementary and alternative medicine. The most effective treatment reported was hormonal therapy with 10 respondents reporting that it had been very effective (62%). The majority of respondents indicated that their needs are being met by their current treatments and that they have not had issues accessing their current therapy. The most commonly reported expectation for a new drug was being able to maintain quality of life (83%). Respondents indicated that they wanted a delay in the onset of symptoms, a reduction in the side effects they experience from their current medications or treatment and expected an increased ease of use.

Provincial Advisory Group (PAG) Input

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Decision factors for treatment discontinuation
- Place in therapy and sequencing with currently available treatments
- Switch from ongoing therapies for patients with positive mutation

Economic factors:

- Management of high-grade adverse events
- Access to next-generation mutation testing and optimal timing thereof

Registered Clinician Input

A total of four individual clinician inputs were provided for the review of Olaparib (Lynparza) for mCRPC: one each from British Columbia, Alberta, Ontario and Nova Scotia. The inputs were submitted for the review of olaparib as monotherapy for the treatment of adult patients with mCRPC and HRR gene mutations (germline and/or somatic) who have progressed following prior treatment with a new NHA. Androgen receptor-axis-targeted therapies (ARATs) such as enzalutamide and abiraterone, docetaxel, cabazitaxel, and radium 223 were reported to be currently available treatments for mCRPC in Canada. There are currently no standard funded biomarker-directed regimens specific for patients with mCRPC who harbour HRR gene mutations, therefore according to clinician input, olaparib would be meeting a significant unmet need.

Clinicians at CCO and BC Cancer stated that the patient population in the funding request aligns with their clinical practice and represents a significant unmet need. Approximately 20-25% of patients with mCRPC could harbour alterations in HRR genes. CCO clinicians stated that the indication in a post NHA setting can be applied to clinical practice widely, so long as the applicable alterations are identified. Similarly, the clinician at CPSA indicated that they would use this treatment in patients with mCRPC who had progressive disease after treatment with a NHA, and who have been identified to have a germline or somatic BRCA1/2 or ATM mutation. The clinician from NS stated that they do not believe the drug under review should be approved for all HRR mutation patients but should be approved for the mutations in cohort A from the PROFOUND trial. This recognizes that in cohort A the positive results are largely driven by BRCA2 mutations (partly due to the low numbers of BRCA1 and ATM). For cohort A, this meets an unmet need for those patients who are BRCA1/2 mutated.

Clinicians stated that they would prescribe this drug to patients with HRR gene mutated mCRPC who are progressing after NHA, and either before or after taxane chemotherapy depending on a patient's fitness and preferences. These patients do not have alternative effective therapies, and this drug is significantly different from other available therapies. Additionally, there are no subpopulations who should be restricted from receiving this therapy, if eligible HRR alterations have been identified. CPSA clinicians stated that the drug under review is comparable in efficacy to taxane chemotherapy (though limited by cross trial comparisons of very different patient populations) but demonstrates a significantly improved tolerability. The advantage of olaparib is that it would be tolerable in patients who are not eligible for taxane or platinum-based chemotherapy.

Clinician input stated that the drug under review could be sequenced as follows; 1) as first line mCRPC; 2) second line mCRPC as per the study, post ARAT; 3) third line mCRPC, post ARAT and chemotherapy; and 4) subsequent lines mCRPC. Many patients have had multiple lines of therapy such as ARAT, docetaxel, and cabazitaxel. According to clinicians, olaparib should be an option for these patients, where they would not have been eligible in second- or third-line settings. Clinicians indicated that the drug under review would not replace an available treatment but would be preferred to other therapies for patients with HRR gene alterations after NHA, due to the ease of administration, tolerability and efficacy.

In BC, companion diagnostic testing is available but not funded. Germline genetic testing is available in Alberta, but not somatic testing. Somatic testing would be required for implementation of the drug under review. In Ontario, testing to identify HRR alterations are not standardly funded for all mCRPC patients. HRR alteration testing should be implemented as patients would need access to testing in order to be eligible for the treatment under review. In NS, BRCA 1/2 somatic testing has just recently started for other

tumours. The capacity to use this testing in the prostate cancer therapeutic space would need to be discussed. Testing for ATM and other mutations are not currently available.

Summary of Supplemental Questions

In the absence of head-to-head trials, the investigator submitted an indirect treatment comparison (ITC) comparing olaparib with other relevant treatments for men with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who have progressed following prior treatment with an NHA. Based on the results from the NMA, the investigator concluded that results favoured olaparib in showing a PFS benefit versus cabazitaxel, docetaxel, and NHA therapy; but olaparib was favoured for OS benefit only versus NHA therapy. The results from the sensitivity anchored MAIC comparing olaparib and cabazitaxel [redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).*

Finally, the results from the adjusted exploratory unanchored MAIC on OS [redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).*

There were some limitations of the NMA that should be considered. First, the investigator was unable to assess the effect of olaparib relevant to the other enzalutamide, abiraterone, cabazitaxel and docetaxel among BRCA1/2 and ATM carriers because this information was not available in all studies. This could bias the results of the NMA because HRR mutations may be associated with prognosis, where BRCA2 and ATM genotype carriers have been shown to be associated with poor clinical outcomes.[9] Thus, the inclusion of the CARD and FIRSTANA may bias the estimates from the ITC in favour of cabazitaxel and docetaxel since all patients in Cohort A of the PROfound trial had a mutation in either the BRCA2 and ATM genotype. There was also a high degree of heterogeneity among the trials included in the NMA, which may imply that there are systematic differences between the patient populations among the included studies. Although the investigator conducted an anchored MAIC to account for this heterogeneity, the impact it has is still unclear because the results of anchored MAIC may be biased due to the exclusion of many important effect modifiers. Due to the above limitations, the comparative efficacy estimates obtained are likely biased, and it is not possible to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with olaparib.

The investigator also conducted an unanchored MAIC to compare the effect of olaparib to and radium-223. However, the investigator was unable to assess the effect of olaparib compared with radium-223 among BRCA1/2 and ATM carriers because this information was not available in the iEAP trial. Additionally, it is unclear which prognostic and effect modifiers were considered in the weighting process and it is unclear what impact these missing factors will have on the results of the unanchored MAIC. Due to the high level of risk of bias for these results, no firm conclusions are recommended based on these results.

Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for olaparib

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>Age</td><td>Patients were enrolled in the trial if they were 18 years or older.

Cohort A (mean [range])
<table><tr><td></td><td>Olaparib</td><td>Control</td></tr><tr><td>Age (years)</td><td>68 (47–86)</td><td>67 (49–86)</td></tr></table>
Cohort A+B (mean [range])
<table><tr><td></td><td>Olaparib</td><td>Control</td></tr><tr><td>Age (years)</td><td>69 (47–91)</td><td>69 (49–87)</td></tr></table></td><td>Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>CGP noted that while patients in the PROfound trial where slightly younger than patients seen in clinical practice, the PROfound results are fully applicable to patients seen in Canadian clinical practice.</td></tr>
<tr><td></td><td>Organ dysfunction</td><td>Patients were included in the trial if they had the following organ function:
-Hemoglobin ≥ 10.0 g/dL with no blood transfusions
-Absolute neutrophil count (AUC) ≥ 1.5 x 10^9/L
-Platelet count ≥ 100 x 10^9/L
-Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
-Aspartate aminotransferase (Serum Glutamic Oxaloacetic Transaminase) / Alanine aminotransferase (Serum Glutamic Pyruvate Transaminase) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case they must be ≤ 5x ULN.
-Creatinine clearance estimated of ≥51 mL/min using the Cockcroft-Gault equation for males or based on a 24 hour urine test</td><td>Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The CGP noted that the clinical parameters set in the trial seem reflective of patients in Canadian clinical practice. The CGP suggested it is up to the discretion of the treating clinician to apply some flexibility in terms of using olaparib in patients with slightly lower lab parameters/organ dysfunction.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Ethnicity or Demographics</td><td>Patients were not excluded based on their ethnicity.

Patients were enrolled in the trial if they had an ECOG performance status of 0 to 2.

Cohort A (n [%])
<table>
<tr><td>Ethnicity</td><td>Olaparib</td><td>Control</td></tr>
<tr><td>White</td><td>109 (67.3)</td><td>55 (66.3)</td></tr>
<tr><td>Black or African American</td><td>2 (1.2)</td><td>1 (1.2)</td></tr>
<tr><td>Asian</td><td>43 (26.5)</td><td>19 (22.9)</td></tr>
<tr><td>Other</td><td>1 (0.6)</td><td>1 (1.2)</td></tr>
<tr><td>Missing</td><td>7 (4.3)</td><td>7 (8.4)</td></tr>
</table>
Cohort A+B (n [%])
<table>
<tr><td>Ethnicity</td><td>Olaparib</td><td>Control</td></tr>
<tr><td>White</td><td>163 (63.7)</td><td>85 (64.9)</td></tr>
<tr><td>Black or African American</td><td>7 (2.7)</td><td>1 (0.8)</td></tr>
<tr><td>Asian</td><td>69 (27.0)</td><td>36 (27.5)</td></tr>
<tr><td>Other</td><td>2 (0.8)</td><td>1 (0.8)</td></tr>
<tr><td>Missing</td><td>15 (5.9)</td><td>8 (6.1)</td></tr>
</table></td><td>If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.</td><td>The trial results are fully applicable to the Canadian landscape. The CGP does not expect different treatment effect based on ethnicity.</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Intervention	Previous lines of therapy	Prior receipt of other anti-prostate cancer therapies was allowed but not a study entry requirement. Overall prior lines and sequencing of treatments was variable but appeared balanced across study groups. Most patient in either study group had received prior docetaxel, some patients had received both docetaxel and cabazitaxel. Most patients had received either enzalutamide or abiraterone, while some patients had received both abiraterone and enzalutamide.	Is there a known difference in effect based on prior lines of therapy that might yield a different result in a Canadian setting?	The CGP noted that there is a limited number of available therapies for prostate cancer and sequencing of prior agents is variable in Canadian clinical practice, depending on what is available, what therapies patients would have received previously, and patient and physician preferences. The CGP noted that variability of sequencing of prior treatments in the PROfound study seemed reflective of Canadian clinical practice and balanced across study groups. The CGP would not expect sequencing of prior lines of therapies in the PROfound study to have an unbalanced impact on study outcomes.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Comparator	Standard of Care	Patients in the control group of the PROfound trial received investigator's choice of enzalutamide or abiraterone acetate with prednisone.	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	The CGP noted that sequencing of alternate NHAs upon progression (i.e., first line enzalutamide followed by second line abiraterone or vice versa) is rarely done in Canadian clinical practice as not funded in most provinces. However, the CGP felt that the PROfound trial results are still fully generalizable to the Canadian clinical practice setting. Furthermore, due to the COVID pandemic funding restrictions have been loosened in some places and Canadian clinicians have been sequencing NHAs (as was done in the trial) to avoid having patients come into hospital for treatment and avoid toxicity from taxane chemotherapy.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Outcomes	Appropriateness of Primary and Secondary Outcomes	Primary: • rPFS by BICR in Cohort A Secondary: • Confirmed ORR by BICR in Cohort A • rPFS by BICR in Cohort A+B • Pain progression in Cohort A • OS in Cohort A	Does the selection on outcomes limit the interpretation of the trial results with respect to the target population?	The CGP agreed that the primary outcome rPFS is a clinically meaningful endpoint for this incurable disease and guides treatment selection in clinical practice. Upon relapse after olaparib, treatment options are limited with generally shorter survival times. Extending the period patients remain progression-free is important as the transition to progressive disease is a clinically relevant event that is associated with a higher burden of symptoms, decrease in quality of life, and shorter time to death. The primary outcome of rPFS was supported by secondary outcomes in favour of olaparib, such as OS and pain progression.
Setting	Countries participating in the Trial	The PROfound trial was conducted in 206 study centers in 20 countries, which includes Argentina, Australia, Austria, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Japan, Netherlands, Norway, South Korea, Spain, Sweden, Taiwan, Turkey, United Kingdom and United States. [redacted][3]	If the trial was conducted in other countries, is there any known difference in the practice pattern between those countries and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to achieve the outcomes.	The trial results are fully applicable to the Canadian landscape. The CGP does not expect different treatment effect based on different disease management practices across countries.

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

BICR = blinded independent central review, CGP = CADTH Clinical Guidance Panel, ECOG = Eastern Cooperative Oncology Group, NHA = new hormonal agent, ORR = objective response rate, OS = overall survival, rPFS = radiographic progression-free survival

1.2.4 Interpretation

Burden of Illness

Worldwide, prostate cancer is the second most frequent cancer diagnosis made in men (after lung cancer) and the fifth leading cause of cancer-related death.[10] In Canada, 1 in 7 men will be diagnosed with prostate cancer during their lifetime. In 2020, the Canadian Cancer Society reports 23,300 men were diagnosed with prostate cancer and 4200 men died of this devastating disease[11] Despite significant progress in the field, metastatic prostate cancer remains an incurable disease, underscoring the need for novel therapeutic strategies beyond standard treatment options such as chemotherapy and hormonal treatments. Advances in our basic understanding of prostate cancer has revealed that approximately 20-30% of patients have mutations in HRR genes, which increases tumor susceptibility to a new class of drugs called the PARP inhibitors.[12]

Need

Metastatic castration resistant prostate cancer is an incurable disease where management options focus on delaying disease progression, prolonging survival, and improving quality of life. Patients who harbor HRR gene mutations have been found to have worse outcomes than patients without these mutations.[13] Until recently, there were no treatments specifically directed at mCRPC patients who harbor HRR mutations.

Currently, NHAs such as abiraterone or enzalutamide, are the preferred option for the first-line treatment of patients with mCRPC.[14] For patients with disease progression on one NHA, treatment options include taxane-based chemotherapy (docetaxel, cabazitaxel [approved only after docetaxel]), radium-223 (for patients with bone predominant disease), and the other NHA (abiraterone, enzalutamide). There is growing evidence that alternating drugs with different mechanisms of action is preferable to using the same drugs with the same mechanism of action sequentially (e.g., hormone therapy followed by chemotherapy is preferable to hormone therapy followed by hormone therapy). Accordingly, patients progressing on an NHA in the first line mCRPC setting, are usually offered taxane-based chemotherapy at the time of progression. However, many patients are not eligible to receive taxane chemotherapy because of their age and co-morbidities and additionally would not be candidates for radium-223 due to non-bone predominant disease. The CGP estimated that about 50% of patients receive taxane chemotherapy and about 20% receive radium-223 in Canadian clinical practice. Median overall survival for patients with mCRPC who have failed NHA therapy (and have or have not previously received taxane chemotherapy) rarely exceeds one year.[15,16]

Thus, there is a great unmet need for effective new therapies for patients with mCRPC who harbour HRR mutations (BRCA1, 2 and ATM mutations) and who are not eligible for standard of care therapies. As well there is a need for treatments with new mechanisms of action to avoid the negative effects on efficacy from cross-resistance between existing treatments.

Choice of comparator in the PROfound trial

The PROfound trial[1,2] is a multinational, open-label, randomized phase III trial, that assessed the efficacy and safety of olaparib versus investigator's choice (i.e., enzalutamide or abiraterone acetate) for adult patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in HRR genes BRCA or ATM who have progressed following prior treatment with a NHA.

The comparator arm in the PROfound trial was investigator's choice of NHA (i.e., enzalutamide or abiraterone). Sequencing of alternate NHAs upon progression (i.e., first line enzalutamide followed by second line abiraterone or vice versa) is rarely done in Canadian clinical practice and not funded in most provinces. However, the CGP felt that the PROfound trial results are generalizable to the Canadian clinical practice setting as it has been suggested that NHAs have similar efficacy compared to docetaxel in the post-NHA setting.[5] Furthermore, due to the COVID pandemic funding restrictions have been loosened in some places and Canadian clinicians may be encouraged to alternate NHAs upon progression to avoid having patients come in to hospital for treatment and avoid toxicity from taxane chemotherapy.

Currently, only indirect comparisons can be made between olaparib and other relevant comparator treatments such as taxane chemotherapy or radium-223 as no trial to date has directly compared these drugs for patients with mCRPC and mutations in the HRR genes BRCA or ATM who have disease progression following prior treatment with an NHA. Refer to Section 7 for a summary and critical appraisal of sponsor-submitted indirect treatment comparisons (ITCs).

The CGP noted that the results from the NMA favoured olaparib for PFS in the comparison with cabazitaxel, docetaxel, and NHA therapy and for OS in the comparison with NHA therapy. Comparative OS results between olaparib and cabazitaxel or docetaxel did not show differences. The results from a sensitivity analysis using anchored MAIC methods comparing olaparib with cabazitaxel, [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).* The results from an exploratory unanchored MAIC comparing olaparib with radium-223 suggested [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).* However, the CGP agreed with the CADTH Methods Team, that due to several limitations identified in the ITCs caution must be used in interpreting the comparative efficacy estimates. Given the absence of a direct comparison, there is no robust evidence to ascertain which of the agents (i.e., olaparib, docetaxel, cabazitaxel, or radium-223) has superior efficacy. Therefore, the CGP concluded that patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection.

Effectiveness

The PROfound trial was an open-label, randomized trial that evaluated the efficacy and safety of olaparib in mCRPC patients with an HRR gene mutations and who failed prior treatment with an NHA. The key inclusion criteria were men with confirmed mCRPC who progressed on treatment with enzalutamide or abiraterone that was administered for metastatic or nonmetastatic castration-resistant prostate cancer, qualifying HRR mutation in tumor tissue, normal organ and bone marrow function, and an ECOG performance status of 0 to 2.[1] Patients were permitted in the trial if they had previous taxane chemotherapy.[1] Patients with a BRCA1, BRCA2 or ATM mutation were included in Cohort A, while patients with mutations among 12 other genes involved in the HRR pathway were included in Cohort B. The population in Cohort A was reflective of the CADTH requested reimbursement criteria. Patients in both Cohorts A and B were randomized in a 2:1 ratio to receive either olaparib (300 mg twice daily) or investigator's choice (enzalutamide [160 mg/daily] or abiraterone acetate [1000 mg/daily with 5 mg of prednisone twice daily]). Randomization was stratified by previous taxane chemotherapy (yes vs. no) and measurable disease at baseline (yes vs. no).[1] The primary endpoint was rPFS by BICR in Cohort A and key secondary outcomes were ORR by BICR in Cohort A, rPFS by BICR in Cohort A+B, time to pain progression based on the BPI-SF item 3 "worst pain in 24 hours" and overall survival (OS) in Cohort A. The primary and key secondary outcomes were included in the multiplicity strategy to maintain the overall Type 1 error rate.

The patient characteristics in Cohort A were consistent with the characteristics of patients commonly seen in Canadian clinical practice. Among those in Cohort A, the median age in the olaparib group was 68 years and 67 years in the control group, more than half of all patients had measurable disease at baseline (59% in olaparib and 55% in control) and the majority of patients received a previous taxane (65% in the olaparib and 63% in the control groups).[1] Twenty percent in the olaparib group had previously received both enzalutamide and abiraterone as compared to 17% in the control group.

The trial met its primary endpoint at the primary data cut-off date (4-June-2019). For Cohort A, the median rPFS was 7.39 months with olaparib versus 3.55 months in the control group. Olaparib was associated with statistically significant prolonged rPFS (BICR assessed) compared with the control group (HR: 0.34, 95% CI: 0.25 to 0.47; P<0.001), which is considered to be clinically meaningful. For cohort A+B the median rPFS as assessed by BICR in the olaparib group was [redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* Treatment with olaparib was associated with statistically significant prolonged rPFS compared to the control group (HR: 0.49, 95% CI: 0.38 to 0.63; P<0.001).

At the 04-June-2019 data cut-off date treatment with olaparib was associated with an improvement in ORR as assessed by BIRC (OR: 20.86 [95% CI: 4.18 to 379.18]) and time to pain progression (HR: 0.44 [95% CI: 0.22 to 0.91)] in Cohort A.

At the final analysis (20-March-2020 data cut-off date), the median OS was 19.1 months in the olaparib group and 14.7 months in the control group. Olaparib was associated with a statistically significant improvement in OS as compared to the control group in Cohort A (HR=0.69, 95% CI 0.50, 0.97; p=0.02), which is considered to be clinically meaningful. At the March 20, 2020 data cut-off date, 56 (67.5%) patients in Cohort A and 30 (62.5%) patients in Cohort B switched over to receive olaparib as subsequent treatment.[17] Patient crossover could confound the results of the final OS analyses in favour of the comparator group. However, RPSFT models were conducted for OS to adjust for patients in the control group who subsequently received olaparib and the results were similar to the unadjusted results.

It was reported that olaparib appeared to be associated with a protective effect against the risk of rPFS as assessed by BICR as compared to the control group across most pre-specified subgroups, including previous taxane use (yes/no).[1]

Genotypes

Exploratory subgroup analyses for rPFS and OS by genotype carrier status in the overall trial population (cohort A+B) suggested that patients with BRCA1 and/ or BRCA2 alterations derive more benefit with olaparib compared with the control group (investigator's choice of NMA), while there was no treatment difference between olaparib and the control group in patients with ATM alterations. However, these results should be interpreted with caution because they are considered exploratory and not adjusted for multiplicity. At this point there is insufficient evidence to restrict olaparib to a specific genotype and the CGP anticipated that clinicians will use olaparib in patients with BRCA1, BRCA2 and ATM mutations, as per Health Canada indication and the reimbursement request.

With respect to the additional 12 gene alternations included in cohort B (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and RAD54L), the CGP noted that while these rarer mutations require further exploration, the CGP cautioned against eliminating the option of olaparib for patients who harbour these rare mutations as many of these patients have aggressive disease with very few therapeutic options. The CGP felt that it would be reasonable to offer olaparib to patients in cohort B which is in line with the FDA indication for olaparib; FDA indication: "For the treatment of adult patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone." The CGP noted that emerging data on predictive biomarkers and population-based analyses will be important to inform practice in the future.

Safety

At the time of the final analysis, 20-March-2020, duration of treatment was 7.6 months (range: 0.03 to 28.9) in the olaparib group and it was 3.9 months (range: 0.6 to 29.1) in the control group.[1] Olaparib was well tolerated and consistent with previous data from olaparib monotherapy. No new toxicities were encountered in the PROfound trial when compared to other agents in a similar class. The proportion of AEs for all grades were 96% in the olaparib group and 88% in the control group, the AEs of grade ≥ 3 were 52% and 40% in the olaparib and control groups, and any serious AEs were 37% and 30% in the olaparib and control groups, respectively. The most commonly reported all grade AEs occurring more frequently in the olaparib group included anemia, nausea, fatigue or asthenia, and decreased appetite. The differences in grade 3 or greater AEs and serious AEs between both groups were mainly driven by anemia. Most commonly reported grade 3 or greater AEs and serious AEs in both groups included anemia, fatigue or asthenia, urinary tract infection, and pneumonia (note: pneumonia was only reported as serious AE and not reported as grade 3 or greater AE). Adverse events were manageable by treatment interruption or dose modification and supportive treatment. Overall, the CGP agreed with the registered clinicians providing input that olaparib has a management toxicity profile.

In the absence of direct comparative safety data to docetaxel, the CGP agreed with the registered clinicians that olaparib appears to have favorable toxicity compared with docetaxel and would be tolerable in patients who are not eligible for taxane chemotherapy as typical toxicity from chemotherapy could be avoided with olaparib.

Exploratory data collected on patient reported outcomes during the PROfound trial suggested that olaparib did not show a negative effect on quality of life compared with investigators' choice of an NHA (i.e., enzalutamide or abiraterone)

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to olaparib compared with investigator's choice of NHA (i.e., enzalutamide or abiraterone) in the treatment of patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who have progressed following prior treatment with an NHA. This conclusion is based on evidence from one high-quality RCT that demonstrated clinically meaningful and statistically significant benefits in rPFS and OS. The safety profile of olaparib was acceptable and appears to be better than experienced with taxane chemotherapy with overall no detrimental impact on HRQoL. The CGP agreed that rPFS and OS are clinically meaningful endpoints for this incurable disease. Upon relapse after olaparib, treatment options are limited with generally shorter survival times. Extending the period patients remain progression-free is important as the transition to progressive disease is a clinically relevant event that is associated with a higher burden of symptoms, decrease in quality of life, and shorter time to death.

In making this recommendation, the Clinical Guidance Panel considered:

- In Canada, docetaxel is the most commonly used treatment in patients progressing on an NHA in the mCRPC setting. Many patients are not eligible to receive taxane chemotherapy because of their age and co-morbidity. Therefore, additional non-cytotoxic options providing similar benefits with less toxicity risk and a more convenient oral route of administration are recognized as an unmet need by clinicians and patients. As with most conditions, it's beneficial to have more than one option for treatment from both a supply chain perspective (i.e., interruptions in supply from one manufacturer) and from a patient tolerance perspective.
- There is no robust evidence to ascertain which of the agents (i.e., olaparib, docetaxel, or radium-223) has superior efficacy. Therefore, all these agents remain potential options. The most appropriate treatment for an individual patient will depend on patient preference, individual toxicity profiles, and access to treatment.
- Olaparib is the first treatment specifically for patients with mCRPC who have HRR gene alterations and have progressed after NHA therapy. Currently, there is no standard of care for patients who harbour HRR gene mutations.
- There is no sufficient evidence to determine whether olaparib should preferentially be used in patients who have already received docetaxel prior to progressing on an NHA or not. The exploratory subgroup analysis from the PROfound trial suggested a benefit in patients irrespective of prior taxane use. The use of taxane based chemotherapy in mCRPC greatly depends on patient preference, as many patients are either unfit or unwilling to receive taxane. The CGP agreed that prior taxane use should not be an exclusion for reimbursement of olaparib. The CGP noted that since olaparib is a genomically driven treatment, the most important indication is in applicable HRR alterations regardless of prior docetaxel use in the mCRPC setting.

Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
Eligible Patient Population	
PAG is seeking guidance on whether the following patients would be eligible for treatment with olaparib:	
• patients with ECOG PS > 2.	• The PROfound trial included patients with ECOG PS of 2 or less. Most patients in the trial had ECOG PS of 0 or 1. The CGP noted that approximately 15% of patients seen in clinical practice have worse performance status than patients included in the PROfound trial (ECOG greater than 2). While the CGP agreed that the benefit for patients with an ECOG status of greater than 2 cannot be formally concluded from the PROfound trial, the CGP felt it would be reasonable to offer olaparib to patients with ECOG PS of greater than 2 especially in patients whose poor ECOG PS may be directly related to the underlying prostate cancer or tumor-related symptoms.
• patients who have had previous treatment with DNA-damaging cytotoxic chemotherapy (e.g., platinum or mitoxanthrone)	• The PROfound trial excluded patients with previous treatment with DNA-damaging cytotoxic chemotherapy. In amendment 3 (4 June 2018) it was clarified that patients could have received prior treatment with DNA-damaging cytotoxic chemotherapy for non-prostate cancer. The CGP felt it would be reasonable to generalize the PROfound trial results to patients who have had previous treatment with DNA-damaging cytotoxic chemotherapy (e.g., platinum or mitoxanthrone) because olaparib has a completely different mechanism of action and no overlapping toxicities.
• patients with brain metastases	• The PROfound trial excluded patients with known brain metastases. The CGP noted that brain metastases are rare in patients with mCRPC. The CGP recommended discretion of the treating physician for use of olaparib in patients with brain metastases. Possible considerations may include the stability of the brain metastases and if already treated.
• patients who were unable to tolerate either enzalutamide or abiraterone	• The CGP noted that there is currently no evidence on switching patients who are intolerant to enzalutamide to abiraterone or vice versa. However, the CGP noted that switching therapies in this context would appear reasonable and beneficial to patients who generally do better with than without treatment.
• patients who have not experienced an NHA	• The PROfound trial included patients who must have progressed on prior NHA (i.e., enzalutamide and/or abiraterone) for the treatment of metastatic prostate cancer and/or CPRC. Only very few patients in the overall study population received a NHA before the development of mCRPC. The CGP noted that patients who were NHA naïve were excluded from the PROfound study. There is currently insufficient evidence to generalize the results of the PROfound trial to these patients.

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
PAG noted that patients with specific alterations in any of the 15 HRR genes were included in the trial and seeks confirmation that the overall effect is generalizable to every tested alteration.	While Cohort A included three gene alterations (BRCA1, BRCA2, and ATM) Cohort B included additional 12 gene alternations (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and RAD54L). The Health Canada indication is restricted to gene alterations in Cohort A. Analyses in Cohort B were not alpha controlled, and the PROfound trial was not designed or powered to detect a statistically significant treatment effect in Cohort B. While the CGP agreed that the rarer mutations included in Cohort B require further exploration, they cautioned against eliminating the option of olaparib for patients who harbour these rare mutations as many of these patients have aggressive disease with very few therapeutic options. The CGP felt that it would be reasonable to offer olaparib to patients in cohort B which is in line with the FDA indication for olaparib; FDA indication: “For the treatment of adult patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone." The CGP noted that emerging data on predictive biomarkers and population-based analyses will be important to inform practice in the future.
If recommended for reimbursement, PAG noted that patients currently treated with a taxane-based regimen would need to be addressed on a time-limited basis. Hence, PAG seeks advice on whether such patients could be switched to olaparib if their tests results are found to be positive.	The CGP agreed that patients with mCRPC and BRCA1, BRCA2 or ATM mutations who have received prior NHA therapy, are currently receiving a taxane-based regimen, and have not progressed would need to be addressed on a time-limited basis.
Implementation Factors	
PAG noted that in the trial, disease progression was evaluated according to imaging-based findings. However, in actual practice, clinicians often use a combination of radiographic, biochemical and clinical factors, and usually determine progression and discontinuation of therapy upon worsening of 2 of these 3 criteria. Hence, PAG seeks a clear definition of disease progression (e.g., through a combination of radiographic, biochemical and clinical results) and advice on criteria for treatment discontinuation.	Commonly clinicians will seek confirmation of progression in all possible areas, i.e., PSA progression, clinical progression (i.e., well-being of patient), and radiographic progression. At least two out of these three criteria should be confirmed to discontinue treatment. PSA and radiographic progression tend to align with each other. However, if a patient has PSA progression alone (no radiographic progression or development of symptoms attributable to cancer progress) then a patient may continue treatment. If radiographic progression occurs without PSA progression or loss of clinical benefit, treatment may continue beyond radiographic progression. According to the PROfound trial protocol the investigational product could be discontinued based on objective radiographic progression by BICR alone (criteria for bone progression required a confirmation scan ≥ 6 weeks later). The CGP agreed that the trial parameters in the PROfound trial set for treatment discontinuation are generalizable to the Canadian clinical practice as radiographic and PSA progression tend to align with each other. The CGP agreed that the trial parameters as well as the Health Canada Product Monograph treatment discontinuation criteria are reasonable. ”It is recommended that LYNPARZA treatment be continued until progression of the underlying disease or unacceptable toxicity. Patients receiving LYNPARZA for mCRPC should also

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
	receive a GnRH analog concurrently, or should have had bilateral orchiectomy."[18]
• PAG has concerns that the high rate of grade 3 and 4 anemia observed with olaparib therapy could impact quality of life significantly and would require resources to manage. PAG noted that resources will be required for blood work for monitoring anemia and to conduct blood transfusions for severe anemia. Familiarity with olaparib in ovarian cancer can help anticipate and manage these effects.	• The CGP noted they would not anticipate the extend of grade 3 and 4 anemia to be different between olaparib and any other systemic therapy in this setting. Therefore, the CGP did not anticipate that additional resources would be required to manage anemia with olaparib compared to currently relevant comparators.
• PAG is seeking guidance on potentially stopping olaparib to manage toxicity and then re-starting the therapy.	• The CGP agreed with the recommendations regarding dose reduction as set out in the Health Canada product monograph. "Treatment may be interrupted to manage adverse events and dose reduction can be considered. The recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 500 mg. If a further dose reduction is required, the recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 400 mg."[18] In the PROfound trial, treatment with olaparib could be interrupted or reduced due to any observed toxicities. Repeated dose interruptions were allowed for a maximum of 4 weeks; the study investigators were to be informed if the interruption lasted longer than this period. The CGP felt that the parameters set out in the trial which allowed a 4-week dose interruption before re-starting olaparib seemed reasonable.
Sequencing and Priority of Treatment	
Circumstances where olaparib would be preferable to standard docetaxel chemotherapy.	The CGP noted that olaparib would be preferable in patients who harbour BRCA1, BRCA2 or ATM mutations following progression on NHA therapy. These tumors are biologically more aggressive, and it makes the most sense to use a more targeted therapy as early as possible in the disease course. Many patients are ineligible for docetaxel chemotherapy or refuse this treatment based on side effects. Therefore, olaparib would be an option for these patients. Additionally, the drug under review is taken orally, therefore it is easier for both patients and the system to administer, especially during the COVID-19 pandemic.
Options after failure of olaparib including potential NHA re-treatment.	In the absence of sufficient evidence to inform sequencing in patients with BRCA1, BRCA2 or ATM mutations who have received prior NHA therapy and who have progressed on olaparib, the CGP noted that patients should have available standard options in the mCRPC algorithm. Eligible patients could receive taxane chemotherapy, or second line NHA therapy in chemo-ineligible patients depending on provincial funding. Radium-223 could also be an option for patients with bone-only metastases. Despite it not being studied well, platinum-based chemotherapy is another option, though more

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
	data on its efficacy are required before this can uniformly be implemented as a standard of care.
Sequences of drugs leading to olaparib including reserving the latter for patients who have progressed on all NHAs and taxane options.	As previously mentioned, the CGP noted that olaparib would be preferable in patients who harbour BRCA1, BRCA2 or ATM mutations following progression on NHA therapy. These tumors are biologically more aggressive, and it makes the most sense to use a more targeted therapy as early as possible in the disease course. Olaparib should not be reserved for patients who have progressed on all NHAs and taxane options. As many studies have demonstrated, sequential NHA is not effective and many patients are not eligible for taxane chemotherapy. The option to use olaparib after an NHA as per the study inclusion criteria should be an option. There is not sufficient evidence to determine whether olaparib should preferentially be used in patients who have already received docetaxel prior to progressing on an NHA or not. The exploratory subgroup analysis from the PROfound trial suggested a benefit in patients irrespective of prior taxane use. The use of taxane based chemotherapy in mCRPC greatly depends on patient preference, as many patients are either unfit or unwilling to receive taxane. The CGP agreed that prior taxane use should not be an exclusion for reimbursement of olaparib. The CGP noted that since olaparib is a genomically driven treatment, the most important indication is in applicable HRR alterations regardless of prior docetaxel use in the mCRPC setting.
For patients who received docetaxel in metastatic castrate sensitive space, is there evidence and interest for using olaparib in the castrate resistant space?	The CGP noted that the number of patients who receive docetaxel in the mCSPC space has significantly declined over the last several years. The CGP felt that it would be reasonable to use olaparib in the mCRPC space for patients who received docetaxel in the mCSPC space. The CGP noted that some data suggest that patients who have received docetaxel in the mCSPC space are resistant to docetaxel when their disease develops to mCRPC. Since olaparib is a genomically driven treatment, the CGP felt that the most important indication is in applicable HRR alterations regardless of prior docetaxel use in the mCSPC setting.
Companion Diagnostic Testing	
PAG noted that the HRR assay used in the trial was the Lynparza HRR assay and would like to know if other assays or homegrown methodologies could be used instead.	The CGP noted that it would be ideal to have the Lynparza HRR assay. However, if not available other assays to establish HRR would be acceptable.
PAG reflected on the relative clinical value of the HRR companion test. It is unclear if the test results from the HRR assay would significantly alter patient management, for instance by predicting disease course or response to treatments. PAG seeks additional guidance on the broader use of HRR and BRCA test results in prostate cancer. This guidance would help inform the optimal time (e.g., at diagnosis, during treatment with an NHA, upon progression)	The CGP noted that they would prefer to have testing done rather early in the treatment trajectory than later. Preferred timing would be either at: - diagnosis to be able to inform family members and plan out treatment approaches, or - during treatment with NHA to be able to treat patients with olaparib upon progression. If testing would be initiated at the time of progression, time may run out

Provincial Advisory Group (PAG) Implementation Questions	CADTH Clinical Guidance Panel (CGP) Response
where BRCA and/or HRR testing should be performed.	before test result come back and patients will have to be started on an alternative treatment.

BICR = blinded independent central review; BRCA = BReast CAncer gene; CGP = Clinical Guidance Panel, CRPC = castration resistant prostate cancer; ECOG PS = Eastern Cooperative Oncology Group Performance Status, GnRH = gonadotropin-releasing hormone; HRR = homologous recombination repair; mCSPC = metastatic castration sensitive prostate cancer; mCRPC = metastatic castration resistant prostate cancer; NHA = novel hormonal agent; PAG = Provincial Advisory Group; PSA = prostate serum antigen.

2 Background Clinical Information

2.1 Description of the Condition

Prostate cancer is the most common cancer among Canadian men (excluding non-melanoma skin cancers); it is the third leading cause of death from cancer. In 2020, it is estimated that 23,300 men will be diagnosed with prostate cancer, this represents 20% of all new cancer cases in men. It was predicted that, in 2020, 4,200 men will die of prostate cancer, this represents 10% of all cancer deaths in men.[11] One in four patients with prostate cancer will die from the disease.[19]. Patients who die will usually progress to the mCRPC stage, with a 5-year survival rate of approximately 30%.[20]

Castrations resistant prostate cancer is defined as prostate cancer disease progression in the setting of castrate testosterone levels. Biochemical progression as manifested by a rising PSA alone is often the initial sign of disease progression before developing metastatic disease to bone or visceral organs.[21]

Both germline and somatic alterations in DNA repair genes occur in between 20-30% of patients with mCRPC.[22] Metastatic castration resistant prostate cancer mutations in the BRCA (BRCA1 and/or BRCA2) are the most common HRR gene mutations (BRCA2 is more prevalent than BRCA1) with ATM being the second most frequently mutated HRR gene.[22-25] It has ben suggested that patients with mCRPC who carry an HRR gene mutation have a poorer prognosis compared with noncarrier mCRPC patients.[13,26]

BRCA1 and BRCA2 genes are human tumour suppressor genes and a key component in homologous recombination (HR), a repair pathway of double-stranded DNA breaks.[27,28] HR deficiency (HRD) such as pathogenic BRCA mutations causes cells to repair via less precise and more error-prone repair pathways such as non-homologous end-joining (NHEJ); inhibition of poly (ADP-ribose) polymerase (PARP) can confer synthetic lethality in cells with HRD.[29]

It is well established that BRCA2 gene mutations cause a higher risk of prostate cancer, with an estimated relative risk of 2.5–8.6 fold by 65 years of age, and they are associated with earlier-onset, clinically significant disease.[30] Male BRCA1 carriers have a two- to five-fold increased chance of prostate cancer. It has been suggested that targeted screening of these men could be warranted based on recent evidence. Currently, genetic and somatic testing for BRCA1/2 mutations for prostate cancer screening are not eligible to most Canadians under provincial programs.[31]

2.2 Accepted Clinical Practice

Treatment options for localized prostate cancer include prostatectomy, radiation therapy (intensity modulated radiation therapy or brachytherapy) or active surveillance for patients with lower risk disease. Despite local ablative treatment, some men with localized prostate cancer develop recurrent disease as evidenced by a biochemical recurrence (elevation in PSA) with or without signs of metastases. In addition, some men may present with de novo metastatic disease. For nearly three-quarters of a century medical or surgical castration (ADT) has been first-line therapy for recurrent or metastatic prostate cancer. ADT suppresses gonadal androgen production and usually consists of treatment with either an LHRH antagonist or agonist, or bilateral orchiectomy. The addition of a non-steroidal antiandrogen to ADT has been shown to improve OS in meta-analysis of randomized trials. Nearly all patients with mCSPC initially respond to ADT but all will eventually progress to castration-resistant prostate cancer (CRPC).[32]

For patients with biochemical-only progression and no evidence of metastasis, observation is often recommended. Although no secondary hormonal therapy has been found to extend survival for patients with CRPC, initial therapy with the addition of an anti-androgen such as bicalutamide or an androgen synthesis inhibitor such as ketoconazole can be used.[21] If patients are treated with combined androgen blockade, anti-androgen withdrawal as well as low dose prednisone are considered options. In general, early chemotherapy with docetaxel is not recommended for those without metastatic disease outside the context of a clinical trial. There has been no widely accepted standard of care for patients with non-metastatic CRPC as no phase 3 study has demonstrated improved survival.[33]

Treatment for Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Since 2004, cytotoxic chemotherapy with docetaxel has been the standard of care for mCRPC patients progressing on first- or second- line ADT. Docetaxel showed significant yet modest improvements in survival (median of 3 months) and quality of life for patients with mCRPC. Until recently, the therapeutic options for patients progressing on docetaxel were limited. According to the most recent Canadian guidelines for the management of mCRPC , re-treatment with docetaxel or cabazitaxel can be considered for some patients.[34]

Although effective, docetaxel is a palliative treatment and eventually all patients develop progressive disease. Radium-223 is an alpha-emitting radiopharmaceutical which has been approved by Health Canada in 2013 for treatment of symptomatic bone metastasis in patients with CRPC with no visceral metastasis based on a modest survival advantage over placebo (14.9 vs 11.3 months, HR 0.70, 0.58-0.83, P<0.001).[35] However, the spectrum of mCRPC treatment now includes several new treatment options, particularly for patients having already received docetaxel therapy. These treatments provide several additional months of survival compared to mitoxantrone. These three such novel drugs are cabazitaxel, abiraterone and enzalutamide.[34,36]

For patients who have progressed on docetaxel, recent data supports the use of both chemotherapy, such as cabazitaxel, or alternatively, new hormonal therapies (NHAs) such as enzalutamide and abiraterone. Cabazitaxel, a novel semi-synthetic taxane was shown to increase overall survival as well as response rates and time progression when compared to mitoxantrone.[37] Both enzalutamide,[38] an androgen receptor antagonist, and abiraterone acetate,[39] an androgen synthesis inhibitor, were compared to placebo and prednisone respectively in the phase 3 setting and were found to be associated with improved overall survival. Enzalutamide is approved across the spectrum of prostate cancer, from non-metastatic prostate cancer to metastatic castration resistant prostate cancer (before or after docetaxel chemotherapy).

For those patients with mCRPC, who are asymptomatic or minimally symptomatic, secondary hormonal maneuvers as described above are often used. Chemotherapy with docetaxel has previously been recommended for those with a good performance status.

There are currently no standard funded biomarker-directed regimens specific for patients with mCRPC who harbour HRR gene mutations, therefore, olaparib would meet a significant unmet need and will be incorporated into the treatment algorithm for patients with mCRPC.

3 Summary of Patient Advocacy Group Input

One input was provided by the Canadian Cancer Survivor Network (CCSN) for the review of Olaparib (Lynparza) for mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who have progressed following prior treatment with an NHA. CCSN conducted an online survey via Survey Monkey between September 8th and October 5th, 2020. The survey was distributed through the CCSN newsletter and social media channels. In addition, various prostate support groups throughout Canada assisted with distribution of the survey. The survey was marketed towards patients and caregivers of patients with mCRPC. Responses were also accepted from patients (and their caregivers) with various stages and types of prostate cancer diagnoses. A total of 19 patients and 2 caregivers completed the survey. Of the 19 patient respondents: seven were from British Columbia, five were from New Brunswick, four were from Ontario, and three were from Nova Scotia. The two caregivers were from British Columbia and Nova Scotia. Seven respondents (five patients and two caregivers) had experience with mCRPC (37%). The remaining patient respondents had various stages of prostate cancer ranging from stage 1 to stage 3. None of the participants had any experience with the drug under review.

The most common symptoms of prostate cancer reported by patients were fatigue and general loss of condition (63%), difficulty in getting an erection (52%), and problems with urination (37%). Twelve patient respondents indicated that the most important symptom to manage is fatigue and general loss of condition (63%). Seven respondents mentioned that urination problems were essential to manage. The caregiver respondents noted that patients were less energetic than pre-diagnosis, and that fatigue was a difficult symptom to manage. 17 of the 19 respondents (89%) received treatment for their prostate cancer. The most common type of treatment received by respondents was hormonal therapy (i.e., ADT, LHRH). Other reported treatments include chemotherapy, radiation therapy, enzalutamide, clinical trials, surgery, and complementary and alternative medicine. The most effective treatment reported was hormonal therapy with 10 respondents reporting that it had been very effective (62%). The majority of respondents indicated that their needs are being met by their current treatments and that they have not had issues accessing their current therapy. The most commonly reported expectation for a new drug was being able to maintain quality of life (83%). Respondents indicated that they wanted a delay in the onset of symptoms, a reduction in the side effects they experience from their current medications or treatment and expected an increased ease of use.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

The most common symptoms of prostate cancer reported by respondents were fatigue and general loss of condition (n=12, 63%), difficulty in getting an erection (n=10, 52%), and problems with urination (n=7, 37%). Approximately 21% of participants have issues with a loss of bladder and bowel control; 26% indicated they are living with uncertainty; and 21% live with mental health issues such as anxiety, panic attacks, and depression. 12 patient respondents indicated that the most important symptom to manage are fatigue and general loss of condition (63%). Seven respondents (37%) mentioned that urination problems were essential to manage.

Both caregiver respondents reported that the patient they care for is not as energetic as they were pre-diagnosis. The fatigue that comes with prostate cancer makes it difficult for patients to complete daily tasks and caregivers struggle with watching their spouse in pain.

3.1.2 Patients' Experiences with Current Therapy

Seventeen patients received treatment for their prostate cancer. The treatments received can be found in Table 4. Other treatments not mentioned in Table 4 received by only one patient included: clinical trials, surgery, complementary and alternative medicine.

Table 4: Survey Respondent Treatments Received

Type of Treatment Received	Number of Patients
Chemotherapy	2
Hormonal Therapy (i.e., ADT, LHRH)	12
Radiation Therapy	2
Enzalutamide	2

ADT = androgen deprivation therapy; LHRH = luteinizing hormone releasing hormone.

The patient input indicated that the most effective treatment appears to be hormonal therapy as 10 respondents indicated that it had been very effective (62%) and five respondents said it was somewhat effective (31%). Seven patients reported that surgery had been effective (n=4 very, 57%; n=3 somewhat, 43%). Patients were asked to rate their responses on a 4-point scale from "very effective" to "not effective at all". The majority of respondents (n=15, 79%) indicated that their needs are being met by their current treatments and that they have not had issues accessing their current therapy (n=16, 84%).

3.1.3 Impact on Caregivers

No caregiver response on experience with currently available treatments was described.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

From the patient survey responses, the most commonly reported expectation for a new drug was being able to maintain their quality of life (n=15, 83%). Nine respondents indicated that they wanted a delay in the onset of symptoms (50%). 10 patients wanted a reduction in the side effects they experience from their current medications or treatment (56%), and eight patients indicated they expected an increased ease of use (44%).

Most participants indicated that they would prefer a new medication without side-effects or with fewer side effects than their current treatment. The following respondent quotes indicate what side effects or symptoms they would be willing to tolerate in a new drug:

- *Some bloating.*
- *Probably anything less than the usual side-effects from chemo.*
- *Loss of appetite (short term while receiving treatment). Energy loss (short term while receiving treatments).*
- *I have none [side effects] now so unsure what I could tolerate having issues with.*
- *None [side effects], a new drug without side effects. If I change [to a new treatment] I will only shift to different side effects.*
- *That is a tough question to answer as the drug side effects, I have had and/or am having are tolerable, but they certainly do affect my quality of life. However, I also realize that without them I would not be alive!*
- *Definitely not tiredness like fatigue or nausea.*
- *A number of conditions if it prolonged life and quality of life.*
- *I have tolerated Xtandi well. I would hope Lynparza would be no worse in its side effects.*
- *Reduced levels of Zolodex [Zoladex] side effects noted above (fatigue, sweating, emotional swings).*

- *So far I have a lot of side effects from everything I have taken. For my state of cancer, it would be best to have less.*
- *Not having to go to the bathroom in the middle of the night.*

3.2.2 Patient Experiences to Date

None of the participants in the survey had experience with the drug under review.

3.3 Companion Diagnostic Testing

Not applicable.

3.4 Additional Information

The patient group wants to stress that since many advanced prostate cancer cases become castration-resistant, it is imperative that the development of a new drug attend to this specification. The patient group stated that although many of the participants in the survey do not currently have mCRPC, they would benefit from a drug which manages this disease due to the risk of their cancer progressing.

Two patient respondents reported that COVID-19 restrictions have made it more difficult for them to access their treatment. One patient noted that they have only had phone appointments while their cancer progresses.

4 Summary of Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the CADTH website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Decision factors for treatment discontinuation
- Place in therapy and sequencing with currently available treatments
- Switch from ongoing therapies for patients with positive mutation

Economic factors:

- Management of high-grade adverse events
- Access to next-generation mutation testing and optimal timing thereof

Please see below for more details.

4.1 Currently Funded Treatments

Relapsed or refractory metastatic CRPC previously treated with a new hormonal agent (NHA) i.e., androgen-receptor-axis targeted therapies (ARAT) such as enzalutamide and abiraterone, can be treated with radioisotopes or taxanes. Sequencing of alternate ARATs for CRPC is funded in a few provinces. In some, a second ARAT is allowed if it is preceded by a round of chemotherapy. Docetaxel may be given after ARATs, but cabazitaxel is only funded after progression on docetaxel. Radium-223 is indicated for symptomatic bone-only metastases only and is not funded in all jurisdictions. There is no specific standard of care for patients with a BRCA or HRR gene mutation.

PAG noted that the PROfound trial compared olaparib with physician's choice of abiraterone or enzalutamide. There is concern that these comparators have limited efficacy in this refractory population and as mentioned previously, they are not widely funded in Canada for this group. PAG seeks additional comparison of olaparib against a taxane-based regimen.

4.2 Eligible Patient Population

The reimbursement request of olaparib is as monotherapy for the treatment of adult patients with mCRPC and homologous recombination repair (HRR) gene mutations (germline and/or somatic) who have progressed following prior treatment with an NHA. In view of the characteristics of the patient population and exclusion criteria in the PROfound trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with olaparib:

- ECOG performance score ≥2
- Patients who have had previous treatment with DNA-damaging cytotoxic chemotherapy (e.g., platinum or mitoxanthrone)
- Patients with brain metastases
- Patients who were unable to tolerate either enzalutamide or abiraterone
- Patients who have not experienced an ARAT

PAG noted that patients with specific alterations in any of the 15 HRR genes were included in the trial and seeks confirmation that the overall effect is generalizable to every tested alteration.

If recommended for reimbursement, PAG noted that patients currently treated with a taxane-based regimen would need to be addressed on a time-limited basis. Hence, PAG seeks advice on whether such patients could be switched to olaparib if their tests results are found to be positive.

PAG noted potential indication creep of olaparib to patients in the non-metastatic or castrate-sensitive settings and to those whose cancer is not BRCA or HRR mutated.

4.3 Implementation Factors

The recommended total daily dose for mCRPC is 600 mg olaparib, taken as two 150 mg tablets twice daily. The 100 mg tablet is available for dose reduction and minimizes pill burden; these factors are enablers to implementation. It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity. However, drug wastage will occur with dose modifications from 150 mg to 100 mg tablets. PAG noted that in the trial, disease progression was evaluated according to imaging-based findings. However, in actual practice, clinicians often use a combination of radiographic, biochemical and clinical factors, and usually determine progression and discontinuation of therapy upon worsening of 2 of these 3 criteria. Hence, PAG seeks a clear definition of disease progression (e.g., through a combination of radiographic, biochemical and clinical results) and advice on criteria for treatment discontinuation.

PAG has concerns that the high rate of grade 3 and 4 anemia observed with olaparib therapy could impact quality of life significantly and would require resources to manage. PAG noted that resources will be required for blood work for monitoring anemia and to conduct blood transfusions for severe anemia. Familiarity with olaparib in ovarian cancer can help anticipate and manage these effects. PAG seeks guidance on potentially stopping olaparib to manage toxicity and then re-starting the therapy. PAG noted a potential increase in pharmacy resources for dispensation of olaparib and monitoring of side effects as well as dose modifications.

PAG noted that olaparib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home, and no chemotherapy chair time would be required. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

PAG is seeking to confirm the place in therapy of olaparib and sequencing with other regimens for CRPC, including the scenarios below:

- Circumstances where olaparib would be preferable to standard docetaxel chemotherapy.
- Options after failure of olaparib including potential ARAT re-treatment.
- Sequences of drugs leading to olaparib including reserving the latter for patients who have progressed on all ARAT and taxane options.

4.5 Companion Diagnostic Testing

PAG remarked that BRCA testing is available but not routinely performed in prostate cancer. An HRR gene panel would be required for all potential candidates; however, such a system is not implemented in jurisdictions. PAG noted that the inclusion of BRCA1/2 in the HRR panel may obviate the need for separate testing. Standard BRCA/HRR testing in prostate cancer will increase workloads on laboratories as a large number of patients will be requiring testing for eligibility purposes. PAG noted that the HRR assay used in the trial was the Lynparza HRR assay and would like to know if other assays or homegrown methodologies could be used instead.

PAG reflected on the relative clinical value of the HRR companion test. It is unclear if the test results from the HRR assay would significantly alter patient management, for instance by predicting disease course or response to treatments. PAG seeks additional guidance on the broader use of HRR and BRCA test results in prostate cancer. This guidance would help inform the optimal time (e.g., at diagnosis, during treatment with an ARAT, upon progression) where BRCA and/or HRR testing should be performed.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

A total of four individual clinician inputs were provided for the review of Olaparib (Lynparza) for mCRPC: one each from British Columbia, Alberta, Ontario, and Nova Scotia. The inputs were submitted for the review of olaparib as monotherapy for the treatment of adult patients with mCRPC and HRR gene mutations (germline and/or somatic) who have progressed following prior treatment with a new NHA. Androgen receptor-axis-targeted therapies such as enzalutamide and abiraterone, docetaxel, cabazitaxel, and radium 223 were reported to be currently available treatments for mCRPC in Canada. There are currently no standard funded biomarker-directed regimens specific for patients with mCRPC who harbour HRR gene mutations, therefore according to clinician input, olaparib would be meeting a significant unmet need.

Clinicians at CCO and BC Cancer stated that the patient population in the funding request aligns with their clinical practice and represents a significant unmet need. Approximately 20-25% of patients with mCRPC could harbour alterations in HRR genes. CCO clinicians stated that the indication in a post NHA setting can be applied to clinical practice widely, so long as the applicable alterations are identified. Similarly, the clinician at CPSA indicated that they would use this treatment in patients with mCRPC who had progressive disease after treatment with a NHA, and who have been identified to have a germline or somatic BRCA1/2 or ATM mutation. The clinician from NS stated that they do not believe the drug under review should be approved for all HRR mutation patients but, should be approved for the mutations in cohort A from the PROFOUND trial. This recognizes that in cohort A the positive results are largely driven by BRCA2 mutations (partly due to the low numbers of BRCA1 and ATM). For cohort A, this meets an unmet need for those patients whom are BRCA1/2 mutated.

Clinicians stated that they would prescribe this drug to patients with HRR gene mutated mCRPC who are progressing after NHA, and either before or after taxane chemotherapy depending on a patient's fitness and preferences. These patients do not have alternative effective therapies, and this drug is significantly different from other available therapies. Additionally, there are no subpopulations who should be restricted from this therapy, if eligible HRR alterations have been identified. CPSA clinicians stated that the drug under review is comparable in efficacy to taxane chemotherapy (though limited by cross trial comparisons of very different patient populations) but demonstrates a significantly improved tolerability. The advantage of olaparib is that it would be tolerable in patients who are not eligible for taxane or platinum-based chemotherapy.

Clinician input stated that the drug under review could be sequenced as follows; 1) as first line mCRPC; 2) second line mCRPC as per the study, post ARAT; 3) third line mCRPC, post ARAT and chemotherapy; and 4) subsequent lines mCRPC. Many patients have had multiple lines of therapy such as ARAT, docetaxel, and cabazitaxel. According to clinicians, olaparib should be an option for these patients, where they would not have been eligible in second- or third-line settings. Clinicians indicated that the drug under review would not replace an available treatment but would be preferred to other therapies for patients with HRR gene alterations after NHA, due to the ease of administration, tolerability and efficacy.

In BC, companion diagnostic testing is available but not funded. Germline genetic testing is available in Alberta, but not somatic testing. Somatic testing would be required for implementation of the drug under review. In Ontario, testing to identify HRR alterations are not standardly funded for all mCRPC patients. HRR alteration testing should be implemented as patients would need access to testing in order to be eligible for the treatment under review. In NS, BRCA 1/2 somatic testing has just recently started for other tumours. The capacity to use this testing in the prostate cancer therapeutic space would need to be discussed. Testing for ATM and other mutations are not currently available.

5.1 Current Treatment(s)

The clinician from CCO stated that currently there are no standard funded biomarker-directed regimens specific for patients with mCRPC who harbour HRR gene mutations. The standard available options are identified in the provincial funding of current treatments including: ARATs such as enzalutamide and abiraterone, docetaxel (may be given after ARATs), and cabazitaxel which is only funded after progression on docetaxel. To date there are no genomically directed therapies for mCRPC that are funded in Ontario. The individual clinician from NS indicated that mCRPC patients may be treated with an ARAT or docetaxel as first line and may have a second ARAT or cabazitaxel treatment after docetaxel. In NS, radium is approved on a case by case basis with very strict criteria. There are no approved drugs in NS for patients with known HRR mutations. However, based on preclinical and early

clinical data, if a patient has BRCA 1/2, they would be eligible for treatment with a platinum-based drug or doublet such as cisplatin or carboplatin.

The clinician from BC Cancer noted that NHA switch is not currently funded in BC. Many patients are not eligible to receive taxane chemotherapy because of their age and co-morbidity and additionally would not be candidates for radium-223 (which is restricted to bone only metastases). Thus, olaparib fulfills an important unmet need for patients with metastatic prostate cancer. The clinician from CPSA indicated that there are currently no approved therapies in Alberta for this specific indication (BRCA1/2, ATM mutation). Therefore, olaparib would be meeting an unmet need. Patients would then be eligible to receive other therapies after olaparib, which under the current provincial funding algorithm in Alberta would be either docetaxel or cabazitaxel.

5.2 Eligible Patient Population

Both clinicians at CCO and BC Cancer stated that the patient population in the request aligns with their clinical practice and represents a significant unmet need. Approximately 20-25% of patients with mCRPC could harbour alterations in HRR genes. The clinician from BC Cancer identified that studies have concluded; patients with HRR altered prostate cancer have a more aggressive disease that is often treatment refractory, therefore the clinician advocated to leave the funding definition of HRR gene mutations as non-specific. The PROFOUND trial was not powered to make conclusions around which individual gene alterations predict treatment benefit and further study is required. CCO clinicians stated that the indication in a post NHA setting can be applied to clinical practice widely, so long as the applicable alterations are identified.

The clinician from NS stated that they do not believe the drug under review should be approved for all HRR mutation patients but should be approved for the mutations in cohort A of the PROFOUND trial. This recognizes that in cohort A the positive results are largely driven by BRCA2 mutations (partly due to the low numbers of BRCA1 and ATM). For cohort A, this meets an unmet need for those patients whom are BRCA1/2 mutated. The clinician indicated that the recommendation should state how this drug will be used, whether that is first line or second line (post ARAT as per study), or third line (post ARAT and docetaxel), and that the option for second- or third-line use should be available.

The clinician at CPSA indicated that they would use this treatment in patients with mCRPC who had progressive disease after treatment with an NHA, such as abiraterone or enzalutamide, and who have been identified to have a germline or somatic BRCA1/2 or ATM mutation. They agreed that the eligibility criteria from the landmark PROFOUND trial would be applicable to clinical practice. Additionally, they stated that clinicians and patients would benefit from having access to olaparib for use in patients with other HRR gene mutations such as CDK12, CHEK2, PALB2, etc. As these gene mutations are rare, more real-world experience is required in treating these patients with the drug under review to determine the magnitude of benefit.

5.3 Relevance to Clinical Practice

Three of the four clinician inputs indicated that they had experience with using the treatment under review for mCRPC. The clinician from NS did not have experience with the drug under review at the time of clinician input, however stated that they would be prescribing olaparib to their first mCRPC patient in the following weeks.

Clinicians stated that they would prescribe this drug to patients with HRR gene mutated mCRPC who are progressing after NHA, and either before or after taxane chemotherapy depending on a patient's fitness and preferences. These patients do not have alternative effective therapies, and this drug is significantly different from other available therapies. CPSA clinicians indicated that the drug under review, relative to other NHAs is significantly more effective with similar tolerability. The drug under review is comparable in efficacy to taxane chemotherapy (though limited by cross trial comparisons of very different patient populations) but demonstrates a significantly improved tolerability. The advantage of olaparib is that it would be tolerable in patients who are not eligible for taxane or platinum-based chemotherapy.

The BC physician identified that for those who are chemotherapy naïve, there is the choice of docetaxel and/or cabazitaxel, however most patients with mCRPC are not eligible for chemotherapy due to age, co-morbid disease, and/or preference. Previous studies within the clinician's jurisdiction have indicated that the use of taxane chemotherapy ranges between 20-50% in a patient's lifetime,

dependent on the patient's region. Olaparib is a well-tolerated, oral and effective therapy that would be an important option for patients.

CCO clinicians spoke to how there is currently no funded available treatments that satisfy this biomarker-driven area of need for mCRPC patients. Additionally, there are no subpopulations who should be restricted from this therapy, if eligible HRR alterations have been identified.

Contraindications indicated by the CPSA clinician are significant cytopenia's and poor performance status similar to other agents. The clinician in NS stated that contraindications would be as per the inclusion/exclusion criteria of the phase III PROFOUND trial.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The clinician from NS stated that the drug under review could be sequenced as follows; 1) as first line mCRPC; 2) second line mCRPC as per the study, post ARAT; 3) third line mCRPC, post ARAT and chemotherapy; and 4) subsequent lines mCRPC. Many patients have had multiple lines of therapy such as ARAT, docetaxel, and cabazitaxel. Olaparib should be an option for these patients, where they would not have been eligible in second- or third-line settings for other therapies such as ARAT, docetaxel and cabazitaxel. The clinician indicated that they would hope olaparib be funded for patients in situations 2, 3 and 4, as mentioned above.

CCO clinicians stated that olaparib should be available for all patients who harbour HRR alterations, those who are post NHA therapy, and those who are currently in the mCRPC setting.

Similarly, the clinician from BC Cancer stated that the drug under review would be preferred to other therapies for patients with HRR gene alterations after NHA, due to the ease of administration, tolerability and efficacy.

The CPSA clinician indicated that the drug under review would most likely be used after one line of NHA, and either before or after docetaxel chemotherapy. They noted that olaparib would not replace another agent, but rather be used in addition to other available treatments.

5.4.1 Implementation Question: In what circumstances would olaparib be preferable to standard docetaxel chemotherapy following progression on an ARAT?

Clinicians at CCO stated that the drug under review would be preferable in patients who harbour HRR alterations following progression on NHA/ARAT. The clinician from CPSA indicated that many patients are ineligible for docetaxel chemotherapy or refuse this treatment based on side effects, therefore, olaparib would be an option for these patients. The BC Cancer clinician identified that olaparib would be more favourable in most circumstances than to other therapies (i.e., taxanes, radium-223) because its more tolerable toxicity profile. Additionally, the drug under review is taken orally, therefore it is easier for both patients and the system to administer, especially during the COVID-19 pandemic.

The clinician from NS indicated that olaparib would be preferable for BRCA 1, 2 and ATM patients to receive it in second line. These tumors are biologically more aggressive, and it makes the most sense to use a more targeted therapy as early as possible in their disease course.

5.4.2 Implementation Question: What are the treatment options after failure of olaparib including potential ARAT re-treatment?

The BC Cancer, CPSA and NS clinicians stated that eligible patients could receive taxane based chemotherapy in eligible patients, or second line ARAT therapy in chemo-ineligible patients depending on provincial funding. Radium-223 could also be an option for patients with bone-only metastases. Despite it not being studied well, platinum-based chemotherapy is another option, though more data on its efficacy is required before this can uniformly be implemented as a standard of care.

CCO clinicians identified that patients who have disease progression on prior ARAT/NHA and who have received olaparib (with deleterious HRR alterations), should have available standard options in the mCRPC algorithm. All currently available options have been found to produce activity in patients who have received prior olaparib.

5.4.3 Implementation Question: What is the evidence and clinician perspective regarding optimal sequencing of drugs leading to olaparib? Should olaparib be reserved for patients who have progressed on all ARAT and taxane options?

Clinicians from NS and BC Cancer indicated that olaparib should not be reserved for patients who have progressed on all ARAT and taxane options. As many studies have demonstrated, sequential ARAT is not effective and many patients are not eligible for taxane chemotherapy. The option to use olaparib after an ARAT as per the study inclusion criteria should be an option.

The clinician from CPSA stated that there is no sufficient evidence to determine whether olaparib should preferentially be used either before or after docetaxel. The subgroup analysis from the PROFOUND trial suggested a benefit in patients irrespective of prior taxane use. The use of taxane based chemotherapy in mCRPC greatly depends on patient preference, as many patients are either unfit or unwilling to receive taxane. This should not be used as an exclusion for reimbursement of olaparib.

The clinician input from CCO indicated that biologically, olaparib should be available to all prostate cancer patients who harbour relevant HRR alterations. From the perspective of the PROFOUND trial, and in applying to the real world, the indication post NHA/ARAT in the mCRPC setting would be at minimum a high clinical need. Patients with these HRR alterations, and prior NHA therapy, should be eligible for olaparib and not be required to receive taxane chemotherapy first.

5.4.4 Implementation Question: What is the definition for disease progression and when should olaparib be discontinued?

Clinicians at BC Cancer and CPSA indicated that disease progression is defined as presenting with measurable disease and usually requiring either radiographic progression (defined by PCWG3 criteria and/or RECIST) or clinical progression, with or without PSA progression. The clinician at CCO spoke to how disease progression in the mCRPC setting while using olaparib should reflect the commonly used guidelines in assessing disease progression, which includes a composite of clinically, biochemical, and/or radiological progression.

The clinician from NS identified how in the abiraterone and enzalutamide ARAT trials, patients were required to meet one or more of three criteria to be removed from the study. These criteria include PSA progression, radiographic progression and clinical progression. Therefore, this clinician follows the criteria from those studies, however, for any patient that has significant decline in any of the criteria or wants to change their treatment regimen, it would be discontinued.

5.4.5 Implementation Question: Would you want to prescribe this drug for any patient with an HRR gene alteration i.e., BRCA1 and 2, ATM and cohort B genes i.e., BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L or only for patients with BRCA1,2 and ATM?

The clinician from BC Cancer stated that they would want to prescribe this drug to any patient with an HRR alteration. The PROFOUND trial was not powered to determine efficacy in individual gene populations and combining them in cohort A and cohort B for analysis was arbitrary and not optimal because these genes are not biologically or functionally identical. Emerging data on predictive biomarkers and population-based analyses will be important to inform practice in the future.

Similarly, the CCO clinician stated that ideally patients for all stated alterations per US FDA label would have access to this drug. However, based on currently available data, treatment should be accessible in patients with BRCA1/2 and ATM alterations (cohort A) as current evidence identifies the highest efficacy for this group.

The clinician from CPSA would also like to prescribe olaparib to cohort B patients as more experience with these less common genetic abnormalities are required.

In contrast, the clinician from NS stated they would only prescribe the drug under review to cohort A at this time.

5.4.6 Implementation Question: For patients who received docetaxel in metastatic castrate sensitive space, is there evidence and interest for using olaparib in the castrate resistant space?

All clinicians agreed that there is evidence and interest for using olaparib in the castrate resistant space for patients who received docetaxel in the metastatic castrate sensitive space. The clinician at BC Cancer indicated that data suggests patients who have received docetaxel in the mCSPC space are resistant to docetaxel when their disease develops to mCRPC. The clinician from CCO stated that since this is a genomically driven treatment, the most important indication is in applicable HRR alterations and the patient should be agnostic to prior docetaxel in the metastatic hormone-sensitive prostate cancer (mHSPC) setting. The clinician from NS indicated that the number of patients who receive docetaxel in the mHSPC space has significantly declined in the last five years.

The clinician associated with CPSA stated that there is not any rationale to believe that the disease state a treatment is received in (such as; mCRPC, nmCRPC, mCSPC) makes any difference on disease biology, or effect of subsequent treatment. They suggest that the reimbursement recommendation should be written to only apply to the patient's prior treatments, and not the disease state it was received in.

5.5 Companion Diagnostic Testing

In BC, companion diagnostic testing is available but not funded. The clinician at CPSA stated that germline genetic testing is available in Alberta, but not somatic testing. Somatic testing would be required for implementation of the drug under review. Turnaround time is a potential issue, however with clinician education about when to test, this issue should be minimized.

In Ontario, testing to identify HRR alterations are not standardly funded for all mCRPC patients. HRR alteration testing should be implemented as patients would need access to testing in order to be eligible for the treatment under review. Tissue or blood next-generation sequence (NGS) testing (with capability for germline and somatic alterations) have both been found to be meaningful in identifying these patients.

In NS, BRCA 1/2 somatic testing has just recently started for other tumours. The capacity to use this testing in the prostate cancer therapeutic space would need to be discussed. Testing for ATM and other mutations are not currently available. Germline testing for BRCA 1/2 and ATM would be possible, however, there is a current capacity issue at genetic clinics. Currently, oncology clinicians cannot order germline testing for prostate cancer.

5.5.1 Implementation Question: When should mutation testing occur?

Clinicians from BC Cancer, NS and CPSA indicated that mutation testing should occur in the mCRPC or mCSPC space as soon as metastatic disease is identified. The BC Cancer clinician stated that it is important to identify germline alterations as these patients have poor prognosis and outcomes with currently available therapies.

The clinician from CCO indicated that the rationale for mutation testing would be to test in a metastatic setting for any fresh or archival sample. The delineation between metastatic hormone sensitive or hormone resistant settings is somewhat arbitrary with respect to identifying relevant HRR alterations.

5.6 Implementation Questions

Refer to implementation questions in respective sections above.

5.7 Additional Information

None to report.

6 Systematic Review

6.1 Objectives

To assess the efficacy and safety of olaparib as a monotherapy for the treatment of adult patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in HRR genes BRCA or ATM who have progressed following prior treatment with an NHA.

Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 5: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of olaparib should be included.	Adult patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes *BRCA* or *ATM* who have progressed following prior treatment with an NHA. <u>Subgroups:</u> • Measurable disease at baseline (yes/no) • Genotype carriers (*BRCA1, BRCA2* or *ATM*)	Olaparib	Enzalutamide Abiraterone Cabazitaxel Docetaxel Radium-223	<u>Primary</u> • **OS** • **PFS** • **HRQoL** <u>Secondary</u> • ORR • Time to pain progression • Time to SSRE • PSA response • CTC conversion <u>Safety</u> • **AEs** • SAEs • WDAEs • Dose adjustment, interruption and/or discontinuation • Time to discontinuation

AEs= adverse events; CTC = circulating tumour cells; HRQoL = health-related quality of life; HRR = homologous recombination repair; mCRPC = metastatic castration-resistant prostate cancer; NHA = new hormonal agent; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PSA = prostate specific antigen; RCT = randomized controlled trial; SAEs = serious adverse events; WDAEs = withdrawals due to adverse events

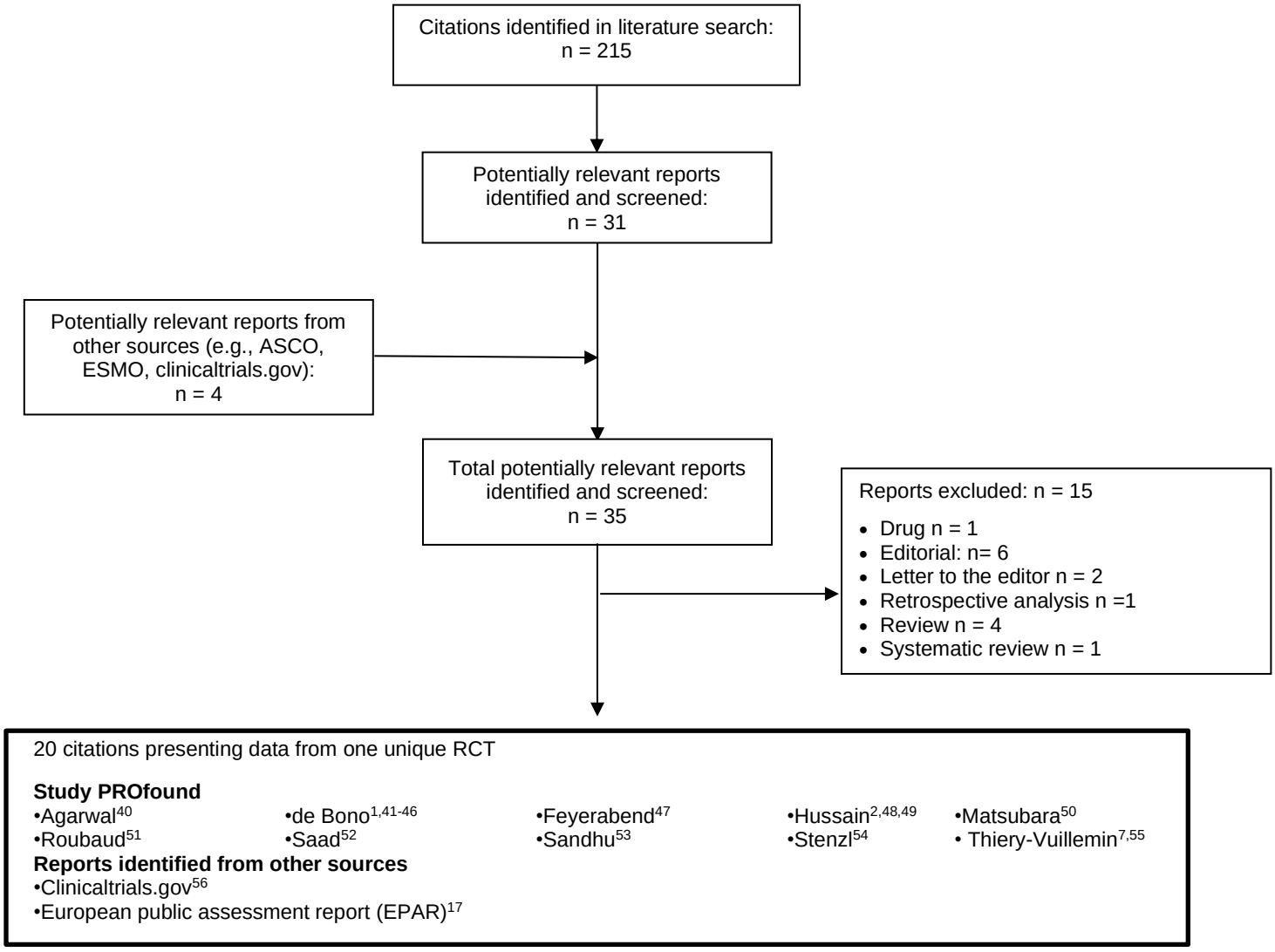
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 215 potentially relevant reports identified, one trial, reported in 18 citations, was included in the pCODR systematic review (Figure 1). Fifteen reports were excluded because one had a different drug, six were editorials, two were letters from the editor, one was a retrospective analysis, four were reviews and one was a systematic review. Additional reports related to the trials were obtained from the Sponsor.

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to the PROfound Trial were also obtained through requests to the Sponsor by CADTH [Clinical Study Report,[3] Clinical Summary Report,[6] Indirect Treatment Comparison,[8] Checkpoint Responses[4]]

6.3.2 Summary of Included Studies

The pCODR systematic review included one multinational, open-label, randomized phase III trial, the PROfound trial[1,2], that assessed the efficacy and safety of olaparib versus investigator's choice (i.e., enzalutamide or abiraterone acetate) for adult patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in HRR genes BRCA or ATM who have progressed following prior treatment with an NHA.

6.3.2.1 Detailed Trial Characteristics

The focus of this review will be on participants who were included in Cohort A of the PROfound trial, which includes patients with a BRCA1, BRCA2 or ATM mutation, since this is the indication under review. However, details on Cohort A+B will also be presented to provide context of the PROfound trial. The summary of the trial and select quality characteristics are presented in Tables 6 to 7.

Table 6: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study PROfound (NCT02987543) **Characteristics** Multi-centre, open-label, randomized phase 3 trial Randomized on a 2:1 ratio **Sample Size** N (randomized to Cohort A) = 245 N (treated in Cohort A) = 245 **Study centres and countries** 206 study centres in 20 countries **Patient Enrolment Dates** April 2017 to November 2018 **Primary data cut-off date** June 4, 2019 **Final Analysis Date** March 20, 2020 **Funding** AstraZeneca and Merck Sharp & Dohme	**Key Inclusion Criteria:** • Male ≥ 18 years of age. • Histologically confirmed diagnosis of prostate cancer. • Candidate for enzalutamide or abiraterone acetate with documented current evidence of metastatic castration-resistant prostate cancer. • Progressed on prior NHA for the treatment of metastatic prostate cancer and/or CRPC. • Serum testosterone levels ≤ 50 ng/dL (≤ 1.75 nmol/L). • Patients without prior surgical castration must be currently taking and continue to take LHRH analog (agonist or antagonist) therapy throughout the duration of study treatment. • Radiographic progression at study entry while on androgen deprivation therapy (or after bilateral orchiectomy). • Qualifying HRR mutation by an assay • Normal organ and bone marrow function • ECOG performance status of 0-2 **Key Exclusion Criteria:** • Any previous treatment with PARP inhibitor, including olaparib. • Previous treatment with DNA-damaging cytotoxic chemotherapy. • Other malignancy (including MDS and MGUS) within the last 5 years except: adequately treated non-melanoma skin cancer or other solid tumors including lymphomas (without bone marrow involvement) curatively treated	**Intervention** Olaparib (300 mg twice daily) **Control** Investigator's choice of: Enzalutamide (160 mg once daily) Or Abiraterone (1000 mg once daily, plus prednisone at a dose of 5 mg twice daily)	**Primary:** • rPFS by BICR in Cohort A **Key Secondary:** • Confirmed ORR by BICR in Cohort A • rPFS by BICR in Cohort A+B • Pain progression in Cohort A • OS in Cohort A **Other Secondary outcomes:** • Time to the first SSRE in Cohort A and Cohort A+B • DoR in Cohort A and Cohort A+B • Time to opiate use for cancer-related pain in Cohort A and Cohort A+B • ORR by BICR in Cohort A and Cohort A+B • PSA response in Cohort A and Cohort A+B • CTC conversion rate in Cohort A and Cohort A+B • Time PFS2 in Cohort A and A+B • HRQoL in Cohort A and Cohort A+B • OS in Cohort A+B

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	with no evidence of disease for ≥5 years. • Patients with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML. • Receiving any systemic anti-cancer therapy (except radiotherapy). • Known brain metastases. • Not evaluable for both bone and soft tissue progression.		

Abbreviations: AML = acute myeloid leukaemia; BICR = blinded independent central view; CRPC = castration-resistant prostate cancer; CTC = circulating tumour cells; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; HRQoL = health-related quality of life; HRR = homologous recombination repair; LHRH = luteinizing hormone-releasing hormone; MDS = myelodysplastic syndrome; MGUS = monoclonal gammopathy of unknown significance; NHA = new hormonal agent; ORR = overall response rate; OS = overall survival; PSA = prostate specific antigen; RCT = randomized controlled trial; rPFS = radiographic progression free survival; SSRE = symptomatic skeletal-related event.

Table 7: Select Quality Characteristics of Included Studies that Assessed the Efficacy and Safety of Olaparib for Patients with mCRPC and Deleterious or Suspected Deleterious Germline and/or Somatic Mutations in HRR genes BRCA or ATM who have Progressed Following Prior Treatment with an NHA

Study	PROfound
Treatment vs. Comparator	Olaparib vs. Control (i.e., investigator's choice [enzalutamide or abiraterone])
Primary outcomes	rPFS by BICR
Required sample size	The trial required a sample size of 240 patients in Cohort A with 143 rPFS events (60% maturity) for the primary analysis. This sample size would provide 95% power to detect a HR of 0.53 for rPFS events with a two-sided significance level (α) of 0.05.[1] The sample size of Cohort B is 100 patients.
Sample size	387 patients were included in Cohort A+B (N for Cohort A: 245 and N for Cohort B: 142)
Randomization method	Randomization was stratified by previous taxane chemotherapy (yes, no) and measurable disease at baseline (yes, no).[1]
Allocation concealment	Centralized using an interactive voice response system/ interactive web response system.
Blinding	Open label. Radiographic assessments were performed at a sponsor designated facility for a blinded independent review.

ITT Analysis	Yes
Final analysis	Yes. The final analysis was on March 20, 2020.
Early termination	No
Ethics Approval	Yes

Abbreviations: BICR = blinded independent central review; HR = hazard ratio; ITT = intention-to-treat; rPFS = radiographic progression-free survival

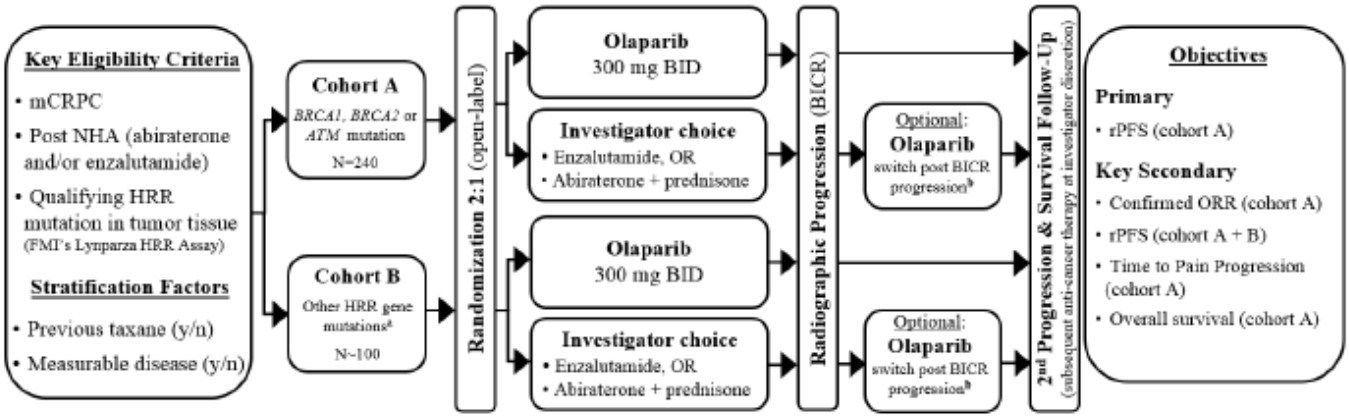
a) Trials

The PROfound trial was as one multinational, open-label, randomized phase III trial, that assessed the efficacy and safety of olaparib versus investigator's choice (i.e., enzalutamide or abiraterone acetate) for adult patients with metastatic castration-resistant prostate cancer (mCRPC) and deleterious or suspected deleterious germline and/or somatic mutations in HRR genes BRCA or ATM who have progressed following prior treatment with a novel hormone agent (NHA). The PROfound trial was conducted in 206 study centers in 20 countries, which includes Argentina, Australia, Austria, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Japan, Netherlands, Norway, South Korea, Spain, Sweden, Taiwan, Turkey, United Kingdom and United States.[1] [redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Patients were included in the trial if they met the following criteria: males aged 18 years and older with a histologically confirmed diagnosis of prostate cancer; progressed on prior NHA (e.g., abiraterone acetate and/or enzalutamide) for the treatment of metastatic prostate cancer and/or CRPC (only 13 patients in the overall study population received a NHA before the development of mCRPC)[57]; radiographic progression while on ADT (or after bilateral orchiectomy); qualifying HRR mutation in tumor tissue by the FMI CLIA HRR (Lynparza HRR) CTA assay; normal organ and bone marrow function and an ECOG performance status of 0 to 2.[1] Patients were permitted in the trial if they had previous taxane chemotherapy.[1] Further details on the inclusion and exclusion criteria are provided in Table 6.

The design of the PROfound trial is illustrated in Figure 2. Patients who had qualifying HRR mutations using the FMI Lynparza HRR Assay were divided into two cohorts. Patients were included in Cohort A if they had a *BRCA1*, *BRCA2* or *ATM* mutation while those in Cohort B had a mutation in 12 other genes involved in HRR (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and RAD54L).[1] Patients in both Cohort A and B were randomized in a 2:1 ratio to receive either olaparib (300 mg twice daily) or investigator's choice (enzalutamide [160 mg/daily] or abiraterone acetate [1000 mg/daily with 5 mg of prednisone twice daily]). Randomization was performed using an interactive voice response system/interactive web response system and randomization was stratified by previous taxane chemotherapy (yes, no) and measurable disease at baseline (yes, no).[1]

Figure 2: Study Design for the PROfound Trial



[a] Cohort B HRR genes include *BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L.*
[b] Subjects randomized to investigator choice arm will be given the opportunity to begin treatment with open-label olaparib (300 mg bid) only after objective radiographic progression by blinded independent central reader (BICR). No intervening systemic anti-cancer therapy following discontinuation of randomized treatment will be permitted. Subjects may continue on olaparib as long as they show clinical benefit as judged by the investigator.

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During the open-label treatment phase, assessments were performed every eight weeks until objective radiological disease progression by BICR.[1] These assessments were done using soft-tissue computed tomography or magnetic resonance imaging of the chest, abdomen and pelvis as well as bone scans using bone scintigraphy commonly performed with technetium-99.[1] Table 8 shows the criteria for bone and soft tissue progression. Bone progression required a second confirmation at least six weeks later.[1]

All patients received their assigned therapy until they had objective radiographic progression by BICR or until they were unable to tolerate their study treatment prior to the primary rPFS analysis.[1] However, after the primary rPFS analysis, all patients received their assigned therapy until they had objective radiographic progression by the study investigator or until they were unable to tolerate their study treatment.[1] Patients could discontinue treatment for the following reasons: patient's decision, adverse event, severe noncompliance with the protocol, bone marrow findings consistent with myelodysplastic syndrome/acute myeloid leukemia, objective radiographic progression as assessed by BICR, clinical progression (i.e., cancer pain requiring chronic administration of opioids; initiation of cytotoxic chemotherapy, radiation therapy, or surgical intervention for complications due to tumor progression; or an ECOG performance status of ≥ 3), or initiation of restricted anticancer therapy.[1] Patients who discontinued their assigned therapy were not withdrawn from the study and they were followed up for progression (if discontinuation in the absence of progression) and OS.[1]

In addition, patients who had investigator-assessed radiographic progression as assessed by BICR before the primary rPFS analysis, or after the primary rPFS analysis, could receive subsequent anticancer therapies based on the investigator's discretion.

Table 8: Requirements for determination and confirmation of imaging-based progression by either bone scan (bone progression) or computed tomography or magnetic resonance imaging (soft-tissue progression)

Visit date	Criteria for bone progression	Criteria for soft-tissue progression
Week 8	▪ ≥2 new lesions compared with baseline bone scan ▪ Requires confirmation scan ≥6 weeks later with >2 additional lesions compared with week 8 scan	▪ Progressive disease on CT or MRI by RECIST 1.1 ▪ No confirmation scan required
Week 16 or later	▪ ≥2 new lesions compared with week 8 bone scan ▪ Requires confirmation scan ≥6 weeks later for persistence or increase in number of lesions	▪ Progressive disease on CT or MRI by RECIST 1.1 ▪ No confirmation scan required

CT, computed tomography; MRI, magnetic resonance imaging; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1

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Patients in the control group who had radiographic progression by BICR were eligible to crossover and receive olaparib. However, patients who had radiographic progression as assessed by the investigator were not permitted to crossover until after the primary analysis. In addition, prior to switching to olaparib, patients were not receiving any intervening anticancer therapy following discontinuation of their randomized treatment and any unresolved toxicities from prior therapy should be controlled (no greater than CTCAE grade 1 at the time of starting olaparib therapy).[1] Patients who crossed over to receive olaparib may continue treatment until investigator's opinion as long as they did not meet any other discontinuation criteria.

The primary endpoint in the PROfound trial was rPFS by BICR using Response Evaluation Criteria in Solid Tumors (RECIST 1.1 soft tissue) and Prostate Cancer Working Group 3 (PCWG3 bone) criteria in Cohort A.[1] Secondary outcomes were confirmed overall response rate (ORR) by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria in Cohort A, rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria in Cohort A+B, pain progression based on Brief Pain Inventory Short Form (BPI-SF) item 3; "worst pain in 24 hours" and opiate analgesic use (AQA score) in Cohort A and overall survival (OS) in Cohort A. Other exploratory outcomes in Cohort A include time from randomization to the first SSRE, time to opiate use for cancer-related pain, soft tissue response, proportion of patients achieving a ≥ 50% decrease in prostate specific antigen (PSA response), circulating tumor cells (CTC) conversion, time to second progression by investigator assessment of radiological or clinical progression or death (PFS2) and HRQoL. These outcomes were also assessed in Cohort A+B. Safety outcomes were assessed in Cohort A + B.

Radiographic progression-free survival by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria was defined as the time to objective disease progression (soft tissue or bone) or death (by any cause in the absence of progression). These definitions are presented in Table 8. The BICR assessments using RECIST 1.1 and PCWG3 criteria only apply to the results of the primary analysis, after this data-cut off, all assessments were performed by the investigator.[1] The rPFS curves were estimated using the Kaplan-Meier curves and treatment differences were determined using a two-sided log-rank test stratified by previous taxane chemotherapy (yes, no) and measurable disease at baseline (yes, no).[1] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% confidence intervals (CIs).[1]

Objective response rate by BICR using RECIST 1.1 and PCWG3 criteria was defined as the proportion of patients with at least one visit response of complete response or partial response in their soft tissue and the absence of progression on bone scan.[1] Patients were only included in this analysis if they had measurable disease at baseline as assessed by BICR.[1] Overall response rate was estimated using a logistic regression stratified by previous taxane chemotherapy (yes vs no).[1] The odds ratio (OR) and corresponding 95% CI is reported using a prespecified two-sided significance level based on the multiplicity strategy.[1]

Time to pain progression in Cohort A was a key secondary outcome in the trial and it was defined as the time to worsening pain. Worsening pain was based on the BPI-SF item 3; "worst pain in 24 hours" and the AQA score. Time to pain progression was classified differently for asymptomatic and symptomatic patients.[1] Asymptomatic patients at baseline (average BPI-SF item 3 score 0 and not taking opioids) were required to have an increase of 2 or more points on the BPI-SF item 3 score from baseline over two follow-up visits or started taking opioids.[1] Symptomatic patients at baseline (average BPI-SF item 3 score > 0 and taking opioids) were required to have an increase of 2 or more points on the BPI-SF item 3 score from baseline over two follow-up visits and an average worst pain score ≥4 with no decrease on average opioid use as measured by a 1 or more point decrease in AQA score (which starts at 2 or higher) or an increase in 1 point or higher for the average opioid use in the AQA score from baseline (or at least a 2 point increase if starting at 0) over two follow-up visits.[1] The time to pain progression curves were estimated using the Kaplan-Meier curves and treatment differences were determined using a two-sided log-rank test stratified by previous taxane chemotherapy (yes, no) and measurable disease at baseline (yes, no).[1] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% CIs with a prespecified two-sided significance level based on the multiplicity strategy. [1]

Overall survival was a key secondary outcome in the trial and it was defined as the time to death due to any cause regardless of whether the patient withdraws from their assigned therapy or received another anti-cancer therapy.[1] Two analyses were performed for OS: the interim analysis and the final analysis. The interim analysis occurred at the primary analysis of rPFS (June 4,2019) and the final analysis occurred when 146 events had occurred (61% maturity) (March 20,2020).[1] An O'Brien Fleming spending function was used for the OS analysis, where a two-sided alpha of 0.01 was used for the interim analysis and an alpha of 0.047 was used at the final analysis.[4] The OS curves were estimated using the Kaplan-Meier curves and treatment differences were determined using a two-sided log-rank test stratified by previous taxane chemotherapy (yes, no) and measurable disease at baseline (yes, no). [1] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% CIs.[1] Prespecified sensitivity analyses were also performed to account for patient cross-over. The analyses used rank preserving structural failure time models (RPSFT) that adjusted for patients on the control group who subsequently received olaparib.[4]

Time to opiate use for cancer-related pain was another secondary outcome and it was defined as the time to opiate use for cancer-related pain among patients who have not received any opiates at baseline.[1] Time to opiate use for cancer-related pain was estimated using the Kaplan-Meier curves and treatment differences were determined using a two-sided log-rank test stratified by previous taxane chemotherapy (yes, no) and measurable disease at baseline (yes, no).[1] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% CIs.[1]

Time to SSRE was another secondary outcome and it was defined as the time to one of the following: use of radiation therapy to prevent or relieve skeletal symptoms; new symptomatic and pathological bone fractures by radiographic documentation (vertebral or nonvertebral); new pathological fracture as assessed by the investigator (classified as low or no trauma and occurred at a site of bone metastasis); spinal cord compression by radiographic documentation; or orthopedic surgical intervention for bone metastasis.[1] The time to pain progression curves were estimated using the Kaplan-Meier curves and treatment differences were determined using a two-sided log-rank test stratified by previous taxane chemotherapy (yes, no) and measurable disease at baseline (yes, no). [1] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% CIs.[1]

PSA response rate was another secondary outcome, and it was defined as the proportion of patients achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline PSA result, which was confirmed by a second PSA assessment at least three weeks later.[1] Patients were included in the analysis if they had a valid baseline and post-baseline PSA measurement.[1]

CTC conversion rate was an exploratory outcome, and it was defined as the percentage of patients with a decrease in the number of CTC from ≥5 cells per 7.5 ml of whole blood at baseline to <5 cells per 7.5 ml after baseline.[1] Only patients with a with baseline values ≥5 cells/7.5 mL at baseline were included in the analysis.[1]

Time to PFS2 was another secondary outcome and defined as the time to investigator assessed progression (subsequent to that used for the primary variable rPFS) or death. PFS2 curves were estimated using the Kaplan-Meier curves and treatment differences were stratified by previous taxane chemotherapy (yes, no) and measurable disease at baseline (yes, no).[1] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% CIs.

The Functional Assessment of Cancer Therapy- Prostate Cancer (FACT-P) and the EQ-5D-5L were used to assess HRQoL in Cohort A and A+B.[1] The questionnaires were administered at baseline, week 8, 16 and 24 and then continued to be administered to all patients (who have not withdrawn consent) for every 8 weeks until 24 weeks post progression,[1] Patients that discontinued treatment prior to having radiographic progression as assessed by BICR or as assessed by the investigator (post primary analysis) were given the assessments for 24 weeks post progression.[1]

The descriptive HRQoL analyses were conducted in the ITT population. Adherence rates were defined as the number of patients who provided both a baseline and at least one post baseline assessment divided by the number of patients randomized.[1] For continuous variables, changes from baseline to week 32 in PRO scores (overall scores, sub scores, and individual items) were analyzed descriptively by treatment group. The FACT-P and EQ-5D-5L scores were analyzed using a mixed-model for repeated measures of all the post-baseline scores for each visit that adjusted for fixed (treatment visit, treatment visit interaction, baseline score, and the two stratification factors) in order to assess the association between treatment assignment and PRO score.[1] It should be noted that the HRQoL analysis was not included in the testing hierarchy, and therefore, no adjustments were made for type 1 error.

FACT-P assesses prostate cancer-related QoL and it has been validated in prostate cancer patients. The instrument measures five domains of health: PWB, Social/Family Well-Being (SWB), Emotional Well-being (EWB), Functional Well-Being (FWB) and Prostate Subscale (PCS). The minimally important difference (MID) was an increase (improvement) or decrease (deterioration) of ≥6 points for the FACT-P total, ≥5 for the trial outcome index, ≥3 for the FACT Advanced Prostate Symptom Index 6 (FAPSI-6) and PCS or ≥2 for the PWB and FWB.[7]

The EQ-5D-5L assesses general health status and health utility measure and it has been validated in cancer populations. It measures five dimensions of health state: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[1] The MID was not reported for the EQ-5D-5L.

The trial was designed to have 95% power to detect a HR of 0.53 for rPFS events with a two-sided significance level (α) of 0.05.[1] The trial requires a sample size of 240 patients in Cohort A and 143 rPFS events (60% maturity) for the primary analysis.[1] One hundred participants were included in Cohort B and the number of included participants was not driven by a formal sample size calculation.[1]

The trial was composed of the following analysis populations: the intention-to-treat (ITT) population, the evaluable for response population, the safety set population and safety switch population.[1] The efficacy analyses were conducted in the ITT population for Cohort A, B and A+B, which was composed of all randomized patients regardless of the actual treatment they received. The evaluable for response group was composed of those who had measurable disease at baseline as per the RECIST 1.1 criteria.[1] The safety analyses were conducted in the safety set population, which was composed of all patients that received at least one dose of the study drug.[1] The safety switch population consisted of those who were randomized to the control group in either Cohort A or B and then crossed over to received olaparib and had at least one dose of olaparib.[1]

The objective of the primary analysis was to assess the effect of the two treatment groups on rPFS by BICR using a two-sided log-rank test, stratified according to the pre-specified factors at an alpha of 0.05 significance level.[1] A multiple testing procedure was used to account for type 1 error.[1] If the primary outcome was statistically significant, then the secondary outcomes were tested using a sequential procedure in the following order: ORR (Cohort A), rPFS (Cohort A+B), time to pain progression (Cohort A) and OS (Cohort A). [1] Two analyses were planned for OS: an interim analysis at the primary analysis and a final analysis. An O'Brien Fleming spending function was used for the OS analysis, where a one-sided alpha of 0.012 was used for the interim analysis and an alpha of 0.021 was used at the final analysis when approximately 146 events (61% maturity) had occurred.[1] Subgroups analyses were planned a priori, and all subgroup analyses are considered exploratory.[1] Cohort B analyses were not included in the multiple testing hierarchy. Cohort B was included in the PROfound trial to assess the efficacy and safety in the overall patient population with any HRR mutation (i.e., Cohort A+B).

Protocol and statistical analysis plan amendments were made to the PROfound trial. The following amendments were made to the study protocol after the start of patient recruitment:[1]

- Amendment 3 (June 4, 2018)

  - Exploratory endpoints were added to compare the effect of olaparib versus investigator's choice of treatment in patients with BRCA1, BRCA2, ATM or HRR qualifying mutations as detected by ctDNA analysis.
  - Inclusion criterion 5 was updated to clarify patients were to have progressed on prior NHA for the treatment of metastatic prostate cancer and/or CRPC; previously this was mCRPC only.
  - Inclusion criterion 10 was updated to state creatinine clearance could be estimated by Cockcroft-Gault equation for males or based on a 24-hour urine test.
  - Exclusion criterion 5 was updated to clarify that patients could have received prior treatment with DNA-damaging cytotoxic chemotherapy for non-prostate cancer.
  - Exclusion criterion 8 was updated to define resting ECG limits.
  - An optional blood sample for germline testing was added.
- Amendment 4 (March 7, 2019)
  - A potential cohort of 42 patients randomized in China was added
  - Access to olaparib after DCO for patients randomized to the comparator group was clarified

The following amendments were made to the statistical analysis plan:[1]

- Updated definitions and added information about how scores are derived for time to pain progression and endpoints using the BPI-SF.
- Removed the text which required the two consecutive subsequent time to pain progression and BPI-SF assessments to be separated by 3-4 weeks. The requirement is 2 consecutive follow-up assessments (with at least 2 weeks between the end of the initial visit and the start of the subsequent visit).
- Added additional information for the imputation rules for OME and AQA scores
- Specified that there needs to be at least 5 responses to perform logistic regression analyses throughout, otherwise a fisher's exact test will be used
- Added evaluable for response analysis set for Cohort A, B and A+B.
- Updated the rPFS censoring approach for censoring patients who have not progressed or died at the time of analysis and for censoring patients who progress or die immediately after two or more consecutive missed visits
- Patients who have not experienced any symptomatic skeletal-related event will be censored at time of death or time of last SSRE assessment (not time of analysis if the patient is living).
- Updated the subgroup analysis to only provide descriptive statistics if there are less than 5 events across both treatment groups.
- Added safety switch analysis set.
- Total Functional Assessment of Cancer Therapy - General (FACT-G) score, sum of PWB, SWB, EWB and FWB was added.
- The protocol stated safety data (including adverse events, laboratory data, concomitant medications and exposure) will be summarized for Cohort A, Cohort B and Cohort A+B. This was updated in the SAP to be produced for Cohort A+B only.

The protocol amendments do not appear to bias nor confound interpretation of the results of the trial because it was not expected to influence the final effect estimates of the trial.

b) Populations

The baseline characteristics of Cohort A and A+B are presented in Table 9.[1] Among those in Cohort A, the median age in the olaparib group was 68 years (range: 47 to 86) and 67 years (range: 49 to 86) in the control group, more than half of all patients had measurable disease at baseline (59% in olaparib and 55% in control) and the majority of patients received a previous taxane (65% in olaparib and 63% in control).[1] In Cohort A, median time from mCRPC to randomization was 23.3 months (range: -6 to 121) in the olaparib group and 22.5 months (range: 1 to 105) in the control group.[17] However, de Bono et al. (2020) reported that there was an imbalance in the patients with visceral metastases (28% in olaparib and 39 % in control), median baseline PSA concentration (62.2 [IQR: 21.9 to 280.4] in olaparib and 112.9 [IQR: 34.3 to 317.1] in control) and patients with an ATM (37% in olaparib and 29% in control) or a BRCA2 alteration (49% in olaparib and 57% in control).[1] Similar imbalances were observed for Cohort A+B (Table 9). However, the Sponsor noted that these imbalances did not have an impact on efficacy endpoints.[4]

Table 10 shows the prevalence of qualifying gene alterations in randomized patients reported for the total number of alterations in any gene and co-occurring alterations. [redacted]

[redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 9: Baseline characteristics for patients enrolled in the PROfound Trial

Characteristic	Cohort A*		Overall population*	
	Olaparib (N=162)	Control (N=83)	Olaparib (N=256)	Control (N=131)
Median age at randomization (range) — yr	68 (47–86)	67 (49–86)	69 (47–91)	69 (49–87)
Age ≥65 years at randomization — n (%)	108 (67)	60 (72)	174 (68)	97 (74)
Metastatic disease at initial diagnosis — n (%)	38 (23)	19 (23)	66 (26)	25 (19)
Missing data	7 (4)	4 (5)	11 (4)	7 (5)
Gleason score ≥ 8 — n/N (%)†	105/157 (67)	54/80 (67)	183/251 (73)	95/127 (75)
Patients with alteration(s) in a single gene — n (%)‡				
BRCA1	8 (5)	5 (6)	8 (3)	5 (4)
BRCA2	80 (49)	47 (57)	81 (32)	47 (36)
ATM	60 (37)	24 (29)	62 (24)	24 (18)
CDK12	NA	NA	61 (24)	28 (21)
Median PSA at baseline (IQR) — µg/l	62.2 (21.9, 280.4)	112.9 (34.3, 317.1)	68.2 (24.1, 294.4)	106.5 (37.2, 326.6)
Measurable disease at baseline§ — n (%)	95 (59)	46 (55)	149 (58)	72 (55)
Metastases at baseline§ — n (%)				
Bone only	57 (35)	23 (28)	86 (34)	38 (29)
Visceral (lung/ liver)	46 (28)	32 (39)	68 (27)	44 (34)
Other	49 (30)	23 (28)	88 (34)	41 (31)
ECOG performance status — n (%)				
0	84 (52)	34 (41)	131 (51)	55 (42)
1	67 (41)	46 (55)	112 (44)	71 (54)
2	11 (7)	3 (4)	13 (5)	4 (3)
Prior next-generation hormonal agent — n (%)¶				
Enzalutamide only	68 (42)	40 (48)	105 (41)	54 (41)
Abiraterone only	62 (38)	29 (35)	100 (39)	54 (41)
Abiraterone+enzalutamide	32 (20)	14 (17)	51 (20)	23 (18)
Previous taxane use — n (%)	106 (65)	52 (63)	170 (66)	84 (64)
Docetaxel only	74 (46)	32 (39)	115 (45)	58 (44)
Cabazitaxel only	2 (1)	0	3 (1)	0
Docetaxel+cabazitaxel	29 (18)	20 (24)	51 (20)	26 (20)
Paclitaxel only	1 (<1)	0	1 (<1)	0

*Cohort A included patients with at least one alteration in *BRCA1*, *BRCA2*, or *ATM*. Cohort B included patient with alterations in any of 12 other prespecified genes: *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. In both cohorts, patients in the control group received the physician's choice of enzalutamide or abiraterone.

†In general, scores on the Gleason scale range from 6 to 10, with higher scores indicating a worse prognosis.

‡In total, 28 patients (21 in Cohort A and 7 in Cohort B) had mutations in more than one gene. Four patients were incorrectly assigned to cohort B (one in the olaparib group had an alteration in *BRCA2*, one in the control group had alterations in *BRCA2* and *CDK12*, and two in the olaparib group had alterations in *ATM*).

§Data were derived from electronic case-report forms as assessed by the investigator.

¶In total, 13 patients received a NHA for disease before a diagnosis of mCRPC; all others received a NHA after the development of mCRPC.

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; NHA, next-generation hormonal agent; n/N, no./total no.; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; yr, years.

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Table 10: Prevalence of qualifying gene alterations in randomized patients reported for (A) total number of alterations in any gene and (B) co-occurring alterations

(A)

Patients, n (%)	Cohort A		Cohort B		Overall population (Cohorts A+B)	
	Olaparib 300 mg bid (N=162)	Control (N=83)	Olaparib 300 mg bid (N=94)	Control (N=48)	Olaparib 300 mg bid (N=256)	Control (N=131)
BRCA1	10 (6.2)	5 (6.0)	0	0	10 (3.9)	5 (3.8)
BRCA2	91 (56.2)	52 (62.7)	1 (1.1)	1 (2.1)	92 (35.9)	53 (40.5)
ATM	64 (39.5)	26 (31.3)	2 (2.1)	0	66 (25.8)	26 (19.8)
BARD1	2 (1.2)	0	1 (1.1)	1 (2.1)	3 (1.2)	1 (0.8)
BRIP1	0	0	2 (2.1)	2 (4.2)	2 (0.8)	2 (1.5)
CDK12	3 (1.9)	2 (2.4)	64 (68.1)	30 (62.5)	67 (26.2)	32 (24.4)
CHEK1	0	0	2 (2.1)	1 (2.1)	2 (0.8)	1 (0.8)
CHEK2	4 (2.5)	1 (1.2)	7 (7.4)	5 (10.4)	11 (4.3)	6 (4.6)
FANCL	0	0	0	0	0	0
PALB2	0	0	4 (4.3)	4 (8.3)	4 (1.6)	4 (3.1)
PPP2R2A	1 (0.6)	3 (3.6)	6 (6.4)	5 (10.4)	7 (2.7)	8 (6.1)
RAD51B	1 (0.6)	1 (1.2)	4 (4.3)	1 (2.1)	5 (2.0)	2 (1.5)
RAD51C	0	0	0	0	0	0
RAD51D	1 (0.6)	0	1 (1.1)	0	2 (0.8)	0
RAD54L	1 (0.6)	0	3 (3.2)	2 (4.2)	4 (1.6)	2 (1.5)

Patients with multiple genes are included across more than one gene.

(B)

Patients, n (%)	Cohort A		Cohort B		Overall population (Cohorts A+B)	
	Olaparib 300 mg bid (N=14)	Control (N=7)	Olaparib 300 mg bid (N=3)	Control (N=4)	Olaparib 300 mg bid (N=17)	Control (N=11)
BRCA1 + ATM	1 (7.1)	0	0	0	1 (5.9)	0
BRCA1 + RAD54L	1 (7.1)	0	0	0	1 (5.9)	0
BRCA2 + ATM	2 (14.3)	0	0	0	2 (11.8)	0
BRCA2 + BARD1	2 (14.3)	0	0	0	2 (11.8)	0
BRCA2 + CDK12	2 (14.3)	2 (28.6)	0	1 (25.0)	2 (11.8)	3 (27.3)
BRCA2 + CDK12 + CHEK2	1 (7.1)	0	0	0	1 (5.9)	0
BRCA2 + CHEK2	2 (14.3)	0	0	0	2 (11.8)	0
BRCA2 + CHEK2 + RAD51D	1 (7.1)	0	0	0	1 (5.9)	0
BRCA2 + PPP2R2A	1 (7.1)	2 (28.6)	0	0	1 (5.9)	2 (18.2)
BRCA2 + RAD51B	0	1 (14.3)	0	0	0	1 (9.1)
ATM + CHEK2	0	1 (14.3)	0	0	0	1 (9.1)
ATM + PPP2R2A	0	1 (14.3)	0	0	0	1 (9.1)
ATM + RAD51B	1 (7.1)	0	0	0	1 (5.9)	0
BARD1 + CDK12	0	0	1 (33.3)	0	1 (5.9)	0
BRIP1 + PALB2	0	0	0	1 (25.0)	0	1 (9.1)
CDK12 + CHEK1	0	0	1 (33.3)	0	1 (5.9)	0
CDK12 + PALB2	0	0	1 (33.3)	1 (25.0)	1 (5.9)	1 (9.1)
PALB2 + PPP2R2A	0	0	0	1 (25.0)	0	1 (9.1)

Only patients with ≥2 qualifying alterations are included. Rows are mutually exclusive.

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c) Interventions

Patients in the intervention group received 300 mg (given as two 150-mg tablets) of olaparib twice daily for a total dose of 600 mg daily.[1] Patients in the control group received investigator's choice of enzalutamide or abiraterone acetate with prednisone. Those treated with enzalutamide received 160 mg once daily while those treated with abiraterone acetate received a 1,000 mg dose once daily in combination with a 5 mg dose of prednisone given twice daily.[1] All patients received their assigned therapy until they had objective radiographic progression by BICR or until they were unable to tolerate their study treatment prior to the primary rPFS analysis.[1] However, after the primary rPFS analysis, all patients received their assigned therapy until they had objective radiographic progression by the study investigator as long as they did not meet any other discontinuation criteria.[1]

At the June 4, 2019 data cut-off, the median duration of therapy was 7.4 months (range: 0 to 22.7) in the olaparib group and 3.9 months (range: 0.6 to 19.5) in the control group.[1] [redacted].[3]

[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Patients were prohibited from receiving the following concomitant treatments:[1]

- Other anti-cancer therapy (i.e., chemotherapy, immunotherapy, hormonal therapy [except LHRH agonist/antagonist], biological therapy or other novel agent [i.e., corticosteroids] if given for anti-cancer indication)
- Live virus and live bacterial vaccines
- Strong or Moderate CYP3A inhibitors, strong or Moderate CYP3A inducers or P-gp inhibitors for those treated with olaparib
- Strong CYP2C8 inhibitors for those treated with enzalutamide

Treatment with olaparib could be interrupted or reduced due to any observed toxicities. Repeated dose interruptions were allowed for a maximum of four weeks; however, the study investigators were informed if the interruption lasted longer than this period. The dose of olaparib could be reduced to 250 mg twice daily and then to 200 mg twice daily. If the patient could no longer tolerate the reduced dose of 200 mg twice daily, then the study treatment was discontinued.

Treatment with enzalutamide could be interrupted due to a ≥ grade 3 toxicity or an intolerable side effect.[1] Treatment could be interrupted for one week or until symptoms improved to a ≤ grade 2 and then treatment could be resumed at the same or a reduced dose (120 mg or 80 mg).[1]

Treatment with abiraterone acetate could be reduced to 250 mg once daily for those with baseline moderate hepatic impairment (Child-Pugh Class B). Treatment was permanently discontinued for patients with baseline moderate hepatic impairment if ALT and/or AST > 5xULN or total bilirubin >3xULN.[1]

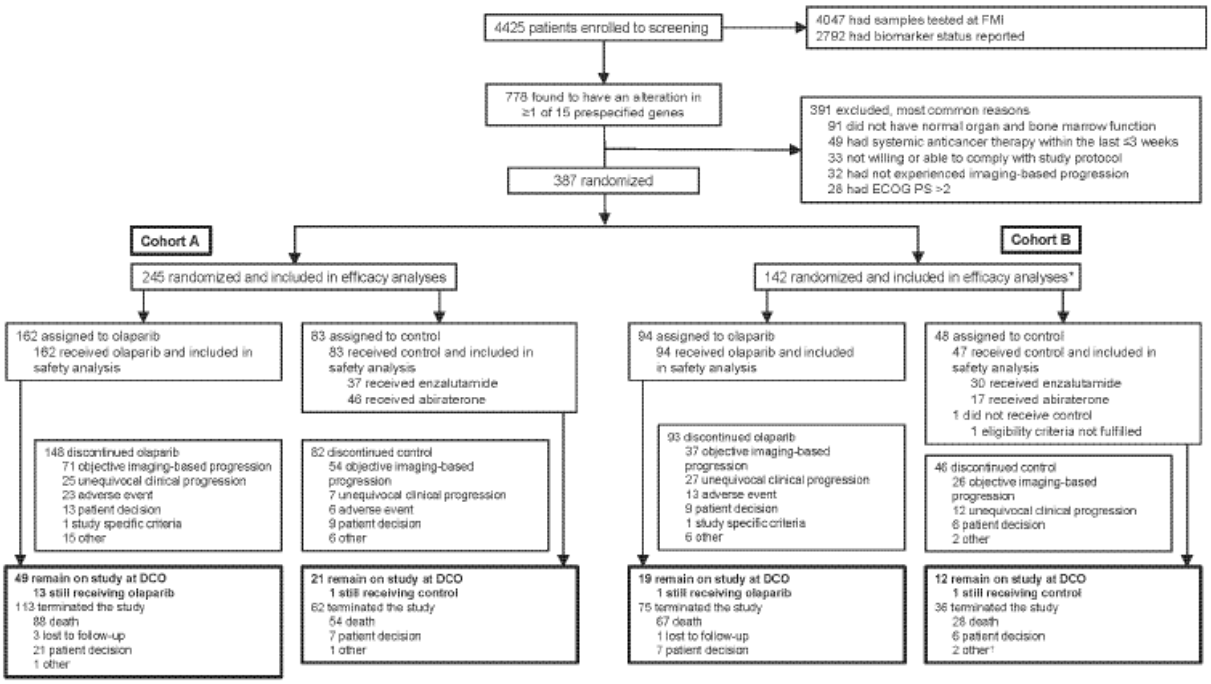
Patients who developed hepatotoxicity during treatment (i.e., ALT and/or AST > 5xULN or total bilirubin > 3xULN) had their dose of abiraterone acetate interrupted until these values return to the patient's baseline value or to AST and ALT ≤2.5xULN and total bilirubin ≤1.5xULN. Based on the investigator, treatment could be restarted at a reduced dose of 750 mg and then reduced to 500 mg. If hepatotoxicity recurs at the reduced dose of 500 mg once daily, then the study treatment should be discontinued.[1]

Patients were permanently discontinued from abiraterone acetate therapy if they had a concurrent elevation of ALT >3xULN and total bilirubin > 2xULN in the absence of biliary obstruction of other causes responsible for the concurrent elevation.[1]

d) Patient Disposition

The patient disposition for the PROfound trial is presented in Figure 3. A total of 4,425 patients were enrolled for screening and 4,047 patients had tumour tissue samples available for testing using the FoundationOne® CDx (F1CDx) device. Sixty-nine percent of these patients (N=2,792) were successfully genotyped and only 28% of these patients (N=778) had an alteration in one or more of the 15 prespecified genes. Fifty percent of the patients with one or more alterations in the 15 prespecified genes met the eligibility criteria and were randomized into the trial (N=387/778).[1]

Figure 3: Patient disposition for the PROfound Trial at the 20-March-2020 data-cut off



*Four patients were incorrectly assigned to Cohort B (one in the olaparib group had an alteration in *BRCA2*, one in the control group had alterations in *BRCA2* and *CDK12*, and two in the olaparib group had alterations in *ATM*); analyses were conducted as assigned. One patient randomized to the control arm in Cohort B did not receive treatment.
†Status was unknown for one patient.
DCO, data cutoff; ECOG PS, Eastern Cooperative Oncology Group performance status.

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Two hundred and forty-five patients were enrolled in Cohort A and 142 patients were enrolled in Cohort B. Among those in Cohort A, 162 patients were assigned to the olaparib treatment group and 83 were assigned to the control treatment (N =37 for enzalutamide and N =46 abiraterone). It was noted that four patients were incorrectly assigned to Cohort B; one in the olaparib group was a BRCA2 carrier, one in the control group was a carrier for BRCA2 and CDK12 and two in the olaparib group were ATM carriers.[4] In addition, one patient randomized to the control group in Cohort B did not receive their assigned treatment.

At the March 20, 2020 data cut-off, in Cohort A, 30.2% of patients in the olaparib group (N=49) remained on study and 13 of these patients were still receiving olaparib (N=13/49); while 70% of patients (N=113) terminated study treatment.[4] The most common reasons for termination were death (77.9%; N = 88) and patient decision (18.6%; N = 21). In the control group, 25.3% of patients in the olaparib group (N=21) remained on study and one of these patients were still receiving control (N= 1/21); while 74.7% of patients (N=62) terminated study treatment.[4] The most common reason for termination was death (87.1%; N=88).

Patients randomized to the control group in Cohort A and B were allowed to cross-over and receive olaparib after the primary analysis. At the June 4, 2019 data cut-off, 51/83 patients in Cohort A and 24/48 patients in Cohort B switched over to receive olaparib.[4] The Sponsor noted that three patients in the control group received olaparib at the time of the June 4, 2019 data cut-off without BICR confirmed progression (off-label commercial use) while all other patients had BICR confirmed progression prior to switching.[4]

After the June 4, 2019 data cut-off, patients were permitted to crossover and receive olaparib after investigator-assessed disease progression since rPFS by BICR was not collected beyond the primary analysis. At the March 20, 2020 cut-off, five additional patients in Cohort A (N=56/83) and six additional patients in Cohort B (N=30/48) crossed-over to receive olaparib.[4]

At the March 20, 2020 data cut off, the proportion of patients who received a subsequent anticancer therapy after discontinuation of the study drug was higher in the control group as compared to the olaparib group for both Cohorts A and A+B (Table 11).[4] In Cohort A, treatment with subsequent olaparib occurred in 2% of patients in the olaparib group and in 67% of those in the control group (Table 11).

Table 11: Subsequent anticancer therapies received by >2 patients in Cohorts A and in A+B who discontinued their assigned therapies at the March 20, 2020 data cut-off

Subsequent therapy, n (%)*	Cohort A		Overall Population	
	Olaparib (N=162)	Control (N=83)	Olaparib (N=256)	Control (N=131)
Any	79 (49)	64 (77)	129 (50)	96 (73)
Olaparib†	3 (2)	56 (67)	3 (1)	86 (66)
Docetaxel	26 (16)	11 (13)	46 (18)	17 (13)
Cabazitaxel	19 (12)	10 (12)	31 (12)	15 (11)
Enzalutamide	16 (10)	1 (1)	30 (12)	1 (1)
Carboplatin	12 (7)	1 (1)	20 (8)	3 (2)
Abiraterone acetate	12 (7)	2 (2)	19 (7)	2 (2)
Lutetium (Lu-177)	6 (4)	0	10 (4)	0
Etoposide	3 (2)	0	4 (2)	0
Paclitaxel	3 (2)	0	3 (1)	0
Radium (Ra-223) dichloride	3 (2)	1 (1)	4 (2)	1 (1)
Cisplatin	2 (1)	0	4 (2)	0
Pembrolizumab	2 (1)	0	5 (2)	0

*Patients with any subsequent anticancer therapy, irrespective of line. Patients could have received more than one anticancer therapy.
†Patients who crossed over upon disease progression with control therapy received olaparib monotherapy as a first subsequent therapy per protocol.

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No major protocol deviations were reported at the June 4, 2019 data cut-off.[17] In Cohort A, 4.9% of patients in the olaparib group had an important protocol deviation as compared to 6.0% in the control group.[17] In Cohort A+B, 7.8% of patients in the olaparib group had an important protocol deviation as compared to 7.6% in the control group.[17]

e) Limitations/Sources of Bias

The randomization method used in PROfound was adequate, and a stratified randomization procedure was used based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results. The efficacy analysis was conducted according to the ITT principal. However, there are a number of limitations and potential sources of bias, which include:

- The PROfound trial used an open-label study design. This study design has the potential to bias outcomes in favour of the treatment group, including: rPFS, PROs and safety. However, bias was minimized because the primary analyses of efficacy endpoints were based on radiographic progression assessments by BICR. For patient reported outcomes and safety, the investigators, patients, and sponsor were not blinded, which may have biased results in favour of olaparib. However, the CGP felt that there were no unexpected adverse events in the trial.
- All patients randomized to the control group were permitted to crossover and receive olaparib once they had objective radiological progression confirmed by a BICR or by the investigator after the date of the primary analysis. At the June 4, 2019 data cut-off, 51/83 (61%) patients in Cohort A and 24/48 (50%) patients in Cohort B switched over to receive olaparib.[4] Patient crossover could confound the results of the final OS and PFS2 analyses as well as the safety outcomes in favour of olaparib. However, RPSFT models were conducted for OS to try and reduce the potentially confounding effects of patient crossover and the results were similar to the unadjusted results.
- The control group may not be the most relevant comparator in Canadian clinical practice because patients were rechallenged with enzalutamide or abiraterone. The comparator in the trial was investigator's choice of NHA (i.e., enzalutamide or abiraterone). Sequencing of alternate NHAs upon progression (i.e., first line enzalutamide followed by second line abiraterone or vice versa) is rarely done in Canadian clinical practice and not funded in most provinces. However, the CGP felt that the PROfound trial results are generalizable to the Canadian clinical practice setting as it has been suggested that NHAs have similar efficacy compared to docetaxel in the post-NHA setting.[5] Furthermore, due to the COVID pandemic funding restrictions may be loosened in some places and Canadian clinicians may be encouraged to alternate NHAs upon progression to avoid having patients come to the hospital and avoid toxicity from taxane chemotherapy.
- [redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* The results of the subgroup analyses stratified by genotype carrier status suggested that olaparib had a protective effect for BRCA1 and/or BRCA2 carriers for rPFS and OS. However, subgroup analyses for BRCA1 carriers alone did not show a significant difference on efficacy outcomes but this may be due to small sample sizes. There were no treatment differences observed for ATM carriers on rPFS and OS. Firm conclusions cannot be made on the basis the subgroup analyses because the trial was neither designed nor powered to reliably analyze the results in these subgroup analyses.
- There was an imbalance in baseline characteristics across the two treatment groups. For instance, there was an imbalance in the patients with visceral metastases (28% in olaparib and 39% in control), median baseline PSA concentration (62.2 [IQR: 21.9–280.4] in olaparib and 112.9 [IQR: 34.3–317.1]) and patients with an ATM alteration (37% in olaparib and 29% in control).[1] In a Checkpoint Response, upon request, the sponsor provided sensitivity analyses for rPFS by BICR to assess the impact of the baseline imbalances for the aforementioned variables. The adjusted rPFS were consistent with the primary results.[4]
- Only the results for rPFS as assessed by BICR in Cohort A+B were included in the testing hierarchy, and thus, results from Cohort A+B should be interpreted with caution.
- Patient-reported and HRQoL outcomes were exploratory endpoints in the PROfound trial and were not included in the statistical hierarchy or adjusted for multiplicity. Furthermore, selection bias over time should be considered when interpreting results of the HRQoL assessment, as the long-term responders tend to be the healthier patients. In addition, there was a high degree of noncompliance for the HRQoL assessments, where only 68% of patients completed the questionnaire.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Two data cut-offs were used for this analysis. The first data cut off was on June 4, 2019, which represents the date of the primary analysis and a median follow-up of 12.57 months (range: 1.87 to 23.89) in the olaparib group and 13.19 months (range: 0.95 to 23.23) in the control group for Cohort A.[1] The second was on March 20, 2020, which represents the date of the final analysis and a median follow-up of 21.91 months (range: 1.87 to 33.41) in the olaparib group and 21.04 months (range: 0.95 to 32.76) in the control group for Cohort A.[4] For the purpose of this review, only the results of Cohort A and Cohort A+B will be presented. Data from Cohort B will not be presented because it is beyond the scope of the review since it does not include BRCA1, BRCA2 or ATM carriers.

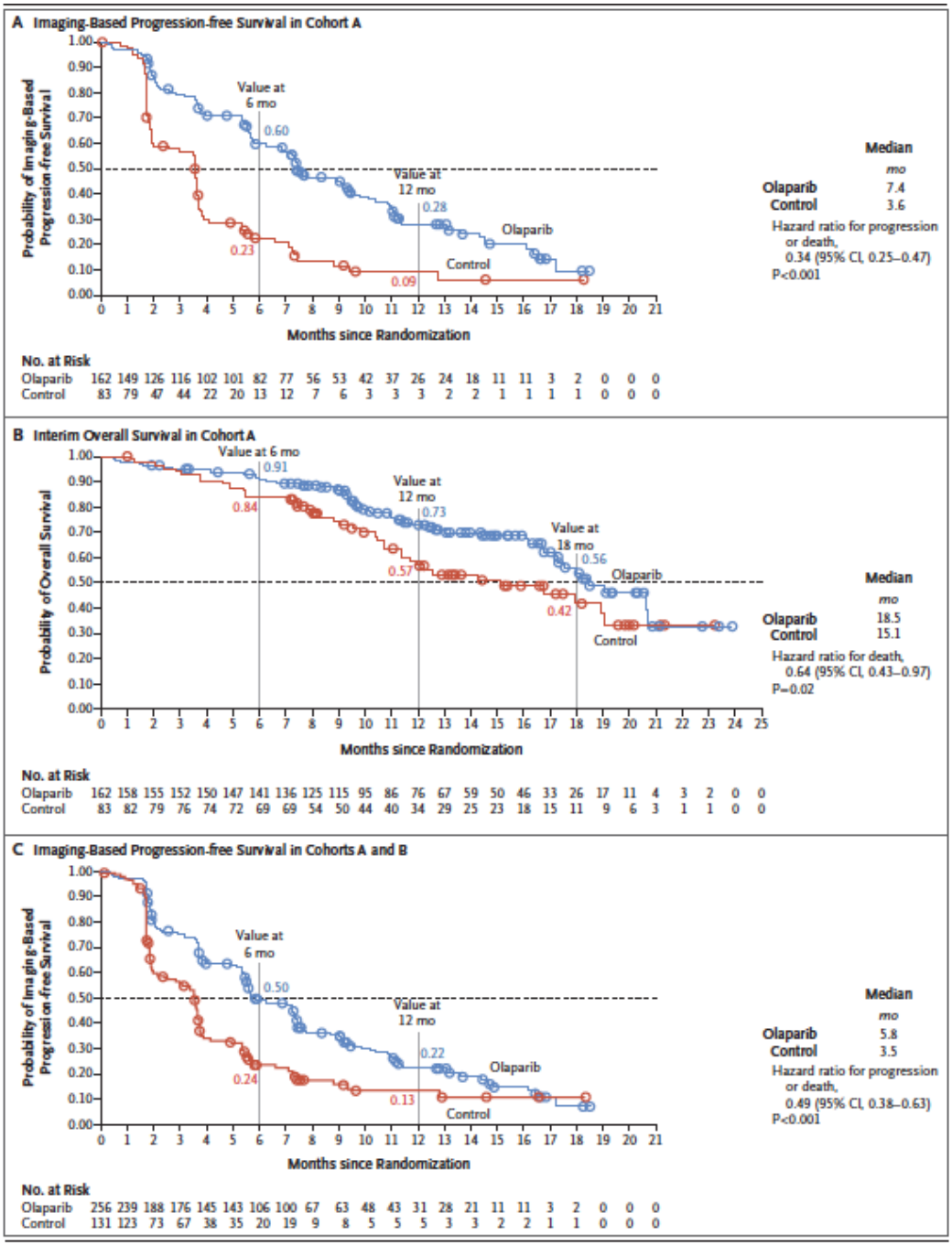
Efficacy Outcomes

Radiographic Progression Free Survival:

Cohort A

Radiographic progression free survival by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria in Cohort A was the primary outcome of the trial. The primary analysis for rPFS occurred on June 4, 2019. At the data cut off, in the olaparib group, 65.4% (N=106) had progressed or died as compared to 81.9% (N=68) of patients in the control group.[6] The Kaplan-Meier curves for rPFS are presented in Figure 4. The median rPFS as assessed by BICR in the olaparib group was 7.39 months (95% CI: 6.24 to 9.33) and it was 3.55 months (95% CI: 1.91 to 3.71) in the control group.[6] de Bono et al. (2020) reported that treatment with olaparib was associated with statistically significant prolonged rPFS as assessed by BICR as compared to control (HR: 0.34, 95% CI: 0.25 to 0.47; p<0.001).[1] A prespecified sensitivity analysis of rPFS as assessed by the investigator showed similar results (HR: 0.24, 95% CI: 0.17 to 0.34; p<0.0001).[1] In the olaparib group, 3.7% of patients were censored for death (N=6) and 0.6% were censored for progression while 2.4% of patients in the control group were censored for death (N=2).[17]

Figure 4 Kaplan–Meier survival curves of rPFS as assessed by BICR for Cohort A (graph A) and Cohort A+B (graph C) and OS (graph B) at the June 4, 2019 data cut-off



Source: N Engl J Med, de Bono et al., 382 :2091-2102. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Cohort A+B

rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria in Cohort A+B was a key secondary outcome in the trial with formal statistical testing since the results for ORR in Cohort A were statistically significant between study groups. [redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* The Kaplan-Meier curves for rPFS are presented in Figure 4. The median rPFS as assessed by BICR in the olaparib group was [redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* Because the results for confirmed ORR were statistically significant between study groups, formal statistical testing for rPFS in Cohort A+B was continued and p-values are considered inferential. de Bono et al. (2020) reported that treatment with olaparib was associated with statistically significant prolonged rPFS as assessed by BICR as compared to control (HR: 0.49, 95% CI: 0.38 to 0.63; p<0.001).[1] A prespecified sensitivity analysis of rPFS as assessed by the investigator showed similar results (HR: 0.36, 95% CI: 0.27 to 0.47).[1]

Subgroup Analysis

The pre-specified exploratory subgroup analyses for rPFS as assessed by BICR using non-stratified Cox HRs with corresponding 95% CI are presented in Figure 5 (A: Cohort A; B: Cohort A+B).[1] Olaparib appeared to be associated with a protective effect against the risk of rPFS as assessed by BICR as compared to control for most of the subgroup categories.[1] However, these results should be interpreted with caution because they are considered exploratory and not adjusted for multiplicity.

Figure 5: Subgroup analysis of rPFS as assessed by BICR for all patients in Cohorts A (A) and A+B (B) at the June 4, 2019 data cut-off

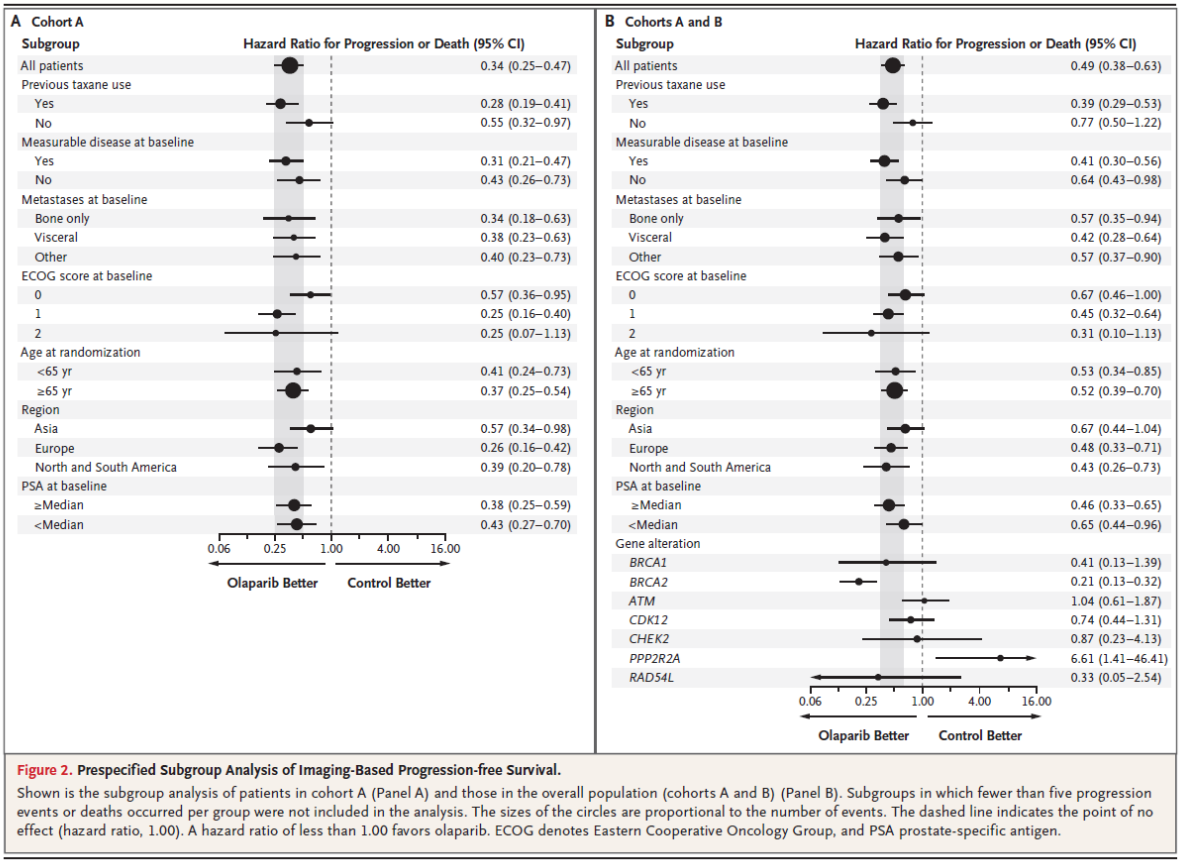


Figure 2. Prespecified Subgroup Analysis of Imaging-Based Progression-free Survival.

Shown is the subgroup analysis of patients in cohort A (Panel A) and those in the overall population (cohorts A and B) (Panel B). Subgroups in which fewer than five progression events or deaths occurred per group were not included in the analysis. The sizes of the circles are proportional to the number of events. The dashed line indicates the point of no effect (hazard ratio, 1.00). A hazard ratio of less than 1.00 favors olaparib. ECOG denotes Eastern Cooperative Oncology Group, and PSA prostate-specific antigen.

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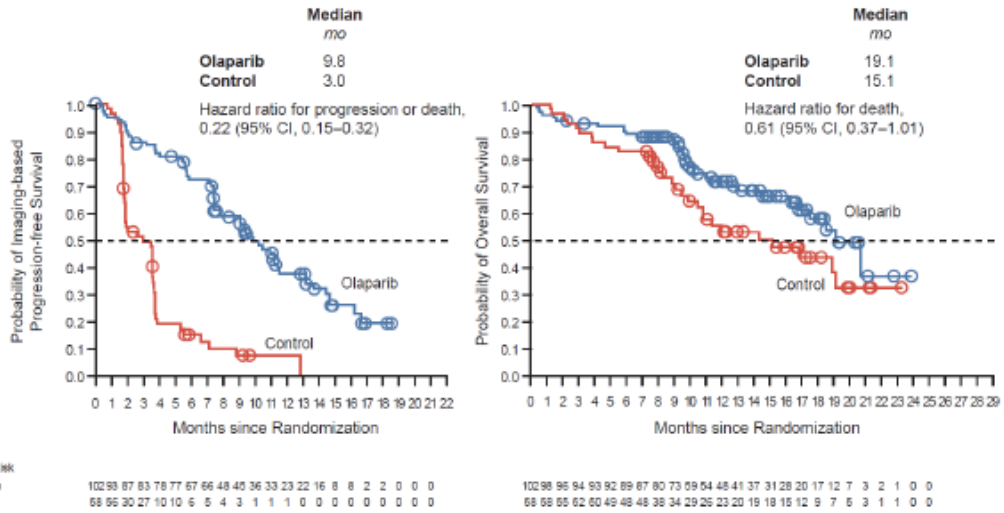
Genotype subgroup analysis in Cohort A+B

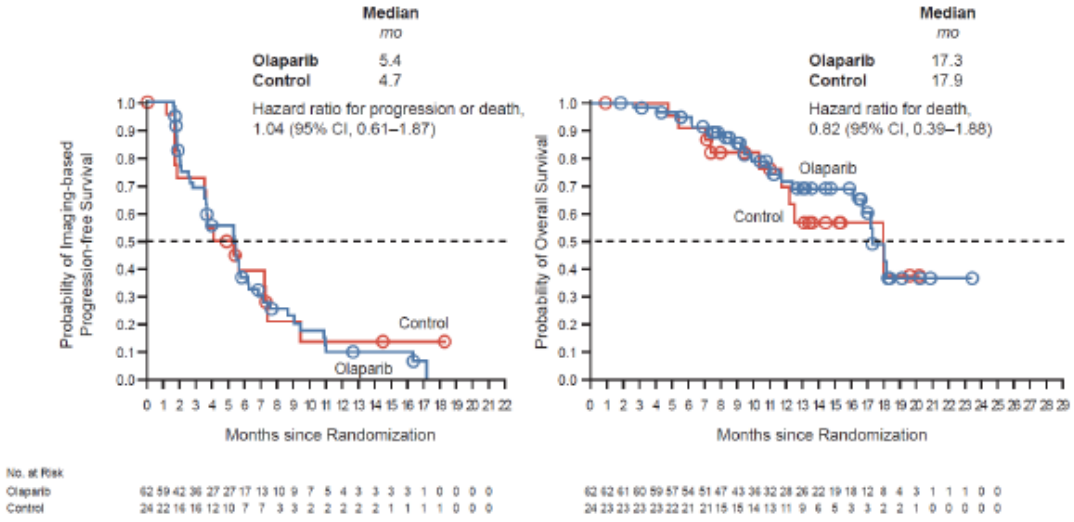
The effect of olaparib relative to the control group on rPFS as assessed by BIRC was stratified by genotype carrier status in Cohort A+B (Figure 6).[1] For BRCA1 and/or BRCA2 carriers, the HR favoured olaparib compared to the control for rPFS as assessed by BICR (HR: 0.22, 95% CI: 0.15 to 0.32) while there was no treatment difference on rPFS as assessed by BICR for *ATM* carriers.[1] However, these results should be interpreted with caution because they are considered exploratory and not adjusted for multiplicity.

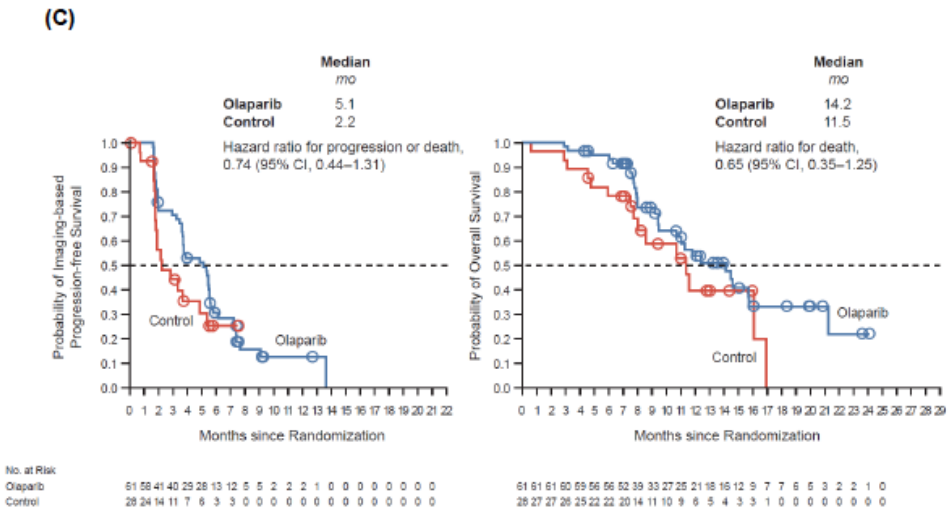
Figure 6: Subgroup analysis of rPFS as assessed by BICR and OS for all patients in Cohort A+B at the June 4, 2019 data cut-off with an alteration in (A) BRCA1 and/or BRCA2, (B) ATM genotype or (C) CDK12

(A) *BRCA1* and/or *BRCA2*



(B)





*Includes patients with an alteration in a single gene

CI, confidence interval; mo, months

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Objective Response Rate

Cohort A

Objective response rate by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria in Cohort A was a key secondary outcome in the trial with formal statistical testing since the results for rPFS in Cohort A were statistically significant between study groups. Eighty-four patients in the olaparib group and 43 in the control group were used in the analysis. At the June 4, 2019 data cut-off, 33% of patients in the olaparib group had confirmed ORR as compared to 2% in the control group.[1] The OR for ORR was 20.86 (95% CI: 4.18 to 379.18; p<0.001).[1]

Cohort A+B

Objective response rate by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria was a secondary outcome for Cohort A+B and 138 patients in the olaparib group and 67 in the control group were used in the analysis. At the June 4, 2019 data cut-off, 22% of patients in the olaparib group had confirmed ORR as compared to 4% in the control group.[1] The OR for ORR was 5.93 (95% CI: 2.01 to 25.40).[1]

Time to Pain Progression

Cohort A

Time to pain progression in Cohort A was a key secondary outcome in the trial with formal statistical testing since the results for rPFS in Cohort A+B were statistically significant between study groups. At the June 4, 2019 data cut off, 13% of patients in olaparib group (N=21) had pain progression as compared to 16.9% (N=14) of patients in the control group.[6] The Kaplan-Meier curves for time to pain progression are presented in Figure 7. The median time to pain progression in the olaparib group was not reached (NR) while it was 9.92 months in the control group.[6] de Bono et al. (2020) reported that treatment with olaparib was associated with statistically significant prolonged time to pain progression as compared to control (HR: 0.44, 95% CI: 0.22 to 0.91; p=0.02).[1] A sensitivity analysis was performed to evaluate the effect of the competing risk on death. The median time to pain progression was 17.2 months in the olaparib group and 5.5 months in the control group and similar results were observed for the sensitivity analysis (HR: 0.501, 95% CI: 0.303 to 0.849).[1]

Figure 7 Kaplan–Meier survival curves of time to pain progression for Cohort A and Cohort A+B at the 04-June-2020 data cut-off

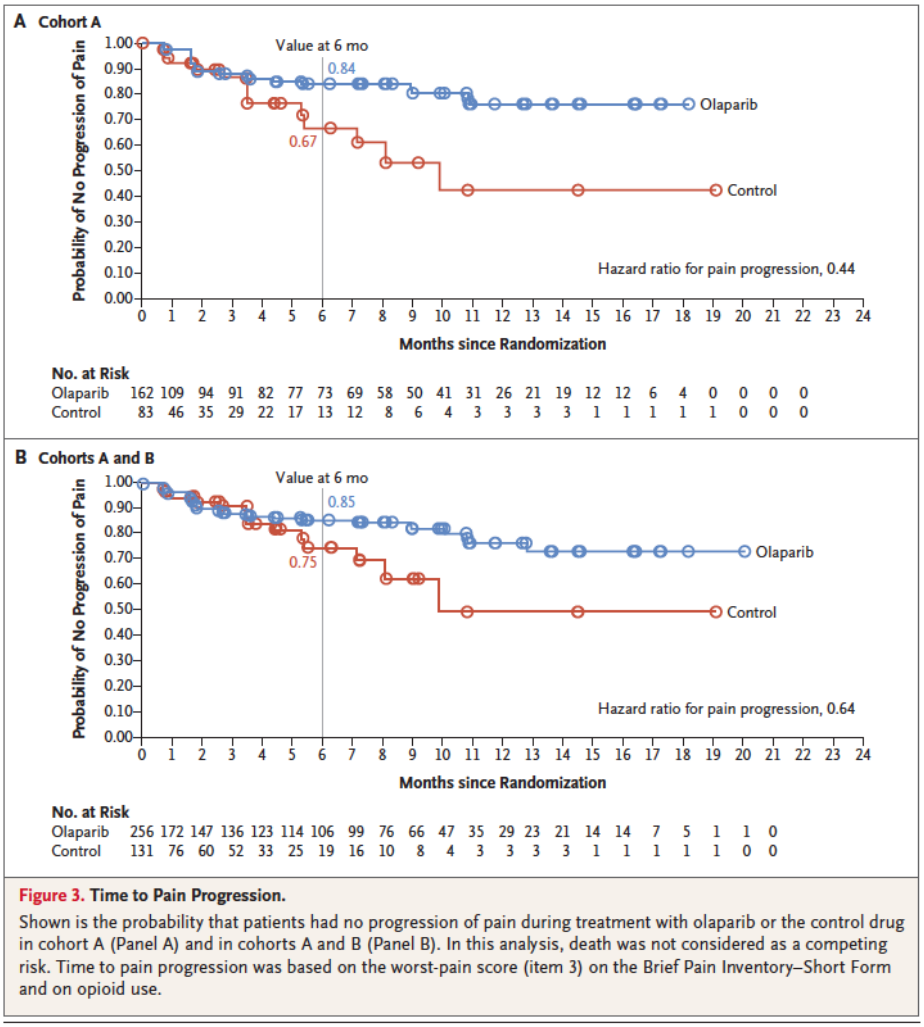

Figure 3. Time to Pain Progression.
Shown is the probability that patients had no progression of pain during treatment with olaparib or the control drug in cohort A (Panel A) and in cohorts A and B (Panel B). In this analysis, death was not considered as a competing risk. Time to pain progression was based on the worst-pain score (item 3) on the Brief Pain Inventory–Short Form and on opioid use.

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Cohort A+B

Time to Pain Progression in Cohort A+B was a secondary outcome. At the June 4, 2019 data cut off, 12.5% of patients in olaparib group (N=32) had pain progression as compared to 12.2% (N=16) of patients in the control group.[4] The Kaplan-Meier curves for time to pain progression are presented in Figure 7. [redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

de Bono et al. (2020) reported that there was no treatment difference between the two groups (HR: 0.64, 95% CI: 0.35 to 1.21; P=0.149).[1] A sensitivity analysis was performed to evaluate the effect of the competing risk on death. The median time to pain

progression was 11.9 months in the olaparib group and 6.9 months in the control group.[1] de Bono et al. (2020) reported a statistically significant result for the sensitivity analysis (HR: 0.596, 95% CI: 0.395 to 0.917).[1]

Overall Survival

Cohort A

Overall survival in Cohort A was a key secondary outcome with formal statistical testing since the results for time to pain progression in Cohort A were statistically significant between study groups. [redacted].[3] [redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Treatment with olaparib was associated with prolonged survival time as compared to control (HR: 0.62, 95% CI: 0.41 to 0.95; P=0.02).[1]

At the final analysis (March 20, 2020), 67% of patients in the control group of Cohort A had crossed-over and received olaparib (N=56).[2] In the olaparib group, 56.2% of patients (N=91) had died as compared to 68.7% (N=57) of patients in the control group.[2] The Kaplan-Meier curves are presented in Figure 8. The median OS was 19.1 months (95% CI: 17.4 to 23.4) in the olaparib group and 14.7 months (95% CI: 11.9 to 18.8) months in the control group.[2] Treatment with olaparib was associated with statistically significant prolonged survival time as compared to control (HR: 0.69, 95% CI: 0.50 to 0.97; P=0.02).[2] Although these results may be confounded due to patient cross-over, the prespecified sensitivity analysis adjusting for patient cross-over showed a similar treatment effect (HR: 0.42, 95% CI: 0.19 to 0.91) (Figure 8).[2]

Figure 8: Kaplan-Meier survival curves of OS and corresponding crossover-adjusted sensitivity analysis for Cohort A at the 20-March-2020 data cut-off

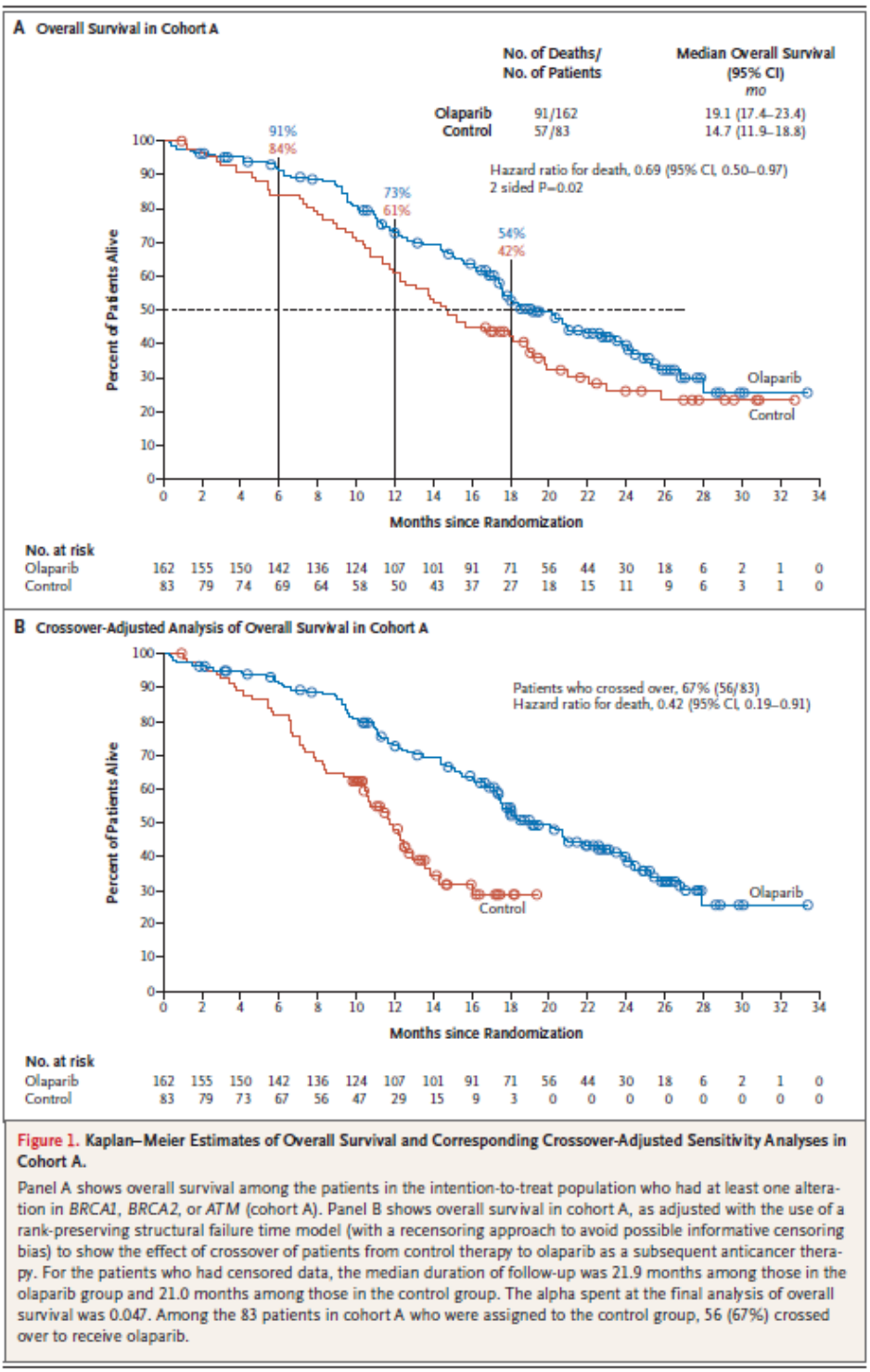

Figure 1. Kaplan–Meier Estimates of Overall Survival and Corresponding Crossover-Adjusted Sensitivity Analyses in Cohort A.

Panel A shows overall survival among the patients in the intention-to-treat population who had at least one alteration in *BRCA1*, *BRCA2*, or *ATM* (cohort A). Panel B shows overall survival in cohort A, as adjusted with the use of a rank-preserving structural failure time model (with a recensoring approach to avoid possible informative censoring bias) to show the effect of crossover of patients from control therapy to olaparib as a subsequent anticancer therapy. For the patients who had censored data, the median duration of follow-up was 21.9 months among those in the olaparib group and 21.0 months among those in the control group. The alpha spent at the final analysis of overall survival was 0.047. Among the 83 patients in cohort A who were assigned to the control group, 56 (67%) crossed over to receive olaparib.

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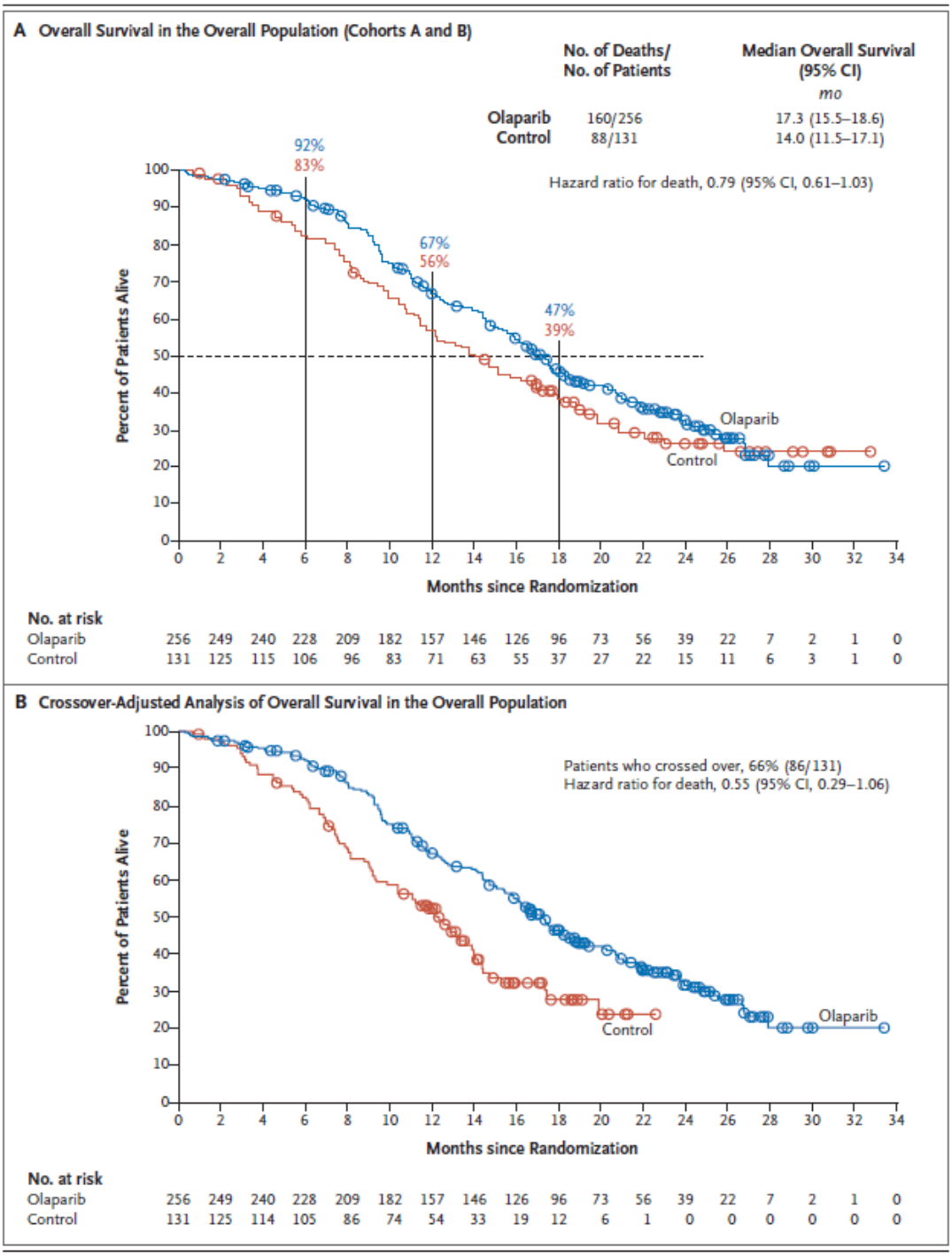
Cohort A+B

Overall Survival in Cohort A+B was a secondary outcome. [redacted][3] [redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* For the interim OS analysis, treatment with olaparib was associated with prolonged survival time as compared to control (HR: 0.67, 95% CI: 0.49 to 0.93).[1]

At the final analysis, 66% of patients in the control group had crossed over and received olaparib (N=86).[2] In the olaparib group, 62.3% of patients in olaparib group (N=160) had died as compared to 67.2% (N=88) of patients in the control group.[2] The median OS was 17.3 months (95% CI: 15.5 to 18.6) in the olaparib group and 14.0 months (95% CI: 11.5 to 17.1) months in the control group.[2] There was no treatment difference between olaparib and the control group on OS (HR: 0.79, 95% CI: 0.61 to 1.03) (Figure 9).[2] Similar results were observed for the crossover adjusted analysis (Figure 9).[2]

Figure 9: Kaplan–Meier survival curves of OS for Cohort A+B at the March 20, 2020 data cut-off



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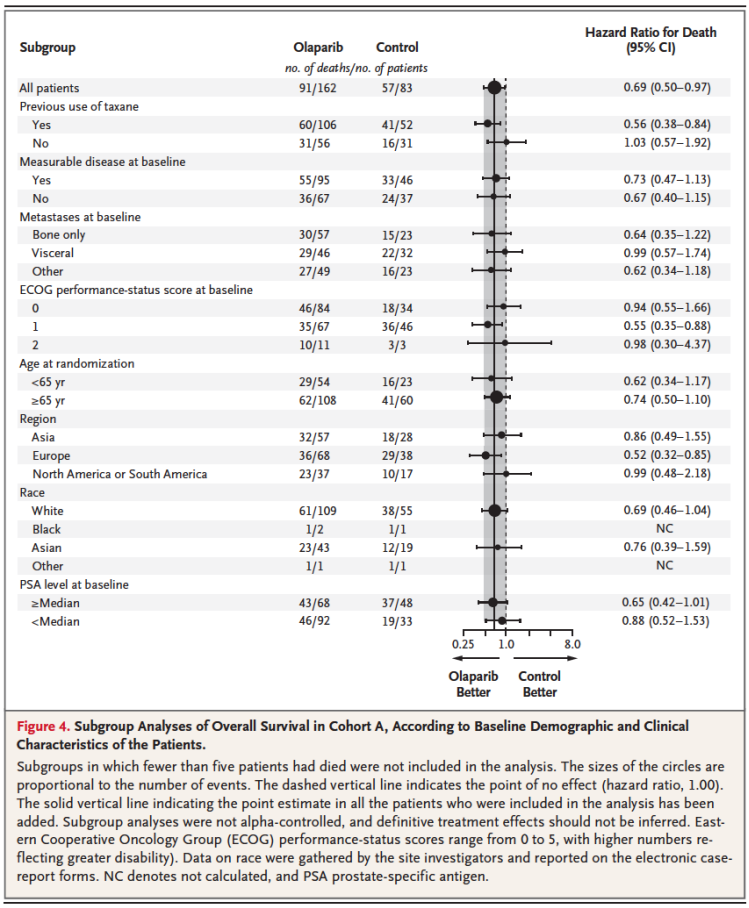
Subgroup Analysis

The pre-specified exploratory subgroup analyses for OS in Cohort A are presented in Figure 10.[2] The treatment effect of olaparib versus control on OS was not consistent across all subgroups. However, these results should be interpreted with caution because they are considered exploratory and they were not adjusted for multiplicity or patient cross-over.

Figure 10: Subgroup analysis of OS for Cohorts A at the March 20, 2020 data cut-off



Subgroup	Olaparib	Control	Hazard Ratio for Death (95% CI)
	no. of deaths/no. of patients		
All patients	91/162	57/83	0.69 (0.50–0.97)
Previous use of taxane			
Yes	60/106	41/52	0.56 (0.38–0.84)
No	31/56	16/31	1.03 (0.57–1.92)
Measurable disease at baseline			
Yes	55/95	33/46	0.73 (0.47–1.13)
No	36/67	24/37	0.67 (0.40–1.15)
Metastases at baseline			
Bone only	30/57	15/23	0.64 (0.35–1.22)
Visceral	29/46	22/32	0.99 (0.57–1.74)
Other	27/49	16/23	0.62 (0.34–1.18)
ECOG performance-status score at baseline			
0	46/84	18/34	0.94 (0.55–1.66)
1	35/67	36/46	0.55 (0.35–0.88)
2	10/11	3/3	0.98 (0.30–4.37)
Age at randomization			
<65 yr	29/54	16/23	0.62 (0.34–1.17)
≥65 yr	62/108	41/60	0.74 (0.50–1.10)
Region			
Asia	32/57	18/28	0.86 (0.49–1.55)
Europe	36/68	29/38	0.52 (0.32–0.85)
North America or South America	23/37	10/17	0.99 (0.48–2.18)
Race			
White	61/109	38/55	0.69 (0.46–1.04)
Black	1/2	1/1	NC
Asian	23/43	12/19	0.76 (0.39–1.59)
Other	1/1	1/1	NC
PSA level at baseline			
≥Median	43/68	37/48	0.65 (0.42–1.01)
<Median	46/92	19/33	0.88 (0.52–1.53)

Figure 4. Subgroup Analyses of Overall Survival in Cohort A, According to Baseline Demographic and Clinical Characteristics of the Patients.

Subgroups in which fewer than five patients had died were not included in the analysis. The sizes of the circles are proportional to the number of events. The dashed vertical line indicates the point of no effect (hazard ratio, 1.00). The solid vertical line indicating the point estimate in all the patients who were included in the analysis has been added. Subgroup analyses were not alpha-controlled, and definitive treatment effects should not be inferred. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers reflecting greater disability). Data on race were gathered by the site investigators and reported on the electronic case-report forms. NC denotes not calculated, and PSA prostate-specific antigen.

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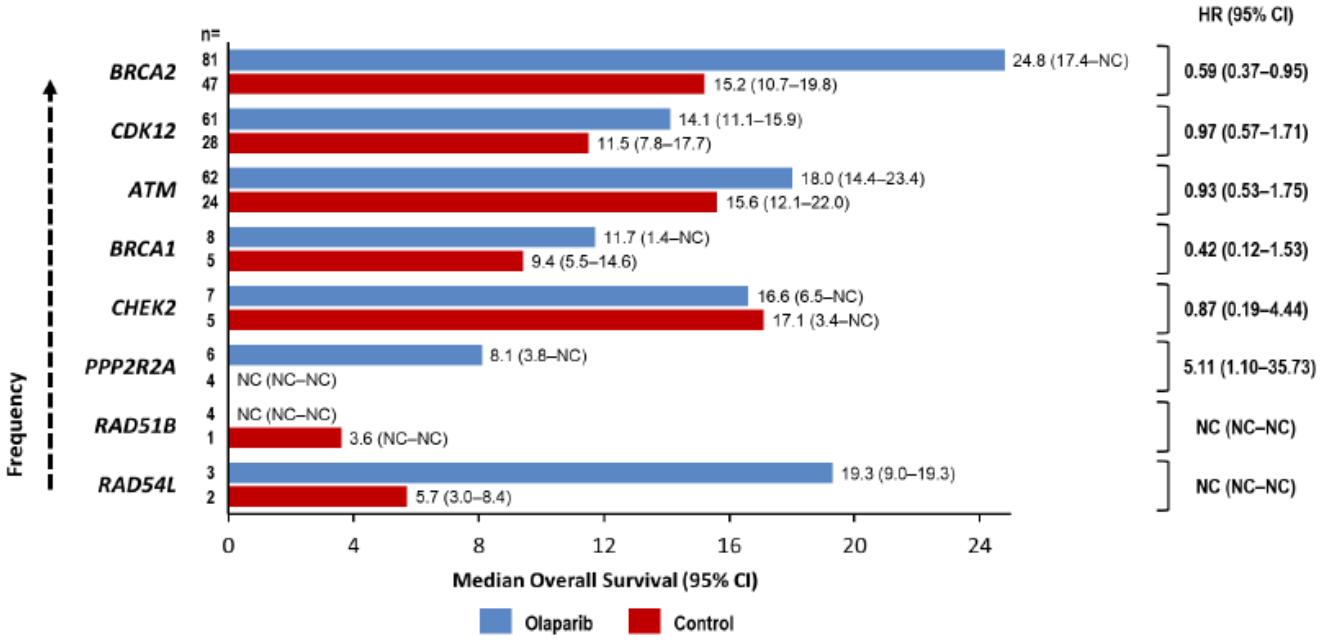
Genotype subgroup analysis

Hussain et al. (2020) also performed subgroup analyses of OS stratifying by genotype carrier status in Cohort A+B.[2] At the March 20, 2020 data cut-off, 52% of BRCA1 and/or BRCA2 carriers treated with olaparib (N=53/102) had died as compared to 71% of those treated with control (N=41/58).[17] The median OS was 20.1 months (95% CI: 17.4 to 26.8) in the olaparib group and 14.4 months (95% CI: 10.7 to 18.9) months in the control group.[17] Results suggested that treatment with olaparib resulted in prolonged survival time as compared to the control group among BRCA1 and/or BRCA2 carriers (HR: 0.63, 95% CI: 0.42 to 0.95).[17] Similar estimates were observed for those who were single BRCA2 carriers, but the association was attenuated among single BRCA1 carriers (Figure

11).[2] In addition, there was no treatment difference between olaparib and the control group on OS for ATM carriers (Figure 11). However, these results should be interpreted with caution due to small sample sizes and no adjustment for multiplicity or patient cross-over.

Figure 11: Gene-by-gene analysis of OS in patients in Cohort A+B with alterations in a single HRR gene at the March 20, 2020 data cut-off. Data at the end of each bar are median OS in months (95% CI)



Note that for secondary and exploratory outcomes, which were not alpha controlled, definitive treatment effects may not be inferred.
CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NC, not calculable; n, number of patients

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Time to opiate use for cancer-related pain

Cohort A

Time to opiate use for cancer-related pain in Cohort A was a key secondary outcome. At the June 4, 2019 data cut off, 37.2% of patients in olaparib group (N=42) used an opiate as compared to 50.0% (N=29) of patients in the control group.[6] The median time to opiate use was 17.97 months (95% CI: 12.68 to NR) in the olaparib group and 7.52 months (95% CI: 3.22 to NR) in the control group.[4] Treatment with olaparib was associated with a prolonged time to opiate use as compared to control (HR: 0.61, 95% CI: 0.38 to 0.99).[6]

Cohort A+B

Time to opiate use for cancer-related pain in Cohort A+B was a secondary outcome. At the June 4, 2019 data cut off, 37.1% of patients in olaparib group (N=65) used an opiate as compared to 47.8% (N=44) of patients in the control group.[4] The median time to opiate use was 17.97 months (95% CI: 11.56 to NR) in the olaparib group and 9.00 months (95% CI: 5.36 to NR) in the control

group.[4] Treatment with olaparib was associated with a prolonged time to opiate use as compared to control (HR: 0.67, 95% CI: 0.46 to 0.99).[4]

Time to SSRE

Cohort A

At the 4-June-2019 data cut off, [redacted].[6] [redacted].[3] [redacted].[6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Cohort A+B

At the 4-June-2019 data cut off, [redacted].[4] [redacted].[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Prostate-specific antigen response

Cohort A

One hundred and fifty-three patients in the olaparib group and 77 patients in the control group were included in the analysis at the June 4, 2019 data cut-off.[1] Forty-three percent of patients in the olaparib group had a PSA response (N=66) as compared to 8% in the control group (N=6).[1]

Cohort A+B

Two hundred and forty-three patients in the olaparib group and 123 patients in the control group were included in the analysis at the June 4, 2019 data cut-off.[1] Thirty percent of patients in the olaparib group had a PSA response (N=73) as compared to 10% in the control group (N=12).[1]

CTC conversion rate

Cohort A

Ninety-seven patients in the olaparib group and 44 patients in the control group were included in the analysis at the June 4, 2019 data cut-off.[1] Thirty percent of patients in the olaparib group had clearance of circulating tumor cells (N=29) as compared to 11% in the control group (N=5).[1]

Cohort A+B

One hundred and fifty-three patients in the olaparib group and 68 patients in the control group were included in the analysis at the June 4, 2019 data cut-off.[1] Twenty-seven percent of patients in the olaparib group had clearance of circulating tumor cells (N=41) as compared to 10% in the control group (N=7).[1]

Time to second progression by investigator assessment of radiological or clinical progression or death

Cohort A

At the March 20, 2020 data cut off, 47.3% of patients in olaparib group (N = 77) progressed or died as compared to 56.5% (N=47) of patients in the control group.[2] The median time to PFS2 in the olaparib group was 15.5 months (95% CI: 14.4 to 18.0) and it was 10.6 months (95% CI: 9.1 to 14.0) in the control group.[2] Hussain et al. (2020) reported that treatment with olaparib was associated with a prolonged PFS2 as compared to control (HR: 0.64, 95% CI: 0.45 to 0.93).[2] These results should be interpreted with caution because they were not adjusted for multiplicity.

Cohort A+B

At the March 20, 2020 data cut off, 54.3% of patients in olaparib group (N=51) progressed or died as compared to 66.7% (N=32) of patients in the control group.[2] The median time to PFS2 in the olaparib group was 9.9 months (95% CI: 8.0 to 11.6) and it was 7.9 months (95% CI: 6.0 to 9.7) in the control group.[2] Hussain et al. (2020) reported that there was treatment difference between olaparib and the control group (HR: 0.77, 95% CI: 0.50 to 1.21).[2]

Quality of Life

FACT-P

The baseline patient compliance rates for the FACT-P in Cohort A+B were 72% for patients receiving olaparib and 71% for patients receiving control while the overall rate was 64% for those who received olaparib (N=256) and 57% for those who received control (N=131).[7] In Cohort A, the baseline patient adherence rates for the FACT-P were 68% for patients receiving olaparib and 70% for patients receiving control while it was 60% for those who received olaparib (N=162) and 53% for those who received control (N=83).[55]

At baseline, the mean (standard deviation) FACT-P total scores were similar between the olaparib and the control group in Cohort A and Cohort A+B (Table 12). Results for the FACT-P from baseline to week 32 for Cohort A and Cohort A+B are shown in Figure 12.[7] Olaparib was associated with a better HRQoL over time as compared to the control group for Cohort A and Cohort A+B.

Table 12: Mean baseline scores for the FACT-P score in Cohort A and Cohort A+B

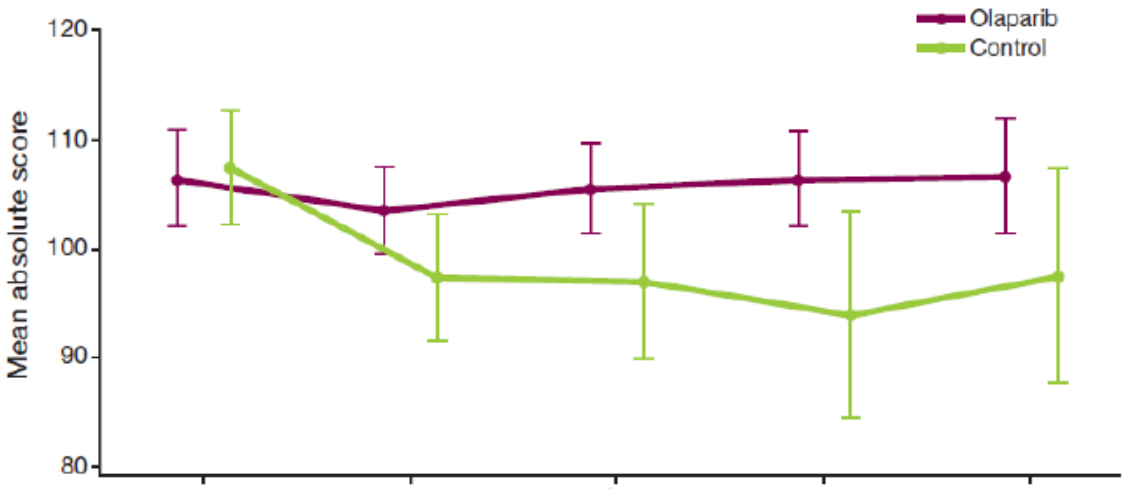
	Overall population		Cohort A	
	Olaparib (N=185)	Control (N=93)	Olaparib (N=110)	Control (N=58)
FACT-P total score (SD)	106.80 (22.35)	107.98 (19.75)	106.37 (23.12)	107.43 (19.63)
TOI (SD)	69.94 (16.72)	70.13 (16.15)	69.65 (17.18)	69.00 (16.23)
FWB (SD)	17.14 (5.88)	17.22 (5.93)	16.95 (6.37)	17.05 (6.01)
PWB (SD)	21.85 (5.29)	21.58 (5.27)	22.04 (5.16)	21.12 (5.59)
PCS (SD)	30.94 (7.79)	31.33 (6.56)	30.65 (7.96)	30.83 (6.48)
FAPSI-6 (SD)	16.21 (5.08)	16.32 (4.49)	16.09 (5.27)	15.64 (4.46)

N = patients with an evaluable assessment at baseline. FAPSI-6, FACT Advanced Prostate Symptom Index 6; FWB, functional wellbeing; PCS, prostate cancer subscale; PWB, physical wellbeing; SD, standard deviation; TOI, Trial Outcome Index.

Source: Thiery-Vuillemin et al. poster, ACSO Annual meeting May 2020[55]

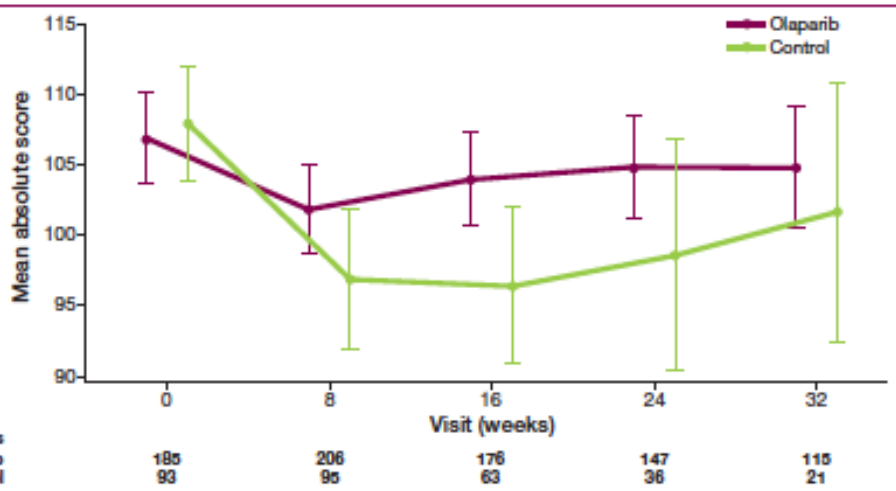
Figure 12: Mean FACT-P total score and 95% CIs over time in Cohort A (A) and Cohort A+B (B) from baseline to week 32

(A)



No. of patients					
Olaparib	110	126	119	100	78
Control	58	62	39	22	15

(B)



No. of patients					
Olaparib	185	206	176	147	115
Control	93	95	63	36	21

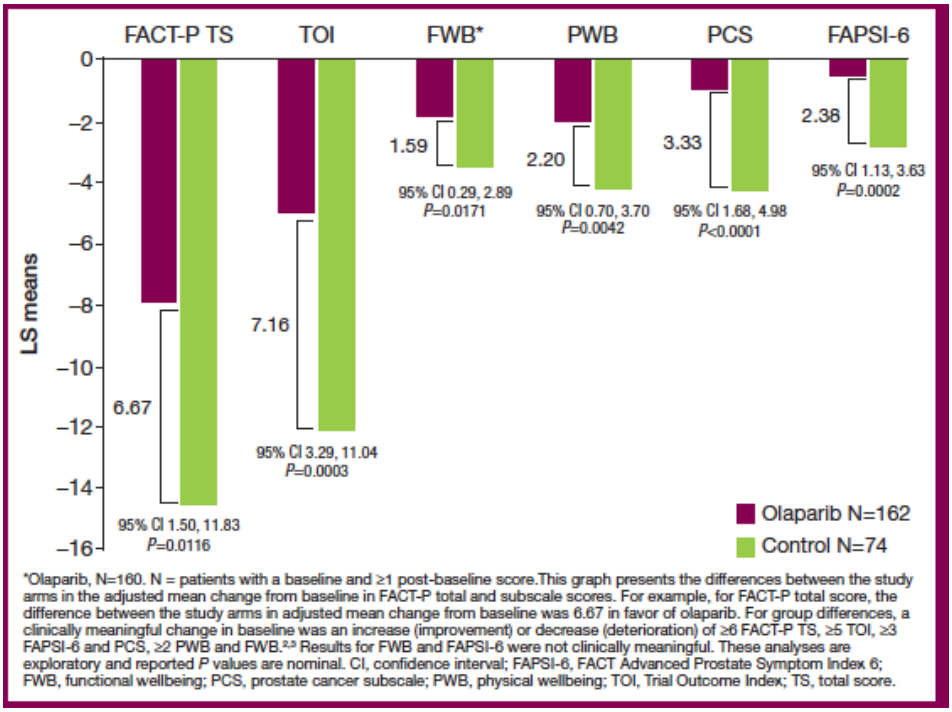
The number of patients varied due to patients having non-evaluable baseline assessments but evaluable post baseline assessments.
CI, confidence interval.

Source: Thiery-Vuillemin et al. poster, ACSO Annual meeting May 2020[55]

The change in least-squares mean for the FACT-P scores at week 32 using a mixed-model for repeated measures is presented in Figure 13. There was a clinically meaningful difference in Cohort A+B for the adjusted mean change from baseline in FACT-P total score, trial outcome index, PWB, and PCS.[7] There was a clinically meaningful difference in Cohort A for the adjusted mean change from baseline in FACT-P total score, trial outcome index and PCS.[7]

Figure 13: Least-square mean changes from baseline for the FACT-P in (A) Cohort A+B and (B) Cohort A

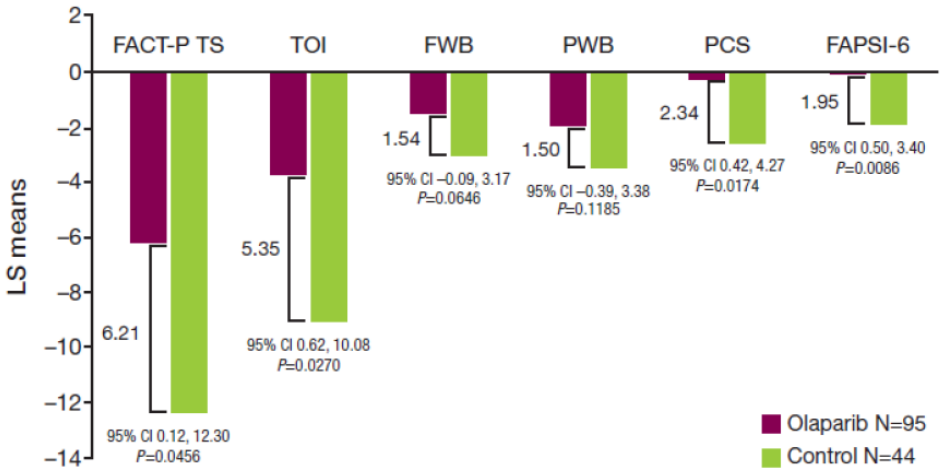
(A)



*Olaparib, N=160. N = patients with a baseline and ≥1 post-baseline score.This graph presents the differences between the study arms in the adjusted mean change from baseline in FACT-P total and subscale scores. For example, for FACT-P total score, the difference between the study arms in adjusted mean change from baseline was 6.67 in favor of olaparib. For group differences, a clinically meaningful change in baseline was an increase (improvement) or decrease (deterioration) of ≥6 FACT-P TS, ≥5 TOI, ≥3 FAPSI-6 and PCS, ≥2 PWB and FWB.[2,3] Results for FWB and FAPSI-6 were not clinically meaningful. These analyses are exploratory and reported *P* values are nominal. CI, confidence interval; FAPSI-6, FACT Advanced Prostate Symptom Index 6; FWB, functional wellbeing; PCS, prostate cancer subscale; PWB, physical wellbeing; TOI, Trial Outcome Index; TS, total score.

Source: Thiery-Vuillemin et al. poster, ACSO Annual meeting May 2020[55]

(B)



N = patients with a baseline and ≥1 post-baseline score. For group differences, a clinically meaningful change in baseline was an increase (improvement) or decrease (deterioration) of ≥6 FACT-P TS, ≥5 TOI, ≥3 FAPSI-6 and PCS, ≥2 PWB and FWB.[3,4] Results for FWB, PWB and FAPSI-6 were not clinically meaningful. These analyses are exploratory and reported *P* values are nominal.

Source: Thiery-Vuillemin et al. poster, ACSO Annual meeting May 2020[55]

EuroQoL 5-Dimension, 5-Level Health State Utility Index

The baseline patient adherence rates for the EQ-5D-5L in Cohort A+B were [redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

[redacted].[3] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

[3] Figure 14 shows the change in EQ-5D-5L over time for patients in Cohort A. [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 14: Mean EQ-5D-5L and 95% CIs over time in Cohort A

*(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*Source: Sponsor Clinical Summary[6]

Harms Outcomes

The safety set in the PROfound trial consisted of patients in Cohort A+B who had received at least one dose of the study treatment.[1] Patients were included in the safety switch analysis set if they were randomized to the control group and crossover to receive olaparib.[1] There was a total of 386 patients in the safety set, with 256 patients in the olaparib group and 130 patients in the control group.[1]

Adverse Events

Hussain et al. (2020) reported that no new safety signals emerged after the later data-cut off (Table 13 and Table 14).[2] Overall, more patients in the olaparib group reported an AE and an AE of grade ≥ 3 as compared to those in the control group (96% versus 88% and 52% versus 40%, respectively) (Table 13 and Table 14).[2] More patients in the crossover group reported an AE of grade ≥ 3 (59%) (Table 13 and Table 14).[2] The most common AEs were anemia (olaparib: 50%, control: 15%, crossover: 52%), nausea (olaparib: 43%, control: 21%, crossover: 29%), and fatigue or asthenia (olaparib: 42%, control: 33%, crossover: 25%).[2] Twenty percent of patients in the olaparib group discontinued their assigned therapies due to an AE as compared to 8% in the control group at the March 20, 2020 data cut-off (Table 13 and Table 14).[2] More patients in the olaparib group than the control group had an AE leading to treatment interruption or a dose reduction (46% versus 19% and 23% versus 5%).[17]

Table 13: Summary of adverse events by category at the primary analysis data cutoff (June 4, 2019) and the overall survival data cutoff (March 20, 2019) in Cohort A+B (safety analysis set) and in the subset of those patients with verified disease progression who crossed over from control therapy to olaparib (crossover)

Category, n (%)	Olaparib (N=256)		Control (N=130)*		Crossover†	
	PFS DCO	OS DCO	PFS DCO	OS DCO	PFS DCO (N=72)	OS DCO (N=83)
Any AE	**244 (95)**	**246 (96)**	**114 (88)**	**115 (88)**	**65 (90)**	**77 (93)**
Any AE of CTCAE ≥3	130 (51)	133 (52)	49 (38)	52 (40)	37 (51)	49 (59)
Any AE with outcome of death	10 (4)	10 (4)	5 (4)	6 (5)	2 (3)	3 (4)
Any AE attributable to study treatment	206 (81)	210 (82)	61 (47)	63 (48)	49 (68)	58 (70)
Any SAE (including with outcome of death)	91 (36)	94 (37)	36 (28)	39 (30)	17 (24)	27 (33)
Any AE leading to discontinuation of treatment	46 (18)	51 (20)	11 (8)	11 (8)	10 (14)	11 (13)

*One patient in the control arm did not receive treatment.
†Patients were allowed to cross over from the control arm to receive olaparib upon verification of disease progression. Safety was not assessed in the three patients in the control arm who received olaparib outside of the study.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cutoff; OS, overall survival; PFS, progression-free survival; SAE, serious adverse event.

Data source: NEJM 2020 Hussain[2]

Table 14: Adverse events occurring in at least 10% of patients in Cohort A+B and in the subgroup of patients who crossed over from control therapy to receive olaparib at the March 20, 2020 data cut-off

Table 1. Adverse Events in the Overall Population (Cohorts A and B) and in the Subgroup of Patients Who Crossed Over from Control Therapy to Receive Olaparib.*

Event	Olaparib (N=256)		Control (N=130)†		Crossover (N=83)‡	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients with event (percent)					
Any adverse event	246 (96)	133 (52)	115 (88)	52 (40)	77 (93)	49 (59)
Anemia§	127 (50)	58 (23)	20 (15)	7 (5)	43 (52)	24 (29)
Nausea	110 (43)	4 (2)	27 (21)	0	24 (29)	2 (2)
Fatigue or asthenia¶	107 (42)	8 (3)	43 (33)	7 (5)	21 (25)	8 (10)
Decreased appetite	80 (31)	4 (2)	24 (18)	1 (<1)	15 (18)	2 (2)
Diarrhea	55 (21)	2 (<1)	9 (7)	0	12 (14)	0
Vomiting	51 (20)	6 (2)	17 (13)	1 (<1)	16 (19)	1 (1)
Constipation	49 (19)	0	19 (15)	0	12 (14)	0
Back pain	36 (14)	2 (<1)	18 (14)	2 (2)	8 (10)	0
Peripheral edema	34 (13)	0	10 (8)	0	3 (4)	0
Cough	29 (11)	0	3 (2)	0	4 (5)	0
Dyspnea	27 (11)	6 (2)	5 (4)	0	4 (5)	1 (1)
Arthralgia	26 (10)	1 (<1)	14 (11)	0	4 (5)	0
Urinary tract infection	21 (8)	5 (2)	15 (12)	5 (4)	12 (14)	3 (4)
Any serious adverse event‖	94 (37)	NA	39 (30)	NA	27 (33)	NA
Interruption of treatment because of adverse event	119 (46)	NA	25 (19)	NA	44 (53)	NA
Dose reduction because of adverse event	60 (23)	NA	7 (5)	NA	27 (33)	NA
Discontinuation of treatment due to adverse event	51 (20)	NA	11 (8)	NA	11 (13)	NA
Death due to adverse event	10 (4)	NA	6 (5)	NA	3 (4)	NA

* Adverse events, regardless of the investigators' assessment of causality, are reported for those that occurred in at least 10% of the patients in either treatment group. Patients who reported multiple adverse events were counted once for each type of adverse event, even if they reported multiple occurrences of a particular adverse event. The safety analysis set included all the patients who had been randomly assigned to receive olaparib or the physician's choice of enzalutamide or abiraterone plus prednisone (control) and received at least one dose of a trial drug. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.03.[23] NA denotes not applicable.

† One patient in the control group did not receive treatment.

‡ Patients in the control group were allowed to cross over to receive olaparib after disease progression in accordance with the protocol. Three patients in the control group who received olaparib outside of the trial were not included in the safety analysis set.

§ The anemia category includes anemia, decreased hemoglobin level, decreased red-cell count, decreased hematocrit level, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia. Among the patients in the overall population, anemia was reported in 49% and a decreased hemoglobin level in less than 1%. Among the patients who crossed over to receive olaparib, anemia was reported in 49%, a decreased hemoglobin level in 1%, decreased red-cell count in 1%, and macrocytic anemia in 1%.

¶ Fatigue or asthenia is a grouped term that includes fatigue, asthenia, or both.

‖ The most common serious adverse events, regardless of the investigators' assessment of causality, are listed in Table S7 in the Supplementary Appendix.

Data source: NEJM 2020 Hussain[2]

Serious Adverse Events

More patients in the olaparib group had a serious adverse event (SAE) as compared to the control group and crossover (37% versus 30% versus 33%) (Table 14 and Table 15).[2] For SAE, more patients in the olaparib group had serious anemia relative to the control group (9% vs 0%) (Table 15).[2]

Table 15: Summary of serious adverse events (irrespective of attribution) occurring in ≥2% of patients in either treatment group among those in Cohort A+B at the 20-March-2020 data cut-off

	Overall population	
	Olaparib (N=256)	Control (N=130)*
	n (%)	n (%)
Any†	**94 (37)**	**39 (30)**
Anemia‡	23 (9)	0
Pneumonia	11 (4)	3 (2)
Fatigue or asthenia§	6 (2)	1 (1)
Urinary tract infection	5 (2)	4 (3)
Pulmonary embolism	5 (2)	1 (1)
Dyspnea	4 (2)	1 (1)
Thrombocytopenia	4 (2)	0
Vomiting	4 (2)	1 (1)
Sepsis	3 (1)	3 (2)
Pyrexia	3 (1)	2 (2)
Nausea	2 (1)	2 (2)
Angina pectoris	1 (<1)	2 (2)
Acute kidney injury	1 (<1)	2 (2)
Dehydration	0	3 (2)
Urinary tract obstruction	0	2 (2)
Fall	1 (<1)	2 (2)

*One patient in the control arm did not receive treatment.
†Patients who reported multiple serious adverse events were counted once for each type of adverse event (even if they reported multiple occurrences of a particular serious adverse event).
‡The anemia category includes anemia, decreased hemoglobin level, decreased red-cell count, decreased hematocrit, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia.
§Grouped term includes fatigue and/or asthenia.

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Deaths

Overall, there were 19 AEs leading to death in the trial (olaparib = 4% [N=10] vs. control = 5% [N=6] and cross-over = 4% [N=3]).[2] Two deaths in the trial were considered to be related to the study drug. One death in the olaparib group from pneumonia and neutropenia and one from pleural effusion in the control group.[2]

6.4 Ongoing Trials

No ongoing trials were identified for this Review.

7 Supplemental Questions

The following supplemental question was identified during the development of the review protocol as relevant to the CADTH review of olaparib as monotherapy for the treatment of men with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who have progressed following prior treatment with an NHA:

- Summary and critical appraisal of the sponsor-submitted ITC comparing olaparib with other relevant treatments for men with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who have progressed following prior treatment with an NHA.

Topics considered in this section are provided as supporting information. All the material in this section was taken from the Sponsor-submitted ITC.[8]

7.1 Summary of Sponsor-Submitted Indirect Treatment Comparison

Objective

To summarize and critically appraise the methods and findings of the sponsor-submitted ITC comparing olaparib with other relevant treatments (i.e., abiraterone, enzalutamide, docetaxel, cabazitaxel, and radium-223) for men with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who have progressed following prior treatment with an NHA. The following comparisons were performed: an NMA comparing olaparib to cabazitaxel and docetaxel, an anchored matching-adjusted indirect comparison (MAICs) comparing olaparib to cabazitaxel and an unanchored MAIC comparing olaparib to radium-223.

Methods

Systematic Review

The investigator provided an ITC based on a systematic literature review (SLR) that evaluated the relative efficacy of olaparib compared with other potentially relevant treatments for patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who have progressed following prior treatment with an NHA. The investigator conducted a quantitative and a qualitative literature search. The quantitative search selected articles if they included patients who failed NHA therapy or patients who had confirmed NHA therapy failure; assessed the effect of olaparib, abiraterone, enzalutamide, docetaxel, cabazitaxel or radium-223; reported on OS, PFS, HRQoL based on the FACT-P instrument and serious adverse events (or grade ≥3 adverse events); compared two or more interventions of interest in isolation and could be incorporated in a connected network containing the PROfound trial. For the qualitative search, the investigator used a set of relaxed eligibility criteria where they reassessed articles that were excluded at the SLR screening phase. Details of the quantitative and the qualitative searches are shown in Table 16.

The SLR was conducted on January 29, 2020 using Embase, MEDLINE, Cochrane Database of Systematic Reviews. Supplementary searches were also performed in ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and the proceedings of recent conferences since 2017: American Society of Clinical Oncology (ASCO), ASCO Genitourinary Cancers, American Urological Association (AUA), European Society for Medical Oncology (ESMO), Global Congress on Prostate Cancer (PROSCA). There were no restrictions on language and year; however, non-English-language publications were excluded at the screening process. Reference lists of identified systematic reviews were also searched for relevant records.

Table 16: Study selection criteria

Item	Qualitative Synthesis	Quantitative synthesis

Population	• Adult patients
	• mCRPC
	  • Progression on an NHA therapy (eg, abiraterone or enzalutamide) AND/OR an agent that is androgen blocking or androgen-depriving
		• Adult patients
		• mCRPC
		  • Progression on an NHA therapy (eg, enzalutamide, abiraterone)

Intervention	*No restriction*	*Any regimens of the following individual therapies were considered relevant to Canadian practice:* • Abiraterone • Enzalutamide • Cabazitaxel • Docetaxel • Radium-223
Comparators	See *Intervention*	See *Intervention*
Outcomes	• Progression-free survival • Overall survival • Adverse events related to treatment • Health-related quality of life • Time to pain progression • Time to first symptomatic skeletal-related event • Time to opiate use for cancer-related pain • Time to radiographic progression • Time to prostate-specific antigen progression	• Progression-free survival • Overall survival • Serious adverse events • Health-related quality of life based on the FACT-P assessment

Item	Qualitative Synthesis	Quantitative synthesis
Study design	• Randomized controlled trials • Single-arm studies • Indirect treatment comparisons and meta-analyses • Systematic literature reviews* • Human studies, excluding animal and *in vitro* studies	• Randomized controlled trials
Study Duration	*No restriction*	
Study Language	• English	• English
Date Restrictions	*No restriction*	

*Data were not extracted; reference lists were cross-checked for additional relevant records.
KEY: FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; NHA = novel hormonal agent

Source: Sponsor-submitted ITC[8]

Abstract and full-text screening were performed in duplicate and discrepancies were discussed with a third reviewer. Data extraction was conducted by a single specialist and it was reviewed by a second specialist. Any discrepancies were discussed with a third

specialist. Risk of bias was assessed using the Quality Appraisal Checklist for Quantitative Intervention Studies. The Investigator did not report whether the risk of bias assessment was performed in duplicate.

Feasibility Assessment

The investigator conducted a feasibility assessment prior to conducting the ITC. The investigator assessed the broad elements of study design, administered interventions, supporting therapies, study eligibility criteria, patient characteristics and outcome definitions of all the studies included in the ITC.

The investigator performed a core NMA that compared the effect of olaparib versus cabazitaxel as well as an additional sensitivity analysis that incorporated docetaxel into the core NMA.

Statistical Analysis

All NMAs were performed using a Bayesian framework. Here, similar interventions (based on dosage and frequency of administration) were grouped as treatment nodes. NMA models were developed using log HRs and standard errors from the included studies. NMAs were conducted using fixed effects models because the networks were constructed using connections with no more than two studies. All analyses were performed using four unique sets of starting values sampled automatically from the prior distributions and were based on burn-in and sampling durations of 20,000 iterations or more. Convergence was monitored quantitatively using the Gelman-Rubin diagnostic (Rhat) and samples were considered to have converged if Rhat was equal to or less than 1.05. Effective sample size and Monte Carlo standard error estimation were used to ensure sufficient post-convergence samples. For model priors and heterogeneity, vague prior distributions that assume no pre-existing information were assigned for the treatment effects and baseline characteristics. The investigator reported that they were unable to assess consistency between the direct and indirect estimates because there were no closed loops in the evidence networks. Pairwise comparisons from the NMAs were presented using league tables, which report HRs and 95% credible intervals (CrIs). A sensitivity analysis was also performed where docetaxel was incorporated into the core NMA.

Results for the NMA

Systematic Literature Results

The SLR identified a total of 6,006 articles. After removing duplicates, 5,993 titles and abstracts were screened, which resulted in 1,788 full-text articles being assessed for eligibility. From the full-text search, 1,301 full-text articles were excluded. The investigator stated that 363 articles that were excluded because the mCRPC patients in the studies did not progress on an NHA therapy were tagged of interest because they included the interventions under review (ie, docetaxel and radium-223). Overall, the qualitative search included 203 articles while the quantitative search included four records reporting on two RCTs, which includes the PROfound and CARD trials.

The investigator stated that the quantitative SLR did not identify any studies that investigated the effect of docetaxel and radium-223. Thus, the investigator selected the FIRSTANA, the iEAP and the ALSYMPCA trials from the qualitative search so the effect of these interventions could be explored in the ITC. These trials were excluded from the quantitative search because patients in the study did not progress on prior NHA therapy or due to study design. The results from the ALSYMPCA will not be included in this Review because the iEAP trial aligns more with the patient population in the PROfound trial.

Summary of the Included Studies

Tables 17 and 18 show details on the study design and patient characteristics of the trials included the NMA.

The CARD trial was an open-label, phase IV study, where 255 patients were randomized to receive cabazitaxel (25 mg/m^3 plus daily prednisone), enzalutamide or abiraterone. Patients in the cabazitaxel group also received prophylactic granulocyte colony-stimulating factor (GCSF) therapy.

FIRSTANA was an open-label, phase III trial that compared cabazitaxel at two doses (25 mg/m^3 and 20 mg/m^3 every three weeks) to docetaxel (75 mg/m^3 of every 3 weeks) in 1,168 patients. All patients received oral prednisone (10 mg per day), and some patients received GCSF either as prophylaxis or for management of febrile neutropenia (though this was avoided during the first treatment

cycle). Patients in the FIRSTANA were not required to have NHA failure and the use of prior chemotherapy and radiotherapy were highly restricted (study treatments were first-line therapy). The primary endpoint in the FIRSTANA trial was OS and secondary outcomes included composite PFS (time to tumor progression, PSA progression, pain progression or death according to RECIST version 1.1) and QoL based on the five subscale scores of the FACT-P instrument.

Table 17: Characteristics of the Studies Included for the Comparisons in the NMAs

Study	Location	Phase and trial design	Blinding	Study start date	Median follow-up*	Key population	Treatments, doses and sample size
PROfound (Source: PROfound CSR)	International	Phase 3 RCT	Open-label	February 2017	DCO1: 12.57 m (olaparib); 13.19 m (icNHA) DCO2: 21.91 m (olaparib); 21.04 m (icNHA)	mCRPC, disease progression on NHAs	• Olaparib 300 mg, bid (n = 162 [Cohort A]) • NHA† (n = 83 [Cohort A])
CARD (Source: de Wit *et al.,* 2019)	Europe	Phase 4 RCT	Open-label	November 2015	9.2 months	mCRPC, prior docetaxel, disease progression on NHAs	• Cabazitaxel 25 mg/m^2, q3w (n = 129) • NHA† (n = 126)
FIRSTANA (Source: Oudard *et al.,* 2017)	International	Phase 3 RCT	Open-label	May 2011	Unclear	mCRPC, disease-progression	• Cabazitaxel 25 mg/m^2, q3w (n = 388) • Cabazitaxel 20 mg/m^2, q3w (n = 389) • Docetaxel 75 mg/m^2, q3w (n = 391)

*Where ranges are listed, the median follow-up reported for each treatment group was considered.
†NHA treatment groups in the PROfound and CARD trials received either abiraterone (1000 mg, qd) or enzalutamide (160 mg, qd).
AUC = area under curve, bid = twice daily, mCRPC = metastatic castration-resistant prostate cancer, NHA = novel hormonal agent, m = months, q3w = every three weeks, q1w = every week, RCT = randomized controlled trial.

Source: Sponsor-submitted ITC[8]

Table 18: Baseline Patient Characteristics for Studies Included in the NMAs

Study	PROfound		CARD		FIRSTANA		
Treatment arm	OLA 300 bid (n = 162 [Cohort A])	NHA* (n = 83 [Cohort A])	CAB 25 q3w (n = 129)	NHA* (n = 126)	CAB 25 q3w (n = 388)	CAB 20 q3w (n = 389)	DOC 75 q3w (n = 391)
Median age (years)	68	67	70	71	68.5	68	69
Age range (years)	47-86	49-86	46-86	45-88	42-85	44-90	41-87
ECOG performance score 0-1 (%)	93	96	95.3	94.4	96.9	95.1	95.7
Visceral metastases (%)	28	39	16.3	19.8	Liver: 10.1 Lung: 12.9	Liver: 8.2 Lung: 14.9	Liver: 9.0 Lung: 12.0
Median PSA (ng/mL)	62.2	112.9	62	60.5	80.04	76	73.92
PSA range (ng/mL)	IQR: 21.9-280.4	IQR: 34.3-317.1	Range: 1.1-15,000.0	Range: 1.5-2868.0	Range: 0.1-6,312.7 IQR: 28.25-235.30	Range: 0.0-3,289 IQR: 29.58-176.10.3	Range: 2.4-6,862.0 IQR: 30.0-195.80
M1 disease at diagnosis (%)	23	23	38	47.6	NR	NR	NR
Gleason score 8-10 (%)	At diagnosis: 67	At diagnosis: 67	At diagnosis: 56.6	At diagnosis: 64.3	At diagnosis; ≥7: 80.4	At diagnosis; ≥7: 76.9	At diagnosis; ≥7: 79
Previous ABI (%)	38	35	43.4	53.2	0.8	0.5	2
Previous ENZA (%)	42	48	55.8	46.8	0.8	1	0.8
Previous ABI and ENZA (%)	20	17	0	0	NR	NR	NR
Previous ABI or ENZA (%)	100	100	100	100	<5%	<5%	<5%
Previous taxane (%)	65	63	100	100	<5%	<5%	<5%
Previous DOC (%)	46	39	100	100	NR	NR	NR
Source	PROfound CSR		de Wit *et al.,* (2019)		Oudard *et al.,* (2017)		

ABI = abiraterone, AUC = area under curve, CAB = cabazitaxel, DOC = docetaxel, ECOG = Eastern Cooperative Oncology Group, ENZA = enzalutamide, IQR = interquartile range, MIT = mitoxantrone, NHA = novel hormonal agent, NR = not reported, PSA = prostate-specific antigen, unavail = unavailable.

Source: Sponsor-submitted ITC[8]

Risk of Bias Assessment

Risk of bias was assessed using the Quality Appraisal Checklist for Quantitative Intervention Studies (Table 19). The investigator reported that there was a low risk of bias for external validity in the PROfound and CARD trials and moderate risk of bias for internal validity in both trials. The internal validity of the PROfound trial was impacted by the open-label design, cross-over and discontinuation rate. The internal validity of the CARD trial was impacted by open-label design, cross-over, the use of supporting therapies (i.e., GCSF) and inconsistent treatment duration between groups. The additional studies selected following the SLR were determined to have similar or lower risk of bias as compared to CARD and PROfound.

Table 19: Summary of quality assessment results for studies considered in quantitative synthesis

Trial name (or first author, year)	External Validity Summary Score (NR, -, +, or ++)	Internal Validity Summary Score (NR, -, +, or ++)
PROfound	++	+
CARD	++	+
FIRSTANA	++	++
iEAP	++	+

++ All or most of the checklist criteria have been fulfilled, where they have not been fulfilled the conclusions are very unlikely to alter.

+ Some of the checklist criteria have been fulfilled, where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter.

– Few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter.

KEY: NR = not reported.

Source: Sponsor-submitted ITC[8]

Feasibility Assessment

The investigator assessed the study design, interventions, study eligibility criteria, baseline patient characteristics and study outcomes prior to developing the ITC.

First, the investigator compared the CARD and PROfound trials. For the study design, the investigator noted that both trials were open-label studies with a median follow-up of less than 20 months. However, CARD was a Phase IV study conducted in only European study centers while PROfound was an international Phase III study. For the interventions, the control intervention was determined to be equivalent in both trials, but the CARD trial administered prophylactic GCSF while this was not done in the PROfound trial. This has the potential to reduce the incidence of treatment-emergent AEs in the cabazitaxel group of the CARD trial. In addition, prophylactic administration of GCSF does not align with the standard of care for metastatic patients in Canada and it might be a source of potential bias for ITCs. Finally, prophylactic GCSF may have allowed for improved maintenance of dose intensity, which would prevent dose reductions or discontinuations, thereby impacting the amount of data evaluable for efficacy outcomes. For the eligibility criteria, the main difference was that the PROfound trial enrolled patients based on the HRR genotype status while the CARD trial did not consider HRR genotype status, which may impact the effect of the drug on important patient outcomes. Additionally, the CARD trial required prior use of at least three cycles of docetaxel, which may indicate that the enrolled patients were more treatment-experienced than those included in the PROfound trial. Finally, histologically confirmed prostate adenocarcinoma was required in the CARD trial but not in the PROfound trial. For the baseline characteristics, the investigator noted differences in PSA levels, more patients in the CARD trial were diagnosed with metastatic disease, less patients had prior docetaxel

use in the PROfound trial and less patients in the CARD trial had visceral metastases. Overall survival and PFS were measured and reported similarly in the PROfound and CARD trials. FACT-P was measured in both trials, but compliance was lower in the PROfound trial as compared to the CARD trial (68% versus >80%). AEs could be compared across the trials.

Second, the investigator compared the FIRSTANA to the PROfound and CARD trials. For the study design, the investigator noted that the FIRSTANA trial had a larger sample size than the PROfound and CARD trials and patient enrollment of the FIRSTANA trial proceeded both trials by 4.5 and 5.75 years, respectively. For the interventions, the administration of cabazitaxel in the FIRSTANA and CARD trials were determined to be equivalent but not all patients in the FIRSTANA trial received GCSF. For the eligibility criteria, the FIRSTANA trial did not restrict enrollment based on HRR genotype status or prior use of NHA therapy and prior chemotherapy was not allowed in the FIRSTANA trial. In addition, the FIRSTANA trial represents a more treatment-naïve mCRPC population as compared to the PROfound and CARD trials. For the patient characteristics, the investigator noted that fewer patients in the FIRSTANA trial had liver or lung metastases as compared to PROfound while the proportion of those with visceral metastases or metastases at diagnosis at baseline was unclear. Additionally, the trials reported different ranges for the Gleason score at diagnosis (i.e.., scores from 7-10 rather than 8-10) and the proportion of patients with any prior NHA as well as any prior taxane use (i.e.., less than 5% to 100%). For the outcomes, the FIRSTANA trial did not include bone lesion progression in their definition of PFS but it included PSA-based progression and pain progression. Moreover, the median PFS for patients receiving cabazitaxel at 25 mg/m^3 every three weeks was longer in the CARD trial as compared to the FIRSTANA trial (i.e., 8.0 and 5.1 months). The investigator noted FACT-P could not be compared across all three trials due to incomplete information. AEs could be compared across the trials.

Overall, the investigator concluded that there was a high degree of clinical heterogeneity between the PROfound and CARD trials but proceeded to conduct a core NMA with a sensitivity analysis including the FIRSTANA trial. However, an anchored MAIC was also conducted between the PROfound and CARD trials on PFS and OS to explore the impact of this clinical heterogeneity (described later). In addition, given the insufficient data, FACT-P and adverse outcomes could not be assessed.

Evidence Networks

The estimates from the PROfound, CARD and FIRSTANA trials are presented in Table 20.

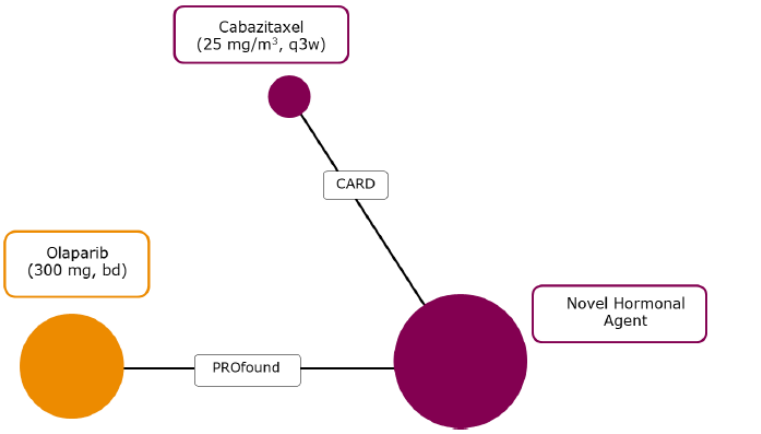
Table 20: Summary of direct estimates for OS and PFS from the PROfound, CARD and FIRSTANA trials

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Source: Sponsor-submitted ITC[8]

The core network of studies is depicted in Figure 15. Only the PROfound and CARD trials were included in the core NMA because the common intervention investigated in these trials was NHA therapy (i.e., abiraterone with prednisone or enzalutamide).

Figure 15: Core network of studies in mCRPC



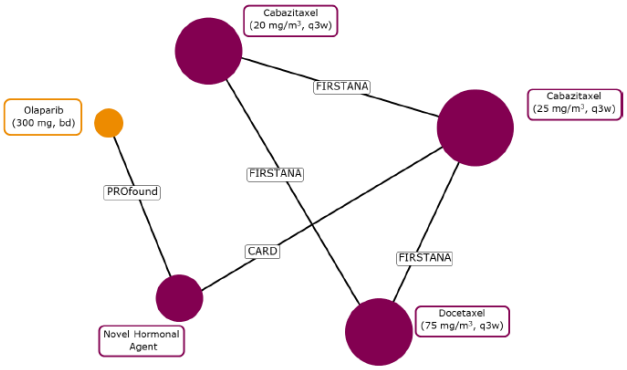
KEY: bid = twice daily; mCRPC = metastatic castration-resistant prostate cancer; q3w = every three weeks; qd = once daily.
Note: Colours are used for highlighting purposes only. Line size is proportional to the number of studies, node size is proportional to the number of patients who received a treatment.

Source: Sponsor-submitted ITC[8]

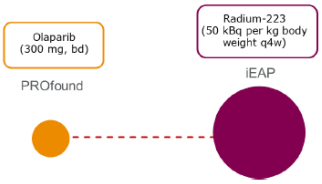
In addition, the Investigator performed a sensitivity analysis where they incorporated the results of the FIRSTANA trial into the core network to assess the effects of docetaxel versus olaparib (Figure 16). The FIRSTANA trial included a similar treatment group as the CARD trial (cabazitaxel at 25 mg/m^3 every three weeks) but it should be noted that the patient population of FIRSTANA were far less treatment-experienced than that of PROfound.

Figure 16: Sensitivity analyses for the comparison of additional mCRPC interventions to olaparib by incorporating docetaxel using an NMA

(A) Incorporating docetaxel using an NMA



(B) Incorporating radium-223 using an unanchored MAIC



KEY: bd = twice daily; iEAP = International Early Access Program; MAIC = matching-adjusted indirect comparison; NMA = network meta-analysis; q3w = every three weeks; q4w = every four weeks.

Note: Colours are used for highlighting purposes only. Line size is proportional to the number of studies, node size is proportional to the number of patients who received a treatment.

Source: Sponsor-submitted ITC[8]

NMA Results

Compared with cabazitaxel and investigators' choice of NHA, olaparib ranked first for PFS. The credible interval for the comparison of olaparib against cabazitaxel was consistent with small to large benefit. Upon incorporation of the FIRSTANA trial into the network, olaparib ranked above all comparators (docetaxel, cabazitaxel and investigators' choice of NHA) for PFS. The credible intervals for the comparison of olaparib against cabazitaxel and docetaxel were consistent with large to moderate benefits. [redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 17: Pair-wise estimates of treatment effects (HR) for PFS using data from the PROfound and CARD trials (A) and (B) CARD and FIRSTANA

A. PROfound and CARD

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

B. PROfound, CARD and FIRSTANA

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Source: Sponsor-submitted ITC[8]

The OS estimates obtained from the PROfound trial represent those from the RPSFT treatment switching model with re-censoring. When an RPSFT treatment switching model with re-censoring was used, olaparib ranked above cabazitaxel for OS, but credible intervals were consistent with clinically meaningful benefits for either comparator. Both treatments had credible intervals compared to investigators' choice of NHA that were consistent with small to large benefits. [redacted] (Figure 18 A). [redacted] (Figure 18 B).[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 18: Pair-wise estimates of treatment effects (HR) for OS using data from the PROfound and CARD trials (A) and (B) CARD and FIRSTANA. The OS estimates obtained from the PROfound trial represent those from the RPSFT treatment switching model with re-censoring

A. PROfound and CARD

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

B. PROfound, CARD and FIRSTANA

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Source: Sponsor-submitted ITC[8]

Overall survival estimates obtained from the PROfound trial representing those from the RPSFT treatment switching model without re-censoring were also considered. In the broader network, which included FIRSTANA, olaparib ranked above all other treatments (docetaxel, cabazitaxel and investigators' choice of NHA) for OS, but credible intervals were consistent with clinically meaningful benefits for each comparator. All treatments had credible intervals compared to investigators' choice of NHA that were consistent with small to large benefits. [redacted] (Figure 19 A). [redacted] (Figure 19 B).[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Figure 19: Pair-wise estimates of treatment effects (HR) for OS using data from the PROfound and CARD trials (A) and (B) CARD and FIRSTANA. The OS estimates obtained from the PROfound trial represent the RPSFT treatment switching model without re-censoring

A. PROfound and CARD

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

B. PROfound, CARD and FIRSTANA

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Source: Sponsor-submitted ITC[8]

Anchored Matching-Adjusted Indirect Comparison

Based on the feasibility assessment for the NMA, there was a high degree of heterogeneity among the trials included in the core NMA. Specifically, clinical heterogeneity was present in the indirect comparison between olaparib and cabazitaxel, which may have affected the results of the NMA. First, HRR genotype status was not included in the eligibility criteria for the CARD trial while it was for the PROfound trial. Patients in the CARD trial were required to have at least three cycles of docetaxel while this was not required in the PROfound trial. The investigator noted that the proportion of patients with visceral metastases was higher in the PROfound trial as compared to the CARD trial. Patients in the CARD trial received a prophylactic administration of GCFS while patients in the PROfound trial did not. Thus, the investigator conducted a sensitivity analysis using an anchored matching-adjusted indirect comparison (MAICs) comparing olaparib versus cabazitaxel. This approach to indirect comparisons can be used to account for sources of bias due to heterogeneity in baseline patient characteristics across studies, but importantly, MAIC cannot account for bias

due to other sources of heterogeneity observed between the CARD and PROfound trials such as differences in patient eligibility criteria.

Methods

Statistical Analysis

The investigator conducted an anchored MAIC comparing the effect of olaparib versus cabazitaxel on PFS and OS as a sensitivity analysis based on the feasibility assessment. Only patients from Cohort A who had prior taxane use were used for this analysis. In order to conduct the anchored MAIC, the investigator's identified patient-level characteristics that could be considered effect modifiers using a series of univariate Cox regression models with a 20% significance level as well as the imbalance statistics. It should be noted that the effect modifier analysis was conducted using data from Cohort A+B (prior taxane only) to improve power and the number of variables to weight on. Thus, covariates were selected for weighting if they were a statistically significant at the 80% level or had a balance statistical difference from one. The investigator created weights for each patient using individual-level patient data from the PROfound trial in order to weight patients in the PROfound trial to match the baseline patient characteristics observed in the CARD trial. The investigator used the Bucher method to obtain matching-adjusted and unadjusted HRs comparing olaparib to NHA. Additional analyses were also conducted for OS using data from the RPSFT model and re-censored and non-re-censored data. The proportional hazards assumption was tested using visual inspection of the log-cumulative hazards plots and the Schoenfeld plots as well as using the Schoenfeld individual tests. The MAIC used a complete case analysis.

Results

Prior to conducting the anchored MAIC between the PROfound and the CARD trials, the investigator excluded covariates that could not be assessed appropriately as an effect modifier because of a lack of data:

- Previous NHA therapy use was excluded because of differences in reporting across the PROfound and CARD trials.
- Prior treatment (radical prostatectomy or radiation therapy of prostate) for localized disease was removed because it was not reported in a similar manner across the trials.
- Duration of first androgen therapy was removed because it was not captured in the PROfound study.
- Time to progression of the prior androgen signaling-targeted inhibitor was removed because it was not collected in the PROfound trial.
- Analgesics use at baseline because it was not categorized in a similar manner across trials.

First, the investigator conducted an assessment of effect modifiers and covariate imbalance analysis for the rPFS and OS endpoints. The investigator reported that alkaline phosphatase levels at baseline, age (rPFS only), ECOG (non-RPSFT OS only) and visceral disease (RPSFT and non-RPSFT data) were considered to be effect modifiers. Thus, the investigator weighed age, ECOG score (0 to 1), presence of lung and liver metastases and baseline alkaline phosphatase.

Next, the investigator reweighted the contributions of patients in the PROfound trial. After the investigator rescaled the weights, they observed outlying values, which may indicate that some patients were contributing more weight, and therefore, the adjusted analysis may be overly influenced by these patients. Overall, the effective sample size (ESS) of the MAIC was [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

The investigator noted that the results of the MAIC should be interpreted with caution given the smaller sample size.

The adjusted MAIC results showed that [redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information*

Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).

Table 21: rPFS HRs generated by MAIC for the PROfound and CARD trials

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April, 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).

Source: Sponsor-submitted ITC[8]

The adjusted MAIC results for the non-RPSFT OS analysis showed that [redacted] (Table 22). [redacted].[8]*(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).*

Table 22: Non-RPSFT OS HRs generated by MAIC for the PROfound and CARD trials

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).

Source: Sponsor-submitted ITC[8]

The adjusted MAIC results for the RPSFT with re-censoring OS analysis showed that [redacted] (Table 23). [redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).*

Table 23: RPSFT with re-censoring OS HRs generated by MAIC for the PROfound and CARD trials

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).

Source: Sponsor-submitted ITC[8]

The adjusted MAIC results for the RPSFT without re-censoring OS analysis showed that [redacted] (Table 24). [redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).*

Table 24: RPSFT without re-censoring OS HRs generated by MAIC for the PROfound and CARD trials

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).

Source: Sponsor-submitted ITC[8]

Unanchored Matching-adjusted Indirect Comparison

The investigator conducted an unanchored MAIC to compare the effect of olaparib versus radium-223 since the trial assessing the effect of radium-223 was a single-arm trial, and hence, there was no common comparator between the two trials.

Methods

Feasibility Assessment

The investigator conducted a feasibility assessment prior to conducting the unanchored MAIC. The investigator assessed the broad elements of study design, administered interventions, supporting therapies, study eligibility criteria, patient characteristics and outcome definitions of all the studies included in the ITC.

Statistical Analysis

The investigator performed an unanchored MAIC between olaparib and radium-223. The investigator only used the bone metastases subgroup of Cohort A from the PROfound trial. First, the investigator selected prognostic factors for weighting. Prognostic factors were selected for weighting if they were reported in both the index and the aggregate trials and were statistically significant using univariate Cox regression model with an 80% significance level. Patients were weighted using the selected variables and then results were reported from a Cox regression for both an unadjusted model and weighted model using the derived patient weights. The proportional hazards assumption was tested using visual inspection of the log-cumulative hazards plots and the Schoenfeld plots as well as using the Schoenfeld individual tests.

Results

Included Studies

iEAP was a single-arm, phase IIIb study that assessed the effect of radium-223 dichloride (radium-223) (50 kBq per kilogram of body weight every four weeks until six injections) with or without concomitant NHA therapy (enzalutamide and/or abiraterone) in 839 patients. The subgroup of patients who used radium-223 alone was included in this analysis (N=507) and concomitant use was

defined as therapy administered after the first injection of radium-223 or therapy started prior to the first injection of radium-223 that was continued during the trial. Although a large proportion of patients were documented to have received prior NHA therapy, there was no requirement of progression on NHA therapy for enrollment in the iEAP study. There were few eligibility criteria related to prior treatment, however, patients with prior hemibody external radiotherapy or very recent use of certain treatments were ineligible (e.g., chemotherapy within four weeks). The primary endpoint was safety and OS and the secondary outcome was patient-reported Brief Pain Inventory (BPI). PFS was not assessed in the trial. Tables 25 and 26 shows details on the study design and patient characteristics of the trials included the MAIC.

Table 25: Baseline Patient Characteristics for Studies Included in the unanchored MAICs prior to matching and adjustment

Study	PROfound		iEAP
Treatment arm	OLA 300 bid (N =162 [Cohort A])	NHA* (N =83 [Cohort A])	Radium-223 (N =507) (note: patients receiving radium in combination with NHA were ignored, as this is not a treatment combination relevant to Canada)
Median age (years)	68	67	71
Age range (years)	47-86	49-86	45-94
ECOG performance score 0-1 (%)	93	96	86
Visceral metastases (%)	28	39	0
Bone metastases only (%)	35	28	100
Median PSA (ng/mL)	62.2	112.9	164
PSA range (ng/mL)	IQR: 21.9-280.4	IQR: 34.3-317.1	Range: 0 – 12150
M1 disease at diagnosis (%)	23	23	NR
Gleason score 8-10 (%)	At diagnosis: 67	At diagnosis: 67	NR
Previous ABI (%)	38	35	NR
Previous ENZA (%)	42	48	NR
Previous ABI and ENZA (%)	20	17	NR
Previous ABI or ENZA (%)	100	100	100
Previous taxane (%)	65	63	NR
Previous DOC (%)	46	39	54
Source	PROfound CSR		O'Sullivan *et al.,* (2015)

ABI = abiraterone, DOC = docetaxel, ECOG = Eastern Cooperative Oncology Group, ENZA = enzalutamide, IQR = interquartile range, MIT = mitoxantrone, NHA = novel hormonal agent, NR = not reported, PSA = prostate-specific antigen.

Source: Sponsor-submitted ITC[8]

Table 26: Characteristics of the Studies Included for the Comparisons in the unanchored MAICs

Study	Location	Phase and trial design	Blinding	Study start date	Median follow-up*	Key population restrictions	Treatments, doses and sample size
PROfound (Source: PROfound CSR)	International	Phase 3 RCT	Open-label	February 2017	12.57-21.04 months	mCRPC, disease progression on NHAs	Olaparib 300 mg, bid (n = 162 [Cohort A]) NHA† (n = 83 [Cohort A])
iEAP (Source: O'Sullivan *et al.*, 2015)	International (Europe, Canada, Israel)	Phase 3b Single-arm	Open-label	July 2012	7.5 months (safety population)	mCRPC, bone metastases, no visceral metastases	Radium-223, 50 kBq, q4w (n = 696) No concomitant NHA: n = 507 (note: This was the focus of MAIC analyses, due to aligning best to real-world use of radium-223).

*Where ranges are listed, the median follow-up times reported for each treatment group were considered.

†NHA treatment group received either abiraterone (1000 mg, qd) or enzalutamide (160 mg, qd).

bid = twice daily, mCRPC = metastatic castration-resistant prostate cancer, NHA = novel hormonal agent, q4w = every four weeks, RCT = randomized controlled trial.

Source: Sponsor-submitted ITC[8]

Feasibility Assessment

The investigator compared the iEAP trial to the PROfound trial. For the study design, the iEAP trial was a single-arm Phase IIIb trial and the lack of randomization in the trial may increase the risk of bias as compared to the PROfound trial. For the interventions, the two trials did not investigate common interventions. For the eligibility criteria, the iEAP trial did not restrict enrollment based on the HRR genotype status or prior NHA therapy use but the iEAP trial selected for patients with multiple bone metastases (symptomatic or asymptomatic) while those with visceral metastases were not included. The iEAP trial may potentially represent a more treatment-naïve mCRPC population than the PROfound trial. For the patient characteristics, the investigator noted differences between the proportion who had visceral metastases and bone metastases, use of NHA therapies and prior docetaxel use. For outcomes, PFS and FACT-P were not assessed in the iEAP trial and indirect comparisons of serious adverse events were not considered feasible.

Results

For the unanchored MAIC, the investigator considered age, race, weight, prior docetaxel, ECOG performance status, pain, hemoglobin, albumin and PSA as prognostic factors. It is unclear whether the investigator considered these as effect modifiers. However, the investigator was unable to consider pain, albumin and PSA because the data were not available or the variables in the iEAP trial had a skewed distribution, which would make weighting between the two trials unfeasible. The CGP considered that prior docetaxel, ECOG performance status, pain, haemoglobin and PSA were important prognostic and effect modifiers. The investigator considered the following prognostic factors in Table 27, and based on the HRs, it is unclear which factors were ultimately used for weighting. Overall, the ESS of the unanchored MAIC was [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

The investigator concluded that the unanchored MAIC may not produce meaningful results, and therefore, these results should be interpreted with caution.

Table 27: Prognostic factors assessed for the unanchored MAIC

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Source: Sponsor-submitted ITC[8]

For OS, the investigator reported that there [redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).*

Critical Appraisal of the Sponsor-submitted ITC

Overall, the SLR provided in the sponsor-submitted ITC was well documented and of high quality. However, the assumptions of the SLR had to be relaxed because the investigator was unable to identify any studies that assessed the effect of docetaxel or radium-223 in men with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who have progressed following prior treatment with an NHA. Thus, the FIRSTANA and the iEAP trials were included into the ITC. The addition of these studies into the ITC could bias the indirect comparisons because of the differences in study design and patient characteristics, which could lead to inaccurate conclusions.

Although the investigator stated that they used the NICE Evidence Synthesis Decision Support Unit (DSU) Technical Support Document (TSD) Series, there are several limitations in the NMA. Table 28 shows a summary of the critical appraisal according to the ISPOR criteria. Overall, the investigator was unable to assess the effect of olaparib, cabazitaxel or docetaxel on BRCA or ATM carriers since these data were not collected in the CARD or FIRSTANA trials. Second, due to the lack of studies, only fixed effects analyses could be conducted, and the investigator did not adjust for baseline clinical heterogeneity or potential effect modifiers. This clinical heterogeneity includes: the HRR genotype status was not included in the eligibility criteria for the CARD trial while it was for the PROfound trial, patients in the CARD trial were required to have at least three cycles of docetaxel while this was not required in the PROfound trial, the proportion of patients with visceral metastases was higher in the PROfound trial as compared to the CARD trial and patients in the CARD trial received a prophylactic administration of GCFS while patients in the PROfound trial did not. However, the investigator did perform an anchored MAIC as an attempt to account for the presence of clinical heterogeneity between olaparib and cabazitaxel due to differences in baseline patient characteristics. Due to the above limitations and the ones outlined in Table 28, the comparative efficacy estimates obtained for the NMA may be biased, and therefore, the results of the NMA should be interpreted with caution.

No indirect treatment comparisons were performed for FACT-P and adverse outcomes.

External validity of the NMA results were limited because the effect of cabazitaxel and docetaxel is unknown among BRCA1, BRCA2 and ATM carriers since the CARD and FIRSTANA trial did not genotype patients upon enrollment. In addition, the data used in these analyses comes from clinical trial populations with specific patient selection criteria, which may not be represent the broader patient population of men with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who have progressed following prior treatment with an NHA. Therefore, the results of this NMA may not be generalizable to the real-world population in Canada.

Table 28: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis

ISPOR Questions	Details and Comments
1. Is the population relevant?	The patient population for the quantitative SLR was relevant to the patient population of men with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who

ISPOR Questions	Details and Comments
	have progressed following prior treatment with an NHA. However, the investigator was unable to identify any trials that assessed the effect of docetaxel in the patient population in the submission. Therefore, in order to assess the effect of docetaxel, the investigator incorporated the FIRSTANA trial into the core NMA. It should also be noted that only the PROfound trial genotyped study participants so the effect of cabazitaxel or docetaxel among BRCA or ATM carriers in unknown.
1. Are any critical interventions missing?	The NMA included olaparib, cabazitaxel, docetaxel and NHA therapy, which were considered relevant interventions for this patient population. Comparisons to radium-223 were made in an unanchored MAIC.
2. Are any relevant outcomes missing?	The NMA reported on rPFS and OS. The SLR also included HRQoL and AEs but the data were not available to construct networks for these outcomes.
3. Is the context (e.g., settings and circumstances) applicable to your population?	The context was applicable to the patient population under review.
4. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes. The search included the major bibliographic databases (MEDLINE, EMBASE, and Cochrane Controlled Trials), as well as conference abstracts. The search was comprehensive, and the investigator included a list of all included and excluded trials. However, to included relevant comparators the investigator had to relax the assumptions of the SLR.
5. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	The trials in the analysis did not form a connected network of RCTs due to a lack of studies.
6. Is it apparent that poor quality studies were included thereby leading to bias?	The quality of studies was evaluated and reported. The investigator reported that the PROfound, CARD, FIRSTANA and iEAP trials had a low risk of bias for external validity and only the FIRSTANA trial had a low risk of bias for internal validity while all other trials had an unclear risk.
7. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Probably at low risk of bias. The investigator noted in the Quality Appraisal Checklist for Quantitative Intervention Studies assessment that all outcome measurements were complete and all-important outcomes were assessed for the three trials included in the NMA.
8. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	Clinical heterogeneity was present in the indirect comparison between olaparib and cabazitaxel, which may have affected the results of the NMA. Firstly, HRR genotype status was not included in the eligibility criteria for the CARD trial while it was for the PROfound trial. Patients in the CARD trial were required to have least three cycles of docetaxel while this was not required in the PROfound trial. The investigator noted that the proportion of patients with visceral metastases was higher in the PROfound trial as compared to the CARD trial. Patients in the CARD trial received a prophylactic administration of GCFS while patients in the PROfound trial did not.
9. If yes (i.e., there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	The imbalances in the potential effect modifiers were identified prior to comparing the individual studies. They were discussed in the publication as a potential limitation to the NMA.
10. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	The Sponsor-submitted NMA used a Bayesian NMA (standard approach) to analyze data on outcomes of interest from the included RCTs.
11. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	The consistency was not evaluated because there were no closed loops in the ITCs.

ISPOR Questions	Details and Comments
12. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	There were no closed loops in the networks.
13. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	The researchers did not attempt to minimize imbalances in the NMA. However, they performed sensitivity analyses to assess the imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the NMA.
14. Was a valid rationale provided for the use of random effects or fixed effect models?	Only fixed-effect models were performed because the networks were constructed using connections with no more than two studies.
15. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable, however, the assumptions about heterogeneity were explored and discussed.
16. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	Subgroup analyses were not conducted to explore potential sources of clinical heterogeneity. However, the investigator did perform an anchored MAIC to assess the impact of heterogeneity.
17. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Graphical representations of the evidence networks and number of RCTs were provided.
18. Are the individual study results reported?	The individual study results were provided for PROfound, CARD and FIRSTANA trials.
19. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	The results of the direct comparisons of the treatments were reported separately from results of the indirect comparisons.
20. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Measures of uncertainty were reported for the direct estimates of effect (95% CI) and for the indirect estimates (95% credible intervals) in the sponsor-provided ITC.
21. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	The probabilities of being the preferred treatments was provided.
22. Is the impact of important patient characteristics on treatment effects reported?	The impact of important patient characteristics on treatment effects was reported and discussed.
23. Are the conclusions fair and balanced?	The conclusions of the NMA seem fair and the limitations are acknowledged. [redacted]. The limitations of the analysis in terms of the small number of studies in the network and the high degree of heterogeneity among the included trials were acknowledged.
24. Were there any potential conflicts of interest?	No conflict-of-interest information was provided; however, the report was submitted by the investigator of the olaparib submission.
25. If yes, were steps taken to address these?	Not applicable.

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

The investigator conducted an anchored MAIC to compare the effects of olaparib to cabazitaxel on PFS and OS since there was a high degree of heterogeneity among the PROfound and CARD trials. This clinical heterogeneity includes: the HRR genotype status was not included in the eligibility criteria for the CARD trial while it was for the PROfound trial, patients in the CARD trial were required to have at least three cycles of docetaxel while this was not required in the PROfound trial, the proportion of patients with visceral metastases was higher in the PROfound trial as compared to the CARD trial and patients in the CARD trial received a prophylactic administration of GCFS while patients in the PROfound trial did not. The investigator accounted for this clinical heterogeneity by including only patients from Cohort A who had prior taxane use; however, they were unable to account for the other sources of clinical heterogeneity that were mentioned above because these data were not available in either one of the trials. Prior to the analysis, the investigator excluded potential effect modifiers, such as previous NHA therapy, prior treatment (radical prostatectomy or radiation therapy of prostate) for localized disease, duration of first androgen therapy, time to progression of the prior androgen signaling-targeted inhibitor and analgesics use at baseline from the analysis because of a lack of data. The CGP commented that these were not relevant effect modifiers and the exclusion of these factors would not impact the analysis. For the analysis, the investigator states that they considered the following effect modifiers in the analysis: neutrophil, alkaline phosophate, haemoglobin, lactate dehydrogenase, enzalutamide, Brief Pain Inventory, Gleason score, age, visceral disease, M1 disease, ECOG and PSA. The CGP noted that haemoglobin, visceral disease, M1 disease, ECOG and PSA were appropriate effect modifiers. Although the investigator attempted to include all relevant effect modifiers, they decided to include these effect modifiers into the weighing process based on a series of univariate Cox regression model with a 20% significance level as well as the imbalance statistics. This does not align with the recommendations in the NICE DSU TSD 18, which states that effect modifiers should be identified a priori based on external sources, such as literature review, expert opinion, or results from external data, and all of the effect modifiers should be included in the weighting process. In other words, the selection of effect modifiers should not be data driven. Thus, the results of the anchored MAIC may be biased because the weighting process did not include haemoglobin, visceral disease, M1 disease, ECOG and PSA, which are important effect modifiers. Overall, the ESS of the anchored MAIC [redacted]; thus, the statistical power and precision of the analysis was greatly reduced due to weighting and the results may be overly influenced by small subsets of patients in the PROfound trial. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* Additionally, the investigator noted that they used the Bucher method to obtain matching-adjusted and unadjusted HRs comparing olaparib to NHA; however, detail on how this approach was implemented were not provided so it is unclear how this method was applied. Finally, the external generalizability of the anchored MAIC in Canada is limited because the investigator was unable to assess the effect of BRCA and ATM carrier status since these data were not provided in the CARD trial. Therefore, the robustness of the internal and external validity of the anchored MAIC is uncertain.

The investigator conducted an unanchored MAIC to compare the effects of olaparib to radium-223 on OS. The clinical heterogeneity includes: the iEAP trial did not restrict enrollment based on the HRR genotype status or prior NHA therapy use but the iEAP trial selected for patients with multiple bone metastases (symptomatic or asymptomatic), differences in the between the proportion who had visceral metastases and bone metastases, use of NHA therapies and prior docetaxel use. The investigator accounted for this clinical heterogeneity by including only the bone metastases subgroup of Cohort A from the PROfound trial; however, they were unable to account for the other sources of heterogeneity because these data were not available in either the iEAP trial or the PROfound trials. The investigator states that they considered the following prognostic factors in the analysis: age, race, weight, prior docetaxel and ECOG. It is unclear whether the investigator considered these both prognostic and/ or effect modifiers but the CGP noted that most of these factors were appropriate prognostic and effect modifiers. However, the investigator excluded potential effect modifiers, such as pain, albumin and PSA because of a lack of data. The CGP noted that pain and PSA represented a prognostic and/ or effect modifiers. Although the investigator attempted to include all relevant prognostic factors, they decided to include these factors into the weighing process based on a series of univariate Cox regression model with a 20% significance level. This does not align with the recommendations in the NICE DSU TSD 18, which states that prognostic and/or effect modifiers should be identified a priori based on external sources, such as literature review, expert opinion, or results from external data, and all of the prognostic and/or effect modifiers should be included in the weighting process. In other words, the selection of prognostic and effect modifiers should not be data driven. Although the cox regression analyses indicated that none of the prognostic factors were significant, it is unclear which prognostic factors were included in the weighting process. The ESS of the anchored MAIC [redacted]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* Since the original sample sizes (before exclusions) was not reported for the PROfound trials, the impact on statistical power and precision of the analysis is unknown. Finally, the external generalizability of the unanchored MAIC in Canada is limited because the investigator was unable to assess the effect of BRCA1/2 and ATM carrier status since this data was not provided in the iEAP trial. Based on these limitations, the unanchored MAIC may not produce meaningful results, and therefore, these results should be interpreted with caution.

Summary

In the absence of head-to-head trials, the investigator submitted an ITC comparing olaparib with other relevant treatments for men with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who have progressed following prior treatment with an NHA. Based on the results from the NMA, the investigator concluded that results favoured olaparib in showing a PFS benefit versus cabazitaxel, docetaxel, and NHA therapy; but olaparib was favoured for OS benefit only versus NHA therapy. The results from the sensitivity anchored MAIC comparing olaparib and cabazitaxel were [redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).* Finally, the results from the adjusted exploratory unanchored MAIC [redacted].[8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until April 2022 or notification by the sponsor that it can be publicly disclosed, whichever is earlier).*

Overall, the NMA included currently approved treatments for the patient population under review, which includes enzalutamide, abiraterone, cabazitaxel and docetaxel. In addition, the NMA included relevant efficacy outcomes, such as PFS and OS, but there were no analyses conducted for any safety endpoints or HRQoL due to a lack of data. However, there were some limitations of the NMA that should be considered. First, the investigator was unable to assess the effect of olaparib relevant to the other enzalutamide, abiraterone, cabazitaxel and docetaxel among BRCA1/2 and ATM carriers because this information was not available in all studies. This could bias the results of the NMA because HRR mutations may be associated with prognosis, where BRCA2 and ATM genotype carriers have been shown to be associated with poor clinical outcomes.[8] Thus, the inclusion of the CARD and FIRSTANA may bias the estimates from the ITC in favour of cabazitaxel and docetaxel since all patients in Cohort A of the PROfound trial had a mutation in either the BRCA2 and ATM genotype. There was also a high degree of heterogeneity among the trials included in the NMA, which may imply that there are systematic differences between the patient populations among the included studies. Although the investigator conducted an anchored MAIC to account for this heterogeneity, the impact it has is still unclear because the results of anchored MAIC may be biased due to the exclusion of many important effect modifiers. Due to the above limitations, the comparative efficacy estimates obtained are likely biased, and it is not possible to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with olaparib.

The investigator also conducted an unanchored MAIC to compare the effect of olaparib to and radium-223. However, the investigator was unable to assess the effect of olaparib compared with radium-223 among BRCA1/2 and ATM carriers because this information was not available in the iEAP trial. Additionally, it is unclear which prognostic and effect modifiers were considered in the weighting process and it is unclear what impact these missing factors will have on the results of the unanchored MAIC. Due to the high level of risk of bias for these results, no firm conclusions are recommended based on these results.

8 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Method Team did not identify other relevant literature proving supporting information for this review.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Genitourinary Clinical Guidance Panel and supported by the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on olaparib for mCRPC. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the Procedures for the CADTH pan-Canadian Oncology Drug Review. The sponsor, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations. This information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

CADTH

Appendix 1: Literature Search Strategy and Detailed Methodology

Literature Search Methods

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials September 2020, Embase 1974 to 2020 October 15, Ovid MEDLINE(R) ALL 1946 to October 16, 2020
Search Strategy:

#	Searches	Results
1	(olaparib* or Lynparza* or AZD2281 or AZD 2281 or KU59436 or KU-59436 or KU0059436 or KU-0059436 or MK7339 or MK-7339 or WOH1JD9AR8).ti,ab,ot,kf,kw,hw,nm,rn.	7531
2	exp Prostatic neoplasms/	382999
3	(prostat* adj3 (neoplas* or cancer* or carcinoma* or adenocarcinoma* or tumor* or tumour* or malignan* or metasta*)).ti,ab,kf,kw.	386623
4	(mHRPC or mCRPC or HRPC or CRPC).ti,ab,kf,kw.	19392
5	or/2-4	461250
6	1 and 5	945
7	6 use medall	151
8	limit 7 to english language	148
9	6 use cctr	70
10	*olaparib/ or (olaparib* or Lynparza* or AZD2281 or AZD 2281 or KU59436 or KU-59436 or KU0059436 or KU-0059436 or MK7339 or MK-7339).ti,ab,kw,dq.	5154
11	exp Prostate tumor/	248168
12	(prostat* adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumor* or tumour* or malignan* or metasta)).ti,ab,dq,kw.	384237
13	(mHRPC or mCRPC or HRPC or CRPC).ti,ab,dq,kw.	19351
14	or/11-13	437500
15	10 and 14	571
16	15 use oemezd	373
17	limit 16 to english language	366
18	17 not conference abstract.pt.	202
19	8 or 9 or 18	420
20	remove duplicates from 19	281
21	17 and conference abstract.pt.	164
22	limit 21 to yr="2015 -Current"	149
23	20 or 22	430

1. **Cochrane Central Register of Controlled Trials (CENTRAL)**
   (searched via Ovid)

2. Grey literature search via**:**

   Clinical trial registries:

   US National Library of Medicine. ClinicalTrials.gov
   https://clinicaltrials.gov/

   World Health Organization

http://apps.who.int/trialsearch/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Health Canada's Clinical Trials Database
https://health-products.canada.ca/ctdb-bdec/index-eng.jsp

The European Clinical Trial Register
https://www.clinicaltrialsregister.eu/ctr-search/search

Search: Lynparza/olaparib, prostate cancer

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Lynparza/olaparib, prostate cancer

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

Search: Lynparza/olaparib, prostate cancer — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[58]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Lynparza/olaparib and prostate cancer.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of February 18, 2021.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[59] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials, Health Canada Clinical Trials Database, and the

European Clinical Trials Registry), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the CADTH Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and CADTH:

- The Methods Team wrote a summary of background clinical information, a systematic review of the evidence, interpretation of the systematic review, and summaries of evidence for supplemental questions.
- The CADTH Clinical Guidance Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- CADTH wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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