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CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

NIRAPARIB (ZEJULA)

(GlaxoSmithKline Inc.)

Indication: As monotherapy for the maintenance treatment of female adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

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Abbreviations

AE	adverse event
AML	acute myeloid leukemia
BICR	blinded-independent central review
BRCA	breast cancer susceptibility gene
BRCAmut	BRCA mutation
BRCAwt	BRCA wild-type
CA-125	cancer antigen 125
CGP	Clinical Guidance Panel
CI	confidence interval
CR	complete response
ECOG PS	Eastern Cooperative Oncology Group performance status
EORTC-QLQ- C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer 30
EORTC-QLQ- OV28 Cancer Module - OV28	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Ovarian
EOT	end of treatment
EQ-5D-5L	European Quality of Life scale, 5-Dimensions
FIGO	International Federation of Gynecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy - Ovarian Symptom Index
gBRCA	germline BRCA mutation
GCIG	Gynecologic Cancer InterGroup
HR	hazard ratio
HRD	homologous recombination deficiency
HRP	homologous recombination proficiency
HRQoL	health-related quality of life
ITC	indirect treatment comparison
ITT	intent-to-treat
KM	Kaplan-Meier
MCID	minimal clinically important difference
MDS	myelodysplastic syndrome

MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not estimable
NMA	network meta-analysis
NVRD	no visible residual disease
OS	overall survival
PAG	Provincial Advisory Group
PAIC	population-adjusted indirect treatment comparison
PARP	poly(adenosine diphosphate [ADP]–ribose) polymerase
PD	progressive disease
PFS	progression-free survival
PFS-2	progression-free survival on next line of therapy
PK	pharmacokinetics
PR	partial response
PRO	patient-reported outcome
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
sBRCAmut	somatic BRCA mutation
SD	standard deviation
TEAE	treatment-emergent adverse event
TFST	time-to-first subsequent therapy
TRAE	treatment-related adverse event
ULN	upper limit of normal
VAS	visual analog scale

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 niraparib (Zejula) as maintenance treatment for patients with newly diagnosed advanced ovarian cancer who are in a complete or partial response to first-line platinum-based chemotherapy. 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 niraparib (Zejula) as maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

The reimbursement request under review by CADTH is for niraparib as maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy. A notice of compliance was issued by Health Canada for niraparib on October 2, 2020 as monotherapy for the maintenance treatment of female adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.[1] The reimbursement request aligns with the Health Canada indication.

The reimbursement request under review by CADTH is for niraparib as monotherapy for the maintenance treatment of female adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy. A notice of compliance was issued by Health Canada for niraparib for this indication on October 2, 2020.[1] The reimbursement request aligns with the Health Canada indication.

Niraparib (Zejula) is an oral inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes PARP-1 and PARP-2, which play a role in DNA repair.[1] Increased niraparib-induced cytotoxicity has been observed in tumour cell lines with or without deficiencies in breast cancer susceptibility genes (BRCA) 1/2[1]. For patients weighing less than 77 kg or with a platelet count of less than 150,000/µL, the recommended dose of niraparib is 200 mg (2 x 100-mg capsules) taken orally once daily; and for patients weighing greater than or equal to 77 kg and who have a platelet count greater than or equal to 150,000/µL, the recommended dose of niraparib is 300 mg (3 x 100-mg capsules) taken orally once daily.[1]

Patients should start treatment with niraparib no later than 12 weeks after their most recent platinum-containing regimen, and treatment should be continued until disease progression or unacceptable toxicity.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The CADTH systematic review included one randomized controlled trial (RCT), the PRIMA trial (n=733).[2] A summary of the trial and its results is provided below.

PRIMA

PRIMA is an ongoing, international, double-blind, placebo-controlled, phase III randomized trial that evaluated the efficacy and safety of niraparib compared to placebo as maintenance treatment in adult patients with newly diagnosed advanced cancer of the ovary, peritoneum, or fallopian tube (henceforth referred to as ovarian cancer).[2] Patients were randomized 2:1 to receive either niraparib or placebo once daily in 28-day cycles for 36 months or until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up.[2,3] Patient enrolment occurred between July 2016 and June 2018. Prior to Protocol Amendment 2 on November 16, 2017, patients received a fixed dose of 300 mg daily study medication (3 x 100 mg niraparib capsules or 3 placebo capsules matched in appearance to niraparib); however, following the amendment, an individualized dose option based on a patient's weight and/or platelet count was implemented. Patients with a baseline body weight of less than 77kg and/or a baseline platelet count of less than 150 000 µL were administered a 200 mg dose once daily (2 x 100 mg niraparib capsules or 2 placebo capsules matched in appearance to niraparib).[3]

To be eligible for the trial, patients had newly diagnosed, histologically confirmed advanced ovarian cancer with high-grade serous or endometrioid features that were classified as stage III or IV according to International Federation of Gynecology and Obstetrics (FIGO) criteria.[2] The following stage III and/or IV patients were eligible for inclusion:

- Stage III with visible residual disease after primary debulking surgery (patients with complete cytoreduction with no visible residual disease [NVRD] after primary debulking surgery were excluded)
- Inoperable stage III disease
- Any stage IV disease
- Stage III or IV patients who were treated with neoadjuvant chemotherapy (patients with NVRD after interval debulking surgery were included)

Enrolled patients had to have received 6 to 9 cycles of first-line platinum-based chemotherapy that resulted in an investigator-assessed complete response (CR) or partial response (PR) after 3 or more cycles.[2,3] Any residual disease following chemotherapy must have been less than or equal to 2 cm, and cancer antigen 125 (CA-125) values had to be either within the normal range or show a decrease of more than 90%. Patients were randomized within 12 weeks after completing the last dose of platinum-based chemotherapy administered on the first day of the last cycle. Patients who received intraperitoneal chemotherapy were eligible.

Tumour samples underwent central testing for breast cancer susceptibility gene (BRCA) mutation (BRCAmut) and homologous recombination status using the myChoice© HRD test by Myriad Genetics.[2] Homologous recombination deficiency (HRD) test scores range from 1 to 100 with higher scores indicating a greater number of genomic abnormalities on the basis of loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions. Any tumour that had a score greater or equal to 42 or had a deleterious or suspected deleterious BRCA1/2 mutation was considered HRD-positive. Prior to Protocol Amendment 1, trial enrollment was restricted to patients considered to be HRD-positive. Following this amendment, the eligibility criterion requiring HRD positivity was removed and homologous recombination status became a stratification factor during randomization. Patients with an undetermined HRD status were eligible to participate in the trial. Tumour samples could be sent prior to the protocol-defined screening period after patients had signed the consent form.

Patients were randomized in a 2:1 ratio to receive niraparib or placebo using a central interactive web response system.[3] Randomization was stratified according to clinical response after first-line platinum-based chemotherapy (CR or PR), receipt of neoadjuvant chemotherapy (yes or no), and tumour homologous recombination status (HRD versus proficient [HRP] or not determined).[2] Unless germline BRCAmut (gBRCAmut) or somatic BRCAmut (sBRCAmut) status was known, randomization could not occur prior to receiving on-study homologous recombination test results. If a patient had a documented deleterious gBRCAmut or sBRCAmut by local testing results, randomization could occur prior to receipt of the test results; accordingly, the patient's tumour was considered HRD-positive for the purpose of stratification (these tumours were still subsequently tested with the myChoice© HRD test). Patients were to receive the first dose of study treatment either on the day of randomization or within 7 days if possible. Laboratory tests were repeated if they were performed more than 7 days prior to the first dose of study treatment.

Efficacy outcomes were assessed according to the intent-to-treat (ITT) principle, defined as all patients who underwent randomization.[3] The primary endpoint of the trial was progression-free survival (PFS) assessed by blinded-independent central review (BICR), evaluated hierarchically in patients with HRD-positive tumours and then in the overall patient population (all trial

patients).[2] PFS was defined as the time from randomization after completion of platinum-based chemotherapy to the earliest date of objective disease progression (PD) on imaging according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or death from any cause. The secondary outcomes assessed in the trial included the following: overall survival (OS), time-to-first subsequent therapy (TFST), progression-free survival on next line of therapy (PFS-2), time-to-CA-125 progression, and patient-reported outcomes (PROs).[2,3] For the assessment of PFS and OS, a hierarchical-testing procedure was used to control for the overall type 1 error. PROs related to health-related quality of life (HRQoL) were assessed using the Functional Assessment of Cancer Therapy - Ovarian Symptom Index (FOSI), the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer 30 (EORTC-QLQ-C30) and Ovarian Cancer Module (EORTC-QLQ-OV28) questionnaires, and the European Quality of Life scale, 5-Dimensions (EQ-5D-5L).[2]

To assess the consistency of the treatment effect, subgroup analyses of PFS (and OS, although these were not reported) were prespecified and performed in the following subgroups of patients: age, race, Eastern Cooperative Oncology Group performance status (ECOG PS), disease stage, primary tumour site, geographic region, HRD status, BRCA status, baseline CA-125 level, use of neoadjuvant chemotherapy, and best response to first platinum regimen.[3] Following Protocol Amendment 2, subgroup analyses based on the fixed and individualized starting dose options were planned.

A total of 733 patients were enrolled in the PRIMA trial, with 487 patients randomized to the niraparib group and 246 patients randomized to the placebo group.[2] In the niraparib group, 247 (50.7%) patients had HRD-positive tumours of whom 152 (31.2%) had a BRCAmut and 95 (19.5%) were BRCA wild-type (BRCAwt), 169 (34.7%) patients had HRP tumours (HRD-negative), and the HRD status was undetermined for 71 (14.6%) patients. In the placebo group, 126 (51.2%) patients had HRD-positive tumours of whom 71 (28.9%) had a BRCAmut and 55 (22.3%) were BRCAwt, 80 (32.5%) patients were HRD-negative, and the HRD status was undetermined for 40 (16.3%) patients.

In the overall population, the median age was 62 years in both treatment groups. The majority of patients were 'White' (niraparib group: 89.5%; placebo group: 89.0%)[4] and had an ECOG PS of 0 (niraparib group: 69.2%; placebo group: 70.7%).[2] The median weight of patients in the niraparib and placebo groups was 66.00 kg and 65.55 kg, respectively.[4] The primary tumour sites (niraparib group versus the placebo group) were ovarian (79.7% versus 81.7%), fallopian tube (13.3% versus 13.0%) and peritoneum (7.0% versus 5.3%), and histological subtypes were serous (95.5% versus 93.5%), endometrioid (2.3% versus 3.7%), and 'other' (2.3% versus 2.4%). Most patients in each treatment group had FIGO stage III cancer (65.3% versus 64.2%), received neoadjuvant chemotherapy (66.1% versus 67.9%), and achieved a CR after their platinum-based chemotherapy (69.2% versus 70.0%).[2] Among patients who received neoadjuvant chemotherapy, 26% had NVRD after interval debulking surgery.[4] Most patients were BRCAwt (63.7% versus 66.3%) and the median time from diagnosis to first dose of study treatment was 7.68 months in the niraparib group and 7.74 months in the placebo group.[4]

In the HRD-positive population, 247 patients were randomized to receive niraparib and 126 patients were randomized to receive placebo.[2] The median age was 58 years in both groups. The majority of patients were 'White' (niraparib group: 88.3%; placebo group: 85.7%)[4] and had an ECOG PS of 0 (niraparib group: 73.7%; placebo group: 77.0%).[2] The median weight of patients in the niraparib and placebo groups was 65.30 kg and 65.10 kg, respectively.[4] The primary tumour sites (niraparib group versus the placebo group) were ovarian (81.4% versus 83.3%), fallopian tube (13.0% versus 10.3%), and peritoneum (5.7% versus 6.3%); and histological subtypes were serous (94.7% versus 92.1%), endometrioid (2.0% versus 4.8%), and 'other' (3.2% versus 3.2%). Most patients in each treatment group had FIGO stage III cancer (65.2% versus 61.9%), received neoadjuvant chemotherapy (63.2% versus 62.5%), and achieved a CR after their platinum-based chemotherapy (74.9% versus 73.8%). [2] The median time from diagnosis to first dose was 7.68 months in the niraparib group and 7.44 months in the placebo group.

Prior to the amendment of the dosing schedule, a total of 473 patients in the overall population, including 315 in the niraparib treatment group, had received the fixed starting dose of 300 mg.[4] After implementation of the revised dosing scheme, a total of 238 patients (156 in the niraparib group; 82 in the placebo group) received either 200 mg or 300 mg in accordance with body weight and platelet count; and of these patients, 122 (25.1%) of patients in the niraparib group and 61 (24.7%) of patients in the placebo group received 200 mg as their individualized dose.[4]

Efficacy

The results for the primary and secondary efficacy outcomes from the PRIMA trial are summarized in Table 1. As of the May 17, 2019 data cut-off date, the median duration of follow-up in the overall population was 13.8 months (range, <1.0 to 28.0),[2] and was 13.9 months (95% confidence interval [CI], 13.8 to 16.0) in the niraparib group and 13.8 months (95% CI, 13.6 to 14.1) in the placebo group.[5] In the HRD-positive population, the median duration of follow-up was 13.9 months (95% CI, 13.7 to 16.4) in the niraparib group and 13.7 months (95% CI, 12.7 to 16.7) in the placebo group.

The PRIMA trial met its primary endpoint, demonstrating a statistically significant longer duration of PFS in the niraparib group compared to the placebo group in both efficacy populations (HRD-positive population and the overall population).[2] In the HRD-positive population, the median PFS was 21.9 months in the niraparib group and 10.4 months in the placebo group corresponding to an absolute median PFS benefit of 11.5 months in the niraparib group (hazards ratio [HR] = 0.43; 95% CI, 0.31 to 0.59; p <0.001).[2] In the overall population, the median PFS was 13.8 months in the niraparib group and 8.2 months in the placebo group, corresponding to an absolute median PFS benefit of 5.6 months (HR = 0.62; 95% CI, 0.50 to 0.76; p <0.001). For both the HRD-positive population and the overall population, estimates of PFS at 6, 12, 18, and 24 months were higher in the niraparib group versus the placebo group at each time point.[4]

The results of prespecified subgroup analyses of PFS in the overall population were consistent with the primary efficacy analysis results, demonstrating a longer duration of PFS in the niraparib group compared to the placebo group except for the following subgroups of patients: ECOG PS of 1, stage IV disease at initial diagnosis, primary peritoneal or fallopian tube as primary tumour site, baseline CA-125 level >upper limit of normal (ULN), and HRD status undetermined. In these subgroups, all the treatment effect estimates favoured treatment with niraparib, but the 95% CI included the null value of 1, suggesting no difference in PFS between the treatment groups. These subgroup analyses were not powered to detect statistically significant differences in outcome between treatment groups and some analyses may have been limited by small sample size.

At the time of the May 17, 2019 data cut-off date, the interim analysis of OS indicated that the data were immature based on a total of 79 deaths (10.8% maturity)[2] with data censored for over 87% of patients in both treatment groups.[4] Overall, the interim OS results showed treatment effect estimates that favoured niraparib compared to placebo but the differences in deaths between the treatment groups were not statistically significant.[2] In the HRD-positive population, 26 patients had died that included 16 deaths (6.5%) in the niraparib group and 10 deaths (7.9%) in the placebo group (HR = 0.61; 95% CI, 0.27 to 1.39). In the overall population, 79 patients had died that included 48 (9.9%) in the niraparib group and 31 (12.6%) in the placebo group (HR = 0.70; 95% CI, 0.44 to 1.11). Median OS estimates were not reported due to low event rate and insufficient follow-up time.

Patient-Reported Outcomes – FOSI, EORTC-QLQ-C30, EORTC-QLQ-OV28, and EQ-5D-5L,

PROs were assessed in the HRD-positive and overall patient population and showed similar results. In both treatment groups (overall population), completion rates were greater than 80% at all assessment timepoints, which was calculated based on the number of patients with an evaluable form at each visit, divided by the number of patients expected to complete the form at that visit. However, for all instruments, the increase in patients completing the end of treatment (EOT) assessment indicated that a sizable proportion of patients did not complete PRO assessments at earlier timepoints particularly after Cycle 13. Overall, the data from all PRO measures did not suggest any between-group differences in symptoms or quality of life (QoL) based on changes in score from baseline among patients receiving niraparib when compared to placebo, except for some worse gastrointestinal symptoms. (i.e., constipation, nausea and vomiting, and appetite loss) in the niraparib group at specific timepoints. However, time-to-worsening analyses, which incorporated data from all timepoints, showed no difference between the treatment groups in the time-to-worsening of gastrointestinal symptoms based on the prespecified minimal clinically important difference (MCID) for the FOSI and the EORTC-QLQ-OV28.

Harms

Overall, the incidence of all categories of treatment-emergent adverse events (TEAEs) was higher in the niraparib group compared to the placebo group.[2] There were no treatment-related deaths reported in the trial and 3 deaths were attributed to AEs (2 in the niraparib group and 1 in the placebo group). The 2 deaths in the niraparib group were related to pleural effusion and intestinal

perforation.[4] An AE leading to treatment discontinuation, dose reduction, or treatment interruption in the niraparib group versus the placebo group occurred in 12.0% versus 2.5%, 70.9% versus 8.2%, and 79.5% versus 18.0% of patients, respectively.[2]

The most common treatment-related TEAEs of any grade that occurred in the niraparib group (versus the placebo group) were anemia (60.5% versus 12.7%), nausea (50.6% versus 20.1%), thrombocytopenia (45.2% versus 3.3%), fatigue (29.8% versus 23.0%), platelet count decreased (26.9% versus 1.2%), neutropenia (26.0% versus 5.7%), and constipation (25.8% versus 5.7%).[5] The most common grade 3 or higher treatment-related TEAEs in the niraparib group (versus the placebo group) were anemia (30.2% versus 0.4%), thrombocytopenia (28.7% versus 0%), platelet count decreased (13.0% versus 0%), neutropenia (12.4% versus 0.8%), and neutrophil count decreased (7.6% versus 0%).

The incidence of any grade and grade 3 or higher TEAEs was lower in patients who received an individualized starting dose of niraparib compared to a fixed starting dose of niraparib, with the exception of neutropenic sepsis, which occurred in one patient treated with an individualized starting dose of niraparib.[2] One patient (0.3%) who had received a fixed starting dose of niraparib experienced myelodysplastic syndrome (MDS) (grade 3 or higher), and no patients in either the individualized starting dose of niraparib or in the placebo group experienced MDS.

Limitations and Potential Sources of Bias

The major limitations and potential sources of bias associated with the PRIMA trial, based on the CADTH Methods Team's critical appraisal of the evidence, are summarized below. The complete list is available in Section 6.

- The trial was double-blind, however, the higher incidence of AEs, dose interruptions, and dose reductions that occurred in the niraparib group had the potential to unmask patients to their assigned treatment. The extent to which spontaneous unblinding of patients and investigators occurred in the trial and the amount of bias that would be introduced is unknown, but the possible influence of this on subjective outcomes like safety and PROs should be considered.
- Although PFS and OS were assessed in the 2 efficacy populations using a hierarchical-testing procedure, there were multiple secondary efficacy outcomes assessed in the trial and numerous predefined subgroup analyses performed that were not adjusted to account for multiple comparison testing to control the risk of type 1 error. As the trial was not powered to test specific hypotheses in these outcomes and subgroups, the results of these analyses should be interpreted as exploratory in nature.
- Protocol Amendment 2 introduced a change to the dosing scheme of the trial that occurred after the enrollment of the majority trial patients (65%) who all received a fixed starting dose of 300 mg. The patients enrolled after the amendment received an individualized starting dose (200 mg or 300 mg according to patient weight and/or platelet count) and received fewer treatment cycles and thus less treatment exposure due to a shorter follow-up period. The results of subgroup analyses performed of PFS by dosing scheme suggested that starting dose did not affect treatment efficacy in either the HRD-positive or the overall population. Although the dosing scheme was changed during the trial, the study sample size was not increased to ensure adequate power to test for differences in outcome based on dosing scheme. In addition, patients were assigned to a dosing scheme based on weight and/or platelet count and not through randomization, so there is the possibility that any differences in baseline characteristics between groups could bias treatment effect estimates. These limitations introduce uncertainty into the analyses performed and therefore these subgroup results should be interpreted with caution. Lastly, the available data by dosing scheme from the trial do not reliably inform on the efficacy associated with the lower starting dose (200 mg) of niraparib.
- According to the CGP, HRD testing is not routinely performed in Canadian clinical practice because the test has not been clinically validated. Therefore, there is uncertainty in the reliability and validity of the trial results based only on HRD status.
- At the time of the primary efficacy analysis, the OS data were at approximately 10.8% maturity[2] and showed no statistically significant difference between the treatment groups in either the HRD-positive or the overall population. The OS data were considered immature and not interpretable at the time of the interim analysis based on the low number of events; therefore, longer-term survival data are required to assess the magnitude of an OS benefit. Patient crossover was not permitted in the trial; however, the longer-term OS data will be confounded by the use of post-trial treatments, which was high in the trial. In the HRD-positive population, 30.2% and 49.6% of patients in the niraparib and placebo groups, respectively, received a subsequent anti-cancer regimen post-progression; and the corresponding percentages in the overall population were 40.9% and 51.2%, respectively.[6]
- For the assessment of PROs, patient compliance rates were reported to be high (>80%) at all assessment timepoints, however, for all instruments, the increase in patients completing the EOT assessment indicated that a sizable proportion

of patients did not complete PRO assessments at earlier timepoints particularly after Cycle 13. Thus, the number of patients included in the analyses of PROs at later assessment timepoints was reduced and the patients left in the trial who completed PRO assessments are likely not representative (i.e., have better HRQoL) of all patients randomized to each treatment group. In this scenario, data are not missing at random since patients who have left the trial are likely sicker (or have died), and therefore, the results at later timepoints are likely biased. Time-to-event analysis of PROs mitigates some of the bias associated with analyses based on mean changes in scores from baseline because all available data are used in the analysis. In trial, the time-to-worsening of symptoms analyses based on the MCID of the FOSI and EORTC-QLQ-OV28 showed no differences between the treatment groups with respect to the time to worsening of ovarian cancer symptoms.

Table 1: Highlights of Key Outcomes in the PRIMA Trial

Outcomes	HRD-positive (n=373)		Overall Population (n=733)	
	Niraparib (n=247)	Placebo (n=126)	Niraparib (n=487)	Placebo (n=246)
Primary Outcome				
PFS by BICR				
Median (95% CI) in months[a]	21.9 (19.3 to NE)	10.4 (8.1 to 12.1)	13.8 (11.5 to 14.9)	8.2 (7.3 to 8.5)
HR (95% CI)[b]	0.43 (0.310 to 0.588)		0.62 (0.502 to 0.755)	
p-value[c]	<0.0001		<0.0001	
Survival distribution function, % (95% CI)				
6-months	86 (81 to 90)	68 (59 to 76)	73 (69 to 77)	60 (53 to 66)
12-months	72 (65 to 77)	42 (33 to 51)	53 (48 to 58)	35 (29 to 42)
18-months	59 (50 to 66)	35 (25 to 45)	42 (36 to 47)	28 (21 to 35)
24-months	47 (36 to 58)	26 (14 to 39)	32 (25 to 39)	23 (14 to 32)
30-months	47 (36 to 58)	26 (14 to 39)	32 (25 to 39)	23 (14 to 32)
Key Secondary Outcomes				
OS				
HR (95% CI)[b]	0.61 (0.265 to 1.388)		0.70 (0.442 to 1.106)	
p-value[c]	0.2323		0.1238	
TFST				
Median (95% CI) in months	NE (24.7 to NE)	13.7 (11.6 to 19.3)	18.6 (15.8 to 24.7)	12.0 (10.3 to 13.9)
HR (95% CI)[b]	0.46 (0.330 to 0.640)		0.65 (0.521 to 0.802)	
PFS-2				
Median (95% CI) in months[a]	NE (25.3 to NE)	NE (NE to NE)	27.2 (25.3 to NE)	NE (NE to NE)
HR (95% CI)[b]	0.84 (0.485 to 1.453)		0.81 (0.577 to 1.139)	
Harms, n (%)	**Niraparib (n=484)**		**Placebo (n=244)**	
Any AE	478 (98.8)		224 (91.8)	
Grade ≥3 AE	341 (70.5)		46 (18.9)	
Any TRAE	466 (96.3)		168 (68.9)	
Grade ≥3 TRAE	316 (65.3)		16 (6.6)	
Any SAE	156 (32.2)		32 (13.1)	
Any treatment-related SAE	118 (24.4)		6 (2.5)	
Any AE Leading to Treatment Discontinuation	58 (12.0)		6 (2.5)	
Any AE Leading to Dose Reduction	343 (70.9)		20 (8.2)	

Outcomes	HRD-positive (n=373)		Overall Population (n=733)	
	Niraparib (n=247)	Placebo (n=126)	Niraparib (n=487)	Placebo (n=246)
Any AE to Treatment Interruption	385 (79.5)		44 (18.0)	
Any AE Leading to Death	2 (0.4)		1 (0.4)	

AE = adverse event; BRCA = breast cancer susceptibility gene; CI = confidence interval; HR = hazard ratio; HRD = homologous recombination deficiency; NE = not estimable; OS = overall survival; PFS = progression-free survival; PFS-2 = progression-free survival on next line of therapy; SAE = serious adverse event; TFST = time-to-first subsequent therapy; TRAE= treatment-related adverse event.

[a] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.

[b] Based on stratified Cox proportional hazards model using randomization stratification factors as above.

[c] Based on stratified log-rank test using randomization stratification factors: administration of neoadjuvant chemotherapy, best response to platinum therapy, and homologous recombination deficiency test result status (for overall population only).

*HR < 1.00 favour the niraparib group.

Data sources: González-Martín 2019,[2] EPAR[4]

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

Ovarian Cancer Canada (OCC) provided input on niraparib as maintenance treatment of adult patients with advanced epithelial ovarian who are in a complete or partial response to first-line platinum-based chemotherapy. Input was gathered from patients and their caregivers through an online survey and interviews conducted between November 26, 2019 to September 21, 2020. Responses were received from a total of 61 women with ovarian cancer from across Canada, which included 52 who completed the online survey and 9 who participated in interviews. The online survey had 5 caregiver survey respondents. Most patient respondents were diagnosed with high-grade serous, stage III-IV ovarian cancer and had experienced at least 1 recurrence and were diagnosed within the last 5 years. Among the women in the sample, no women who completed the online survey and 4 women who were interviewed had direct treatment experience with niraparib.

Patients reported that ovarian cancer highly impacts one's work life, sexual relationship, sleep pattern, well-being, and physical activity. Most respondents had experience with chemotherapy and one-third had experience with a PARP inhibitor that included either olaparib and/or rucaparib. Fatigue, hair loss, neuropathy, bowel problems, and aching joints were treatment-related side effects noted to have a significant impact on one's QoL. Respondents had mixed feelings about the effectiveness of current treatments (excluding niraparib). From the caregiver perspective, work life and sleep patterns were most negatively impacted, and the majority spent one to 3 hours each day completing caregiver tasks. From the patient perspective, most women felt that the possibility of lengthening the time to recurrence, prolonging survival, and improving their QoL were the most important outcomes when considering a new treatment. More women indicated they would require only a mild or moderate improvement in their ovarian cancer to consider treatment with niraparib. Further, OCC noted that most respondents indicated that the potential benefits of niraparib would outweigh the risks, although, no respondents were willing to tolerate bone marrow problems or blood cancer as potential side effects of niraparib and a small percentage of patients were willing to tolerate respiratory problems and high blood pressure. Additionally, the input highlighted that there is a particular need for new treatment options for patients who are BRCAwt. Among the 4 women with niraparib treatment experience, all had experienced at least 1 side effect from treatment. Fatigue, bowel problems, and high blood pressure were the symptoms experienced by most patients (each by 3 patients). Two patients expressed that while none of the side effects were 'acceptable,' most were managed by using additional medications. Overall, 3 of the 4 patients indicated that niraparib had improved their QoL.

Provincial Advisory Group (PAG) Input

Input was obtained from all 9 provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Numerous clinical eligibility criteria
- Criteria for discontinuation of therapy
- Re-treatment with a PARP inhibitor

Economic factors:

- Tests for monitoring safety and effectiveness during maintenance
- Large patient population

Registered Clinician Input

A total of 5 registered clinician inputs were provided for the review of niraparib as maintenance treatment of adult patients with advanced ovarian cancer who are in a complete or partial response to first-line platinum-based chemotherapy: 3 from individual oncologists (1 each from Ontario, British Columbia [BC], and Saskatchewan) and 2 group inputs on behalf of Ontario Health (OH) [Cancer Care Ontario (CCO)] Gynecologic Cancers Drug Advisory Committee (GC DAC) (2 clinicians) and the National BRCA Collaborative through the Society of Gynecologic Oncology of Canada (GOC) (5 clinicians).

Current treatments identified by the clinicians include olaparib for first-line maintenance treatment for patients with a BRCAmut and bevacizumab for high-risk patients (sub-optimally debulked stage III or IV patients) first-line. It was noted that some high-risk patients receive bevacizumab as maintenance therapy; however, it is not universally adopted due to toxicities, resources, and a modest benefit. It was also noted that in Canada, there is no available or consistent treatment for BRCAwt patients; thus, they may be on active surveillance. Most clinicians indicated there is an unmet need in this group of patients.

Overall, the inclusion and exclusion criteria of the pivotal trial were deemed suitable for clinical practice and were noted to capture a broad range of patients except for those who are platinum-resistant, patients with refractory disease (who would be unlikely to benefit), and patients with a worse performance status (only ECOG 0/1 included). For BRCA-mutated patients, clinicians indicated that niraparib has similar efficacy and tolerability (with the exception of thrombocytopenia and hypertension) compared to olaparib. Compared to bevacizumab, clinicians noted niraparib is more tolerated and has a better safety profile and requires less clinic visits as it is an oral drug. Overall, the clinicians considered niraparib to be well tolerated by patients with minimal safety concerns and it demonstrated significant efficacy among different endpoints of the pivotal trial.

All clinicians indicated they would administer niraparib in the patient population included in the pivotal trial (stage III or IV cancers in patients who have a complete or partial response to platinum-based chemotherapy). In addition, both groups suggested niraparib also be used in patients with stage III disease who have undergone primary debulking and have NVRD after surgery. Clinicians stated given there is no validated HRD test currently available, and a modest PFS benefit was demonstrated in the trial for patients without HRD (as assessed by myChoice©) or without a BRCAmut, consideration could be given to administering niraparib to all high-risk, high-grade serous/endometrioid ovarian cancer patients who are not platinum-resistant or refractory. The clinician groups noted that for the BRCA-mutated population, niraparib will be another option (in addition to olaparib if funded). For the high-risk population (bevacizumab candidates in Ontario), niraparib would be an option to replace bevacizumab potentially allowing for bevacizumab to be reserved for platinum-resistant disease. The individual clinicians from Ontario and BC also noted that the pivotal trial demonstrated benefit in all patients; therefore, niraparib should not be limited to any subgroup and they would use niraparib in BRCA-negative patients.

The clinicians expressed different preferences for niraparib over olaparib in BRCA-mutated patients; however, clinicians highlighted the decision would be based on patient tolerance, availability, clinician preference, and the shorter treatment duration of olaparib. Most clinicians preferred niraparib over bevacizumab in patients with a high risk of relapse and would prefer to reserve the use of bevacizumab in the platinum-resistant setting when patients have limited treatment options.

Summary of Supplemental Questions

The following supplemental question was identified during the development of the review protocol as relevant to the CADTH review of niraparib for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy:

- Summary and critical appraisal of a feasibility study of a network meta-analysis (NMA) and unanchored population-adjusted indirect comparison (PAIC) of niraparib, olaparib, and bevacizumab as maintenance therapies in patients with newly diagnosed advanced ovarian cancer

In the absence of direct evidence, the sponsor submitted to CADTH a feasibility assessment for conducting an indirect treatment comparison (ITC) between niraparib and other maintenance therapies for newly diagnosed advanced ovarian cancer. As the submitted feasibility report remains unpublished, a summary of the methods and results of the feasibility assessment were summarized based on published conference sources provided by the sponsor.

Based on the results of each feasibility assessment, the authors concluded that neither a NMA nor an unanchored PAIC could be performed, as in each case, the available evidence did not meet the current guidelines for performing objective comparative clinical effectiveness analyses.[7] The inclusion criteria of the PRIMA trial led to the enrollment of patients with a high risk of disease recurrence, which differed from the study populations of the comparator trials, among other sources of heterogeneity. Due to the identified heterogeneity between the trials available for the indirect comparisons, the comparative analyses were considered inappropriate for use in clinical decision making or reimbursement decisions.

The CADTH Methods Team, in consultation with the CGP, reviewed the 12 eligible RCTs considered in the feasibility assessment and agreed with the authors' conclusion that the trials were not sufficiently comparable for the purpose of conducting an ITC (i.e., NMA or PAIC). The clinical heterogeneity observed across the trials, particularly related to the type of maintenance therapy (e.g., initiated alongside initial chemotherapy versus after chemotherapy), patient populations (e.g., risk of recurrence, imbalances in known treatment effect modifiers) and outcome assessment (e.g., method of assessment, availability of data limiting the analysis to select outcomes) was considered by the CADTH Methods Team and CGP to be a valid concern that would preclude a meaningful analysis and unbiased estimates of relative treatment effect.

See section 7.1 for more information.

Comparison with Other Literature

The CADTH CGP and Methods Team did not identify other relevant literature as 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 from the PRIMA trial of Niraparib as Maintenance Treatment

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from the PRIMA trial[2,4]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>FIGO Stage</td><td>Inclusion criteria in the PRIMA trial required patients to have a disease classified by FIGO criteria:
Patients with stage III or IV inoperable disease, or treated with neoadjuvant chemotherapy and interval debulking surgery (with no constraints on visible residual disease after surgery) were eligible
Patients with stage III disease and visible residual disease ≤ 2 cm after primary debulking surgery and adjuvant/front-line chemotherapy were eligible
Patients with stage IV operable disease (with no constraints on residual disease after surgery) were eligible
<table>
<tr><th rowspan="2">FIGO Stage n (%)</th><th colspan="2">HRD-positive (n=373)</th><th colspan="2">Overall Population (n=733)</th></tr>
<tr><th>Niraparib (n=247)</th><th>Placebo (n=126)</th><th>Niraparib (n=487)</th><th>Placebo (n=246)</th></tr>
<tr><td>International FIGO stage– n (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>III</td><td>161 (65.2)</td><td>78 (61.9)</td><td>318 (65.3)</td><td>158 (64.2)</td></tr>
<tr><td>A</td><td>4 (1.6)</td><td>1 (0.8)</td><td>7 (1.4)</td><td>4 (1.6)</td></tr>
<tr><td>B</td><td>10 (4.0)</td><td>9 (7.1)</td><td>16 (3.3)</td><td>12 (4.9)</td></tr>
<tr><td>C</td><td>140 (56.7)</td><td>67 (53.2)</td><td>285 (58.5)</td><td>138 (56.1)</td></tr>
<tr><td>NS*</td><td>7 (2.8)</td><td>1 (0.8)</td><td>10 (2.1)</td><td>4 (1.6)</td></tr>
<tr><td>IV</td><td>86 (34.8)</td><td>48 (38.1)</td><td>169 (34.7)</td><td>88 (35.8)</td></tr>
</table>
*NS = not specified.

Prespecified subgroup analysis of PFS demonstrated a PFS benefit with niraparib (versus placebo) for the subgroup of patients with stage III disease at initial diagnosis (HR = 0.54; 95% CI, 0.42 to 0.70) but not in the subgroup of patients with stage IV disease at initial diagnosis (HR = 0.79; 95% CI, 0.55 to 1.12). Although these analyses were prespecified, they were not powered to test for differences in treatment effect in these subgroups. Therefore, the results of these analyses should be interpreted as exploratory in nature.</td><td>Do the trial results apply to patients with:
Stage III disease and NVRD after primary debulking surgery?
Stage III/IV disease and > 2 cm of residual disease after surgery and chemotherapy?
Inoperable stage III/IV disease?</td><td>The CGP believes the PRIMA trial results are generalizable to all stage III patients, including those with NVRD after primary debulking surgery and those with > 2 cm of residual disease following primary debulking surgery and chemotherapy.

In the trial, all patients had visible residual disease ≤ 2 cm following primary debulking surgery and chemotherapy; and 26% (n=190) of patients who received neoadjuvant chemotherapy had NVRD after interval debulking surgery. If such patients have a BRCAmut, they may benefit from treatment with niraparib. The size criterion of ≤ 2 cm used in the PRIMA trial is arbitrary, and it is often difficult to measure tumour burden based on a one-dimensional size. Therefore, the CGP recommends treatment with niraparib regardless of residual disease if patients demonstrate a complete or partial radiologic response to surgery and chemotherapy.

Similarly, the CGP also recommends treatment with niraparib in patients with inoperable stage III/IV disease if patients demonstrate a complete or partial radiologic response to chemotherapy as these patients were included in the PRIMA trial.</td></tr>
<tr><td>Intervention</td><td>Prior treatment</td><td>Patients were excluded from the PRIMA trial if they were to receive bevacizumab as maintenance treatment. If patients received</td><td>Do the results of the trial apply to patients</td><td>The CGP believes it is acceptable for patients to switch to niraparib</td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>bevacizumab as part of first-line chemotherapy and did not receive bevacizumab as maintenance therapy, they were eligible as long as the last dose of bevacizumab was ≥28 days prior to signing the informed consent.

A small proportion of patients in the PRIMA trial had prior therapy with bevacizumab:
<table>
<tr><td rowspan="2">Prior Bevacizumab</td><td colspan="2">HRD-positive (n=373)</td><td colspan="2">Overall Population (n=733)</td></tr>
<tr><td>Niraparib (n=247)</td><td>Placebo (n=126)</td><td>Niraparib (n=487)</td><td>Placebo (n=246)</td></tr>
<tr><td>n (%)</td><td>5 (2.0)</td><td>0</td><td>6 (1.2)</td><td>1 (0.4)</td></tr>
</table>
</td>
<td>who have received prior treatment with bevacizumab combined with first-line chemotherapy or as maintenance?</td>
<td>maintenance therapy after they have received bevacizumab as part of initial chemotherapy who otherwise meet the eligibility criteria of the PRIMA trial.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients were excluded from the trial if they had prior treatment with a known PARP inhibitor.</td>
<td>Do the results of the trial apply to patients who have received prior treatment with a known PARP inhibitor?</td>
<td>A patient is unlikely to have had prior treatment with a PARP inhibitor for ovarian cancer in this setting, as this indication is for patients with an initial diagnosis of ovarian cancer. However, there may be cases where a patient has received a PARP inhibitor for another cancer previously (e.g., for breast cancer). In this case, there is no evidence to guide treatment; but the CGP believes that a PARP inhibitor could be considered as maintenance therapy for ovarian cancer after initial surgery and chemotherapy on an individual basis.</td>
</tr>
</table>

BRCA = breast cancer susceptibility gene; BRCAmut = BRCA mutation; BRCAwt = BRCA wild-type; CA-125 = cancer antigen 125; CGP = Clinical Guidance Panel; CR = complete response; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; FIGO =International Federation of Gynecology and Obstetrics; HRD = homologous recombination deficiency; NVRD – no visible residual disease; PARP: poly(adenosine diphosphate [ADP]–ribose) polymerase; PR = partial response.

1.2.4 Interpretation

The use of maintenance niraparib (a PARP inhibitor) in patients with newly diagnosed ovarian cancer treated with surgery and who have demonstrated a response to platinum-based chemotherapy was evaluated in the PRIMA trial.[2] PRIMA is an ongoing, phase III, double-blind, placebo-controlled trial that included female patients 18 years of age and older with newly diagnosed, histologically confirmed, advanced cancer of the ovary, peritoneum, or fallopian tube with high-grade serous or endometrioid features that were classified as stage III or IV according to FIGO criteria. Eligible patients must have received 6 to 9 cycles of first-line platinum-based chemotherapy that resulted in an investigator-assessed CR or PR after 3 or more cycles and had 2 or more post-operative cycles of platinum-based therapy following interval debulking surgery. If stage III, patients must have had a primary debulking surgery with visible residual disease, or an interval debulking surgery (after neoadjuvant chemotherapy) with or without visible residual disease; and all stage IV patients who had interval debulking were eligible. All enrolled patients had to have residual disease measuring less than or equal to 2 cm after completion of chemotherapy. Patients were randomized in a 2:1 ratio to receive niraparib or placebo, with the intent to continue maintenance treatment until unacceptable toxicity, disease progression, or until 3 years of treatment, whichever occurred first. The primary endpoint of the trial was PFS assessed by BICR, with secondary endpoints that included OS, TFST, PFS2, time to CA-125 progression, safety, and PROs. Other exploratory endpoints were also measured.

The trial analyzed outcomes in 2 prespecified efficacy populations, patients who were HRD-positive and the overall trial population, based on hierarchical testing and after a median follow-up time of 13.9 and 13.8 months, respectively. At the primary efficacy analysis data cut-off date, the median PFS in the HRD-positive population was 21.9 months in the niraparib group versus 10.4 months in the placebo group (HR = 0.43; 95% CI, 0.31 to 0.59; p<0.001).[2] In the overall population, the corresponding median PFS was 13.8 months versus 8.2 months (HR = 0.62; 95% CI, 0.50-0.76; p<0.001), respectively[2]. These results correspond to statistically significant absolute improvements in median PFS with niraparib maintenance of 11.5 months in the HRD-positive population and 5.6 months in the overall population. The trial also showed longer TFST with niraparib compared to placebo in both patient populations, and no differences in OS and PFS2 between the treatment groups; however, the data for these endpoints were considered immature at the time of the primary efficacy analysis. The results of prespecified subgroup analyses of PFS indicated that patients with a BRCAmut (n=223), as well as those who were BRCAwt (n=473), regardless of HRD status (HRD-positive: n=373; HRD-negative: n=249), all benefited from niraparib maintenance when compared to placebo.

PROs were assessed using multiple instruments in both the HRD-positive and overall patient populations and showed similar results. For most measures, the available data did not suggest any between-group differences in symptoms or QoL among patients receiving niraparib when compared to placebo, except for some worse gastrointestinal symptoms (i.e., constipation, nausea and vomiting, and appetite loss) in the niraparib group at specific timepoints. However, a time-to-worsening analysis, which incorporates data at all timepoints, showed no difference between the treatment groups in the-time-to-worsening of gastrointestinal symptoms based on the MCID for the FOSI and the EORTC-QLQ-OV28.

The AE profile of niraparib is primarily comprised of hematologic toxicity, fatigue, and hypertension. The most common TEAEs of any grade that occurred in the niraparib group (versus the placebo group) were anemia (63.4% versus 17.6%), nausea (57.4% versus 27.5%), thrombocytopenia (45.9% versus 3.7%), constipation (39.0% versus 18.9%), fatigue (34.7% versus 29.5%), platelet count decreased (27.5% versus 1.2%), and neutropenia (26.4% versus 6.6%). The most common grade 3 or 4 TEAEs in the niraparib group (versus the placebo group) were anemia (31.0% versus 1.6%), thrombocytopenia (28.7% versus 0.4%), platelet count decreased (13.0% versus 0%), and neutropenia (12.8% versus 1.2%). The incidence of MDS was similar in both treatment groups, with 1 patient (0.3%) who had received a fixed starting dose of niraparib experiencing MDS (grade 3 or higher), and no patients who received an individualized starting dose of niraparib or in the placebo group experiencing this AE. The most common myelosuppression TEAEs in the niraparib group (versus the placebo group) were thrombocytopenia (66.3% versus 4.9%), anemia (64.3% versus 17.6%), leukopenia (49.8% versus 13.1%), and neutropenia (42.4% versus 7.8%). Thrombocytopenia was the most common myelosuppression TEAE in the niraparib group that led to a dose interruption (55.6%), dose reduction (47.3%), or a dose discontinuation (4.3%). Overall, 18.0% of patients in the niraparib group and 7.0% of patients in the placebo group experienced treatment-emergent hypertension events and none of these events led to dose discontinuation.

In the overall population, 40.9% and 51.2% of patients received a post-progression anti-cancer therapy in the niraparib and placebo groups, respectively. Platinum-based chemotherapy (including carboplatin, cisplatin, oxaliplatin) was the most common regimen

received by patients in each treatment group, followed by doxorubicin (including adriamycin, liposomal doxorubicin). Of note, 1.4% and 4.5% of patients in the niraparib and placebo groups, respectively, received a PARP inhibitor post-progression.

Following the posting of the pERC Initial Recommendation, the CGP reviewed and discussed the feedback received from all stakeholder groups. While the patient advocacy group (OCC), the PAG, and the sponsor all agreed with pERC's Initial Recommendation to conditionally reimburse niraparib and supported early conversion to a Final Recommendation, the registered clinician group (CCO GC DAC) agreed in part with the Initial Recommendation and did not support early conversion. The registered clinician group cited they had concerns related to the eligible patient population and disagreed with statements that HRD testing has not yet been clinically validated. Specifically, the CCO GC DAC expressed concern with offering niraparib to patients who are HRP/BRCAwt considering the PFS improvement of 2.7 months that was observed for this patient subgroup in the PRIMA trial, which they did not consider to be clinically meaningful, as well as the additional toxicities and surveillance that is required with niraparib. The CCO GC DAC indicated that a validated HRD test would be essential for clinicians to identify the patients who would derive the most benefit from niraparib (i.e., HRD-positive and BRCAmut patients), and disagreed with pERC and the CGP that the Myriad myChoice test is not yet validated. The CCO GC DAC stated that the PRIMA trial provides the highest level of validation of a predictive biomarker, as the trial was powered to assess a difference in outcome for the HRD subgroup, and the results confirm the use of the test for predicting response to niraparib. The CCO GC DAC believe a HRD test is necessary in order to offer niraparib to patients who are BRCA-wt.

The CGP agreed with the CCO GC DAC that PFS benefits are greater in patients who are BRCAmut and HRD when compared with patients who are BRCAwt and HRP. However, the PFS HRs for the BRCAwt (HR = 0.69; 95% CI, 0.54 to 0.88) and the HRP (HR = 0.68; 95% CI, 0.49 to 0.94) patient subgroups were considered statistically significant; and in the HRP patient group represent an improvement in PFS of 2.7 months. The CGP felt that based on the patient advocacy input that was received for this submission, patients value the opportunity to explore the option of niraparib maintenance therapy despite the toxicity. With clinician experience and dose adjustments, the CGP felt that toxicity and quality of life would still be acceptable on niraparib. The CGP could not conclude that patients would feel that the PFS improvement of 2.7 months would be clinically non-significant.

With respect to HRD testing, part of the challenge with the Myriad myChoice test is its proprietary nature. It is not well understood which specific genes other than BRCA play a role in inducing a response to niraparib, and therefore there will be significant difficulty in validating the HRD score outside of the commercial Myriad myChoice test. Further, the cut-off HRD score of 42 is also felt to be arbitrary. Lastly, Myriad myChoice is not widely used outside of making a decision for offering niraparib in ovarian cancer and has not been approved for use with other PARP inhibitors commercially available in Canada or other tumour types; thus, more data are needed to understand its molecular significance. In the meantime, the PRIMA trial met its primary endpoint and demonstrated a PFS benefit in the HRD-positive and the overall trial populations, and therefore the CGP believes that all patients included in the primary endpoint analysis should be considered for treatment.

The CGP agreed that the decision to offer niraparib maintenance therapy in patients who are HRP/BRCAwt should be balanced considering the more modest PFS benefit observed in these groups of patients and potential toxicities. At the same time, the CGP did not agree that patients with HRP/BRCAwt should be excluded from being offered the option of niraparib altogether; rather a careful discussion of benefits versus risks should occur with patients to make an informed decision on treatment.

1.3 Conclusions

The CGP concluded that there is an overall net clinical benefit to niraparib as maintenance treatment in adult patients with newly diagnosed, advanced ovarian, primary peritoneal, and/or fallopian tube cancer who are in complete or partial response to platinum-based chemotherapy. This conclusion was based on the results of one high-quality randomized phase III trial, PRIMA, which demonstrated that niraparib maintenance provides a statistically significant and clinically meaningful prolongation in PFS when compared to placebo, with an acceptable toxicity profile and maintenance of QoL.

In making this conclusion, the CGP considered the following factors:

- Although the PRIMA trial was conducted in patients who had a high risk of recurrence, the CGP believes that the results from the trial are generalizable to all patients with stage III and IV ovarian cancer who demonstrate a response to initial chemotherapy and otherwise meet the trial eligibility criteria.
- The PFS benefit was observed in all trial patients who received niraparib maintenance regardless of BRCA and HRD status. While all patient subgroups examined showed clinically meaningful improvements in PFS, the magnitude of PFS benefit was greater in patients with a BRCAmut and HRD-positive tumours.
- Niraparib is felt to fulfil an unmet need for maintenance treatment in patients with BRCAwt disease, as bevacizumab is less frequently used in the first-line setting, and otherwise there is no other accepted or available maintenance therapy for this group of patients.
- Most patients in the PRIMA trial had high grade tumours of serous or endometrioid histology, and the CGP recommends niraparib treatment in this patient population. However, if a patient has a BRCAmut, all other high-grade histologies may benefit from niraparib, although not included in the trial, and could be considered for maintenance if otherwise eligible.
- HRD testing, while used in the PRIMA trial, has been not clinically validated and therefore is not commonly used in Canadian practice. Therefore, HRD alone should not be used as a sole predictive biomarker to determine treatment eligibility for niraparib maintenance.
- Based on the data from the PRIMA trial, many patients will likely require dose interruption or reduction of niraparib for tolerability. These dose modifications did not impact treatment exposure or efficacy of treatment. The CGP agreed that a consideration to a lower starting dose of 200 mg once daily is reasonable and especially recommended for patients who are at high risk of adverse outcomes and have a weight less than 77 kg and/or a baseline platelet count less than 150 000 µL. While bone marrow suppression is the most notable safety concern with niraparib, based on the PRIMA trial data, the rate of MDS was not higher than in the placebo group and hematologic toxicity did not appear to impact QoL outcomes.

A number of questions were raised by the PAG if niraparib were to be recommended for reimbursement, specifically with respect to the eligible patient population, implementation factors, sequencing of available treatments, and companion diagnostic testing. The CGP's responses to these questions are summarized in Table 3. For the CGP's assessment of generalizability (external validity of the PRIMA trial evidence related to specific factors), refer to Table 2 in Section 1 of this report.

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

PAG Implementation Questions	CGP Response
Currently Funded Treatments	
The standard of care for patients newly diagnosed with advanced ovarian cancer is cytoreductive surgery and platinum-based chemotherapy. For patients with a high risk of relapse, bevacizumab may be added to chemotherapy; however, it is infrequently prescribed in Canada and does not have an approved indication in this setting. Following complete or partial response to upfront chemotherapy, patients can be on active surveillance or continuation maintenance with bevacizumab (if used in conjunction with chemotherapy). Olaparib is under provincial consideration for this indication but only in patients who are positive for a BRCAmut. PAG noted that the PRIMA trial compared niraparib to placebo. PAG seeks additional comparison of niraparib with bevacizumab and with olaparib for BRCAmut tumours.	The sponsor did not provide an ITC of niraparib to relevant comparators (i.e., olaparib or bevacizumab with or without olaparib) based on the results and conclusions of a feasibility assessment[7] they commissioned that indicated an ITC would be inappropriate and lead to biased estimates of comparative efficacy primarily owing to significant clinical heterogeneity in the patient populations of trials evaluating maintenance therapy following first-line chemotherapy. The CGP agreed with the conclusions of the feasibility assessment. In the absence of direct head-to-head comparisons of available maintenance therapies in this setting, the CGP would consider the following treatment choices as maintenance treatment in patients with stage III/IV ovarian cancer and a BRCAmut: • BRCA-mutated, stage III ovarian cancer with optimal or suboptimal primary debulking: olaparib • BRCA-mutated, stage III ovarian cancer with interval debulking or suboptimal primary debulking surgery, and stage IV ovarian cancer: niraparib or olaparib Niraparib was shown in the PRIMA trial to be beneficial in patients with an increased risk of recurrence and a BRCAmut; therefore, if both olaparib and niraparib are funded, physicians and patients will have a choice between the 2 PARP inhibitors. It is unlikely bevacizumab will be used in patients with a BRCAmut given that the benefit of adding bevacizumab to a PARP inhibitor as a maintenance therapy in patients with a BRCAmut is unknown compared to a PARP inhibitor alone. The PAOLA-1 trial,[8] which investigated the addition of adding bevacizumab to olaparib, did not include a PARP inhibitor only arm. Of note, bevacizumab maintenance is used in a limited capacity in the first-line setting and is usually used in patients with inoperable stage III or IV ovarian cancer, or patients who have suboptimal debulking.
Eligible Patient Population	
The reimbursement request of niraparib is as maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy. In view of the characteristics of the patient population and exclusion criteria in the PRIMA trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with niraparib: • ECOG performance score ≥2.	The CGP recommends that niraparib be considered in patients with an ECOG PS of 0-2 with the expectation that most patients with an ECOG PS of 2 will likely improve in functional status

PAG Implementation Questions	CGP Response
	after first-line chemotherapy as they recover from side effects of their treatment, and therefore may benefit from maintenance therapy with niraparib. Patients who have an ECOG PS of 3-4 who do not recover their functional status within 8 to 12 weeks after chemotherapy will likely not benefit from treatment with niraparib.
• Patients who could not receive first-line platinum chemotherapy and received an alternative chemotherapy regimen instead.	The CGP expects that patients receiving an alternative chemotherapy regimen instead of platinum-based chemotherapy would be a rare and unlikely scenario. However, as long as patients in this case have benefited from surgery and chemotherapy (i.e., PR or CR) according to the eligibility criteria of PRIMA trial, the CGP believes these patients should be given the opportunity of niraparib maintenance therapy.
• Patients who have not completed at least 6 cycles of platinum-based or alternate chemotherapy.	The CGP recommends that patients complete all treatment cycles per the PRIMA trial protocol (i.e., 6 to 9), if possible, to achieve the best possible outcome. For patients who can only complete less cycles for various reasons (i.e., allergy or other intolerance) but have demonstrated a response to treatment, it is reasonable to consider niraparib maintenance on an individualized basis.
• Patient with mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer.	There is no evidence to suggest that patients with histologies other than serous or endometroid will benefit from niraparib maintenance, and therefore the CGP does not recommend niraparib maintenance treatment in other histologies. The one exception to this would be for patients with a BRCAmut, in which case patients would be expected to benefit from niraparib regardless of histology. The CGP recommends that all patients with non-mucinous histology get BRCA testing.
• Patient having undergone more than 2 debulking surgeries.	As long as patients otherwise meet the eligibility criteria of the PRIMA trial, the CGP agreed patients who have undergone more than 2 debulking surgeries in the first-line setting may benefit from niraparib and therefore should be eligible for maintenance treatment.
• Patients with intolerance of olaparib.	As long as patients otherwise meet the eligibility criteria of the PRIMA trial, patients with intolerance to olaparib (whose disease has not progressed) may benefit from niraparib.
• PAG seeks an estimate of the maximum time between completion of chemotherapy and commencement of niraparib.	Some patients may require a break from treatment in order to recover from the side effects of chemotherapy. As long as a patient can initiate maintenance treatment within 12 weeks of completing platinum-based chemotherapy (and have not progressed), the CGP believes that these patients can benefit from niraparib.
Implementation Factors	
PAG seeks clarity on the role of CA-125 testing prior to initiation of niraparib, as patients in the trial had to have either CA-125 in the normal range or a CA-125 decrease by more than 90% during their frontline therapy that is stable for at least 7 days (i.e., no increase >15%) prior to starting niraparib.	CA-125 is a surrogate marker for response to treatment, but its rise and fall does not necessarily correspond to the degree of radiologic response such that it can be used to rule out responsiveness of the subsequent treatment. The CA-125 cut offs used in the PRIMA trial were arbitrary. The CGP agreed that in clinical practice, radiologic response is key to predicting efficacy of maintenance therapy. Therefore, as long as patients have a radiologic response to front-line treatment and otherwise meet all other eligibility criteria of the PRIMA trial, the CGP expects these patients will benefit from niraparib maintenance.

PAG Implementation Questions	CGP Response
PAG identified additional eligibility criteria in the study, notably a partial or complete tumour response and no measurable disease of more than 2 cm at the time of study entry. PAG would like to know if all these criteria need to be met for eligibility to niraparib reimbursement.	The CGP believe that a partial or complete tumour response to chemotherapy is important to achieve prior to niraparib maintenance treatment. However, the size criterion of less than 2cm is arbitrary, and it is often difficult to measure tumour burden based on a one-dimensional size. The CGP suggests that as long as a patient had a partial or complete tumour response to chemotherapy according to RECIST criteria and otherwise meets the other eligibility criteria, that niraparib be offered as maintenance therapy.
PAG seeks guidance on potentially stopping niraparib to manage toxicity and then re-starting the therapy.	The CGP recommends a temporary stop of niraparib in cases of significant toxicity followed by re-starting the therapy once the toxicity has resolved or becomes manageable. The CGP recommends appropriate dose adjustment after reinitiating niraparib.
PAG seeks advice on the frequency and type of monitoring during maintenance therapy (e.g., CA-125 testing, CT scans).	The CGP recommends regular bloodwork (i.e., weekly for the first month of therapy, every 4 weeks for the next 11 months, and then periodically thereafter as per the Health Canada product monograph),[1] testing for CA-125 every 3 to 4 months, and routine CT scan at least annually if CA-125 remains stable to verify continued response.
Sequencing and Priority of Treatment	
PAG is seeking to confirm the place in therapy and sequencing with niraparib including the scenarios below:	
• Circumstances where niraparib would be preferable to olaparib should both options be available.	Niraparib would be preferable to olaparib in patients who are BRCAwt, and in patients who are intolerant to olaparib.
• Options after failure of niraparib including potential retreatment with a PARP inhibitor for maintenance in the relapsed/refractory setting.	Currently, there is no evidence from phase III trials to suggest that after failure of niraparib in the first-line setting, retreatment with a PARP-inhibitor for maintenance in the relapse/refractory setting is associated with a survival benefit. Therefore, the CGP does not currently recommend retreatment with a PARP inhibitor in the relapsed/refractory setting. Retreatment with a PARP inhibitor is currently being evaluated in a randomized trial.[9]
• Switching between niraparib and olaparib (if BRCA-mutated) or vice versa in cases of unacceptable toxicity.	The CGP believe that switching between niraparib and olaparib in patients with a BRCAmut in cases of unacceptable toxicity is acceptable practice.
• Retreatment with niraparib following platinum chemotherapy in patients who discontinued maintenance treatment for reasons other than progression.	The CGP feels that retreatment with niraparib in patients who discontinued maintenance treatment for reasons (i.e., intolerance, treatment break) other than progression is acceptable. For patients who complete niraparib maintenance treatment (i.e., 3 years) and then experience disease progression, there currently is no evidence to inform whether retreatment with niraparib (following a response to chemotherapy) would be beneficial.
Companion Diagnostic Testing	
PAG did not identify a companion diagnostic test required for eligibility to niraparib. However, BRCAmut results may help inform choice of therapy between niraparib and olaparib. PAG is seeking confirmation if BRCA and HRD testing are required.	BRCA testing is recommended and reimbursed in most provinces; and testing for both a germline and somatic BRCAmut is recommended. The PRIMA trial used the myChoice® Myriad HRD test to determine patients' HRD status, which is a commercially available proprietary product that has demonstrated a high

PAG Implementation Questions	CGP Response
	correlation between breast cancer samples that had a BRCA defect and HRD scores based on biomarkers that include the HRD-loss of heterozygosity score, HRD-telomeric allelic imbalance score, and HRD-large-scale state transition score. Although BRCA defect and HRD score are correlated, it is currently unclear which genomic changes in HRD are linked with response to PARP inhibitors. Therefore, at this time, until further studies are performed, the CGP does not recommend using routine HRD testing alone for patient selection for niraparib.

BRCA = breast cancer susceptibility gene; BRCAmut = BRCA mutation; BRCAwt = BRCA wild-type; CA-125 = cancer antigen 125; CGP = Clinical Guidance Panel; CR = complete response; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; FIGO = International Federation of Gynecology and Obstetrics; HRD = homologous recombination deficiency; ITC = indirect treatment comparison; PARP: poly(adenosine diphosphate [ADP]–ribose) polymerase; PR = partial response.

2 Background Clinical Information

2.1 Description of the Condition

Epithelial ovarian cancer comprises a heterogeneous group of epithelial malignancies arising from ovaries, fallopian tubes or peritoneum. Ovarian cancer is the eighth leading cause of all deaths in Canadian women and the fifth leading cause of cancer related death. The Canadian Cancer Society estimated that, in 2020, 3,100 women in Canada will have developed ovarian cancer, with 1,950 deaths due to this disease.[10] High-grade serous epithelial ovarian cancer is the most commonly encountered histology, representing 60% of all epithelial ovarian cancers. Unfortunately, because of delayed presentation and diagnosis, almost 70% of women with ovarian cancer are diagnosed in the later stages of disease. Advanced ovarian cancer (stage III-IV) is associated with a high rate of recurrence and poor outcomes. The median time-to-recurrence is approximately 18 months, and median OS is typically less than 4 years. Given the high rate of recurrence, maintenance strategies have been investigated in order to potentially delay or prevent recurrences and give the longest absolute increase in PFS, which is an outcome highly valued by patients. Prolonged use of cytotoxic agents (i.e., alkylators/platinum agents/taxanes) has not shown to improve OS. Improvements have been seen in PFS, but at a cost of increased toxicities. Therefore, most patients with newly diagnosed advanced ovarian cancer go on regular follow up after the completion of chemotherapy, and there is a significant burden of disease morbidity and mortality due to progression of cancer upon recurrence. Consequently, there is a significant unmet need for additional treatment options for most patients with advanced ovarian cancer.

It is now well recognized that 15% to 20% of patients with ovarian cancer have either a pathogenic germline (inherited) or somatic (limited to the tumour) mutation in BRCA1 or BRCA2 irrespective of family history.[11-13] BRCA1 and BRCA2 genes are human tumour suppressor genes and a key component in homologous recombination, a repair pathway of double-stranded DNA breaks.[14-16] 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 and inhibition of PARP can confer synthetic lethality in cells with HRD.[17] It is estimated that approximately 50% of high grade serous ovarian carcinomas (the most common but lethal ovarian cancer) have aberrations in homologous recombination repair pathways.[18] Recently, PARP inhibitors have emerged as an effective therapeutic strategy in ovarian cancer, particularly for those patients with germline or somatic pathogenic BRCAmut. Multiple phase II and III trials have demonstrated a significantly prolonged PFS in patients with recurrent platinum-sensitive ovarian cancer and presence of germline or somatic BRCAmut, as well as in patients with or without HRD.[19-23]

2.2 Accepted Clinical Practice

In patients with high-grade advanced ovarian cancer (stage III-IV), patients are assessed for cytoreductive surgery. The volume of residual disease remaining after cytoreductive surgery correlates inversely with survival – in other words, the higher the volume of residual disease after surgery, the worse the chance of survival and prognosis are.[24-30] Even in patients with optimal debulking, defined as less than 1cm in residual disease size, any remaining visible disease correlates with worsening survival.[27] Thus, the goal of surgery is to remove all macroscopic disease (i.e., complete cytoreduction). This may be possible to achieve upfront, or if it is predicted that the complete cytoreduction is not possible at diagnosis, patients are usually referred for upfront preoperative (neoadjuvant) chemotherapy prior to being considered for interval cytoreduction.

After surgery and chemotherapy treatments are completed, patients are observed for recurrence through active surveillance. However, most patients with initially advanced ovarian cancer eventually experience recurrence. Five-year survival rates vary between 45% in stage IIIA disease to less than 20% in stage IV disease.[31] Although systemic and locoregional treatments options exist for recurrent disease, the cancer is considered incurable at the time of recurrence and prognosis is more guarded.

Bevacizumab with initial chemotherapy followed by maintenance bevacizumab has been examined in large phase III trials. GOG 218 was a randomized, placebo-controlled trial that enrolled 1873 patients with stage III or IV epithelial ovarian cancer after surgical cytoreduction.[32] Patients were randomized to standard chemotherapy, bevacizumab (15 mg/kg) concurrently with standard chemotherapy, or bevacizumab concurrently with standard chemotherapy and continuing as monotherapy maintenance until month 15. Standard chemotherapy consisted of 6 cycles of IV paclitaxel and carboplatin. Due to progressive disease, only 19% of all trial

patients completed planned treatment. At a median follow-up of 17.4 months, compared with standard chemotherapy, there was no difference in median PFS with the addition of concurrent bevacizumab (11.2 months versus 10.3 months). However, median PFS was longer among patients receiving bevacizumab concurrently and after chemotherapy (14.1 months; HR = 0.72; 95% CI, 0.63 to 0.82; p<0.001). At a median follow-up of 102.9 months, there was no improvement in OS between the treatment groups receiving the drug; the median OS across all treatment groups ranged from 41.1 to 43.4 months.[33] Concurrent maintenance treatment with bevacizumab improved PFS and OS specifically in patients with ascites and with stage IV disease (median OS: 42.8 months versus 32.6 months; HR = 0.75; 95% CI, 0.59 to 0.95), but not in women with stage III disease.[33,34]

In the ICON7 trial,[35] 1528 patients with high-risk, early-stage (I or IIA clear cell or grade 3) or advanced epithelial ovarian cancer were randomly assigned to standard IV chemotherapy for 6 cycles with or without bevacizumab (7.5 mg/kg) during chemotherapy and then as maintenance treatment for 12 additional cycles.[35,36] Over 90% of trial patients completed assigned treatment. Due to violation of proportional hazards, results for PFS were reported based on the difference in restricted mean values. At 36 months of follow-up, patients who received bevacizumab had a better ORR (67% versus 48%) and improved median PFS (21.8 months versus 20.3 months; p=0.004), and there was no difference in OS between the treatment groups. At updated analyses performed based on 42 months of follow-up, similar median PFS estimates were observed (24.1 months versus 22.4 months, respectively; p=0.04) and there remained no difference in OS between the treatment groups. For women at high risk of progression (stage III with greater than 1 cm of residual disease after surgery, inoperable stage III, or stage IV), bevacizumab was associated with an improvement in median PFS (18.1 months versus 14.5 months, respectively) and median OS (36.6 months versus 28.8 months) based on exploratory analysis. The final analysis of OS, based on 48.9 months of follow-up, showed no OS benefit between the treatment groups, but again showed an OS benefit among the subgroup of patients at high risk of progression (restricted mean OS: 39·3 months versus 34·5 months). It should be noted that since the analyses in the subgroup of patients at high risk of progression were exploratory, they require prospective validation.

In summary, bevacizumab is thought to provide clinical benefit, and is used in Canadian practice despite no approved indication, for patients with stage IV disease or inoperable or suboptimally debulked stage III, high grade ovarian cancer. Although there is some evidence suggesting that BRCAmut patients don't respond well to bevacizumab, there currently are no biomarkers that can reliably predict response to bevacizumab.[37]

Olaparib has recently been reimbursed in the first-line setting based on data from the SOLO-I phase III trial.[38] This trial enrolled 391 patients with advanced serous or endometrioid ovarian cancer and a BRCAmut who had a complete or partial response to front line, platinum-based chemotherapy and were randomly assigned to maintenance with olaparib or placebo. At a median follow-up of 41 months, olaparib improved PFS compared with placebo (60% versus 27%; HR = 0.30; 95% CI, 0.23 to 0.41). OS at 3 years did not reach maturity but was 84% in the olaparib group and 80% in the placebo group (HR = 0.95; 95% CI, 0.60 to 1.53). In summary, olaparib maintenance treatment after initial management of advanced ovarian cancer was shown to be beneficial in patients with a BRCAmut.

Another phase III trial, PAOLA-1, enrolled patients with advanced high-grade serous or endometrioid cancers who responded to chemotherapy plus bevacizumab.[8] Patients were randomized to maintenance bevacizumab with or without olaparib. Among the subgroup of patients with a BRCAmut, the combination of olaparib plus bevacizumab improved median PFS compared to bevacizumab alone (37.2 months versus 21.7 months; HR = 0.31; 95% CI, 0.20 to 0.47). However, it is unclear whether bevacizumab improved efficacy relative to olaparib alone, a question the PAOLA-1 trial was not designed to answer.

Niraparib, was recently issued a positive reimbursement recommendation by pERC[39] (provincial reimbursement is pending) as maintenance treatment in patients with relapsed or recurrent ovarian cancer based on the results of the NOVA trial.[40] NOVA was a double-blind, placebo-controlled, phase III trial that enrolled 553 patients with predominantly high-grade serous, platinum-sensitive, recurrent ovarian cancer. Patients were randomized to either niraparib maintenance (300 mg once daily oral dose) or matched placebo. The trial categorized patients based on the presence or absence of a gBRCAmut and the type of non-gBRCAmut (i.e., HRD-positive patients, and overall non-gBRCA patients). After a median follow-up of 16.9 months, the trial demonstrated an improvement in PFS with niraparib compared to placebo in all 3 patient populations (p<0.001), with the largest treatment effect observed in patients who had a gBRCAmut (median PFS of 21.0 months versus. 5.5 months; HR = 0.27; 95% CI, 0.17 to 0.41), followed by HRD-positive patients in the non-gBRCAmut cohort (median PFS of 12.9 months versus 3.8 months; HR = 0.38; 95% CI,

0.24 to 0.59), and then the overall non-gBRCAmut cohort (median PFS 9.3 months versus 3.9 months; HR = 0.45; 95% CI, 0.34 to 0.61). Prespecified exploratory analyses of PFS showed a consistent PFS benefit for subgroups of patients in the non-gBRCA patient cohort (HRD-positive and sBRCAmut, HRD-positive and BRCAwt, and HRD-negative). All secondary efficacy outcomes (TFST, chemotherapy-free interval, and PFS-2), except for OS, favoured treatment with niraparib. The OS data were considered immature at the time of the primary efficacy analysis. The most common grade 3 or 4 AEs that were reported in the niraparib group were thrombocytopenia, anemia, and neutropenia. Most patients in the niraparib group required dose modification due to AEs; however, these dose modifications did not affect treatment efficacy.

3 Summary of Patient Advocacy Group Input

Ovarian Cancer Canada (OCC) provided input on niraparib as maintenance treatment of adult patients with advanced epithelial ovarian cancer who are in a complete or partial response to first-line platinum-based chemotherapy. Input was gathered from an online survey and semi-structured interviews (face-to-face, one-on-one via Zoom); there were 52 respondents for the online survey and 9 interviewees. The online survey was conducted in English and French and promoted to those living with ovarian cancer and their caregivers from November 26, 2019 to January 15, 2020. The inclusion criteria for survey respondents were as follows: 1) diagnosis with epithelial ovarian, fallopian tube, or primary peritoneal cancer; 2) treatment with platinum-based chemotherapy; 3) experience of at least 1 recurrence; 4) recurrence occurring at least 6 months after the end of chemotherapy and; 5) experience or no experience with niraparib. The survey was promoted through OCC's database, social media sites, and Facebook groups organized for ovarian cancer survivors and their caregivers. Ovarian cancer patient organizations in the UK, US, and Europe were contacted to promote the survey in an effort to reach women who had taken niraparib; however, there were no women with niraparib experience who completed the online survey. Interviews were conducted from August 24 to September 21 of 2020. Recruitment involved direct outreach from OCC's Regional Directors and re-contacting women who had expressed interest in participating in research studies. Four women with direct treatment experience with niraparib were interviewed. Among the 61 respondents (online survey and interviews), there was representation of all provinces/territories except for Prince Edward Island, Northwest Territories, Nunavut, and Yukon. Ontario (46%), BC (21%), and Quebec (10%) were most commonly reported as locations of ovarian cancer diagnosis and/or treatment. The majority of respondents were diagnosed with high-grade serous ovarian cancer (70%) with stage III-IV disease (91%) and had experienced at least 1 recurrence (88%). Diagnosis with stage IV and I-II ovarian cancer was reported by 12 and 5 patients, respectively. Three patients had low-grade serous ovarian cancer, 2 patients reported a clear cell subtype, and 2 patients reported an endometroid subtype. Forty-five respondents were diagnosed within the last 5 years and the median age of respondents was 57 years (range: 34-81). Of note, the online survey had 5 caregiver survey respondents.

Patients reported that ovarian cancer highly impacts one's work life, sexual relationship, sleep pattern, well-being, and physical activity. Majority of respondents had experience with chemotherapy (93%) and one-third with a PARP inhibitor; namely, 11 women had been treated with olaparib and/or rucaparib. Fatigue, hair loss, neuropathy, bowel problems, and aching joints were treatment-related side effects noted to have a high impact on one's QoL. There were mixed feelings about the effectiveness of current treatments. From the caregiver perspective, work life and sleep patterns were most negatively impacted, and the majority spent 1 to 3 hours each day completing caregiver tasks. OCC noted that most respondents felt that the potential benefits of niraparib would outweigh the risks. The majority of women (>90%) felt that the possibility of lengthening the time to recurrence, prolonging survival, and improving their QoL were factors of high importance and more woman indicated requiring only a mild or moderate improvement in their ovarian cancer to consider treatment with niraparib. However, no respondents were willing to tolerate bone marrow problems or blood cancer as potential side effects of niraparib, and a small percentage of patients were willing to tolerate respiratory problems (12%) and high blood pressure (21%). Accordingly, patients value treatments that improve QoL and prolong survival and/or lengthen the time to recurrence with the possibility of a cure. In addition, there is a particular need for new treatment options for the BRCA-negative population. Among the 4 women with niraparib treatment experience; all had experienced at least 1 side effect: fatigue, bowel problems, and high blood pressure were most commonly experienced (each by 3 patients). Two patients expressed that while none of the side effects were 'acceptable,' most were managed through additional medications. Overall, 3 of the 4 patients indicated that niraparib had improved their QoL.

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

OCC noted that the impact of ovarian cancer on women living with this disease cannot be overstated. When asked to rate how their diagnosis had impacted different areas of their life, all areas were affected in some way, with the highest impact (score of 4-5) on the patients' work life (59.6%), sexual relationship (55.2%), sleep pattern (53.4%), level of well-being (51.8%), and physical activity (47.4) (Figure 1). The following patient quotations highlight the impact of ovarian cancer on patients living with this disease.

"On a daily basis, many times a day, I would think odds are I'm going to die…So I prepared for my death in 3 years…it's like another project, I have a plan, a schedule, a deadline."

"It's had a dramatic impact…I always had great health, it was so perplexing…letting go of any expectation for my future."

"My diagnosis has impacted my overall life. I have not woke up one morning without thinking about it. I would wake up in the middle of the night and cry. I can't make any plans until I see my oncologist, which is every 3 months. The emotional roller coaster that comes with it is so horrific. Although I still work, my career has been negatively impacted, no more professional growth for me."

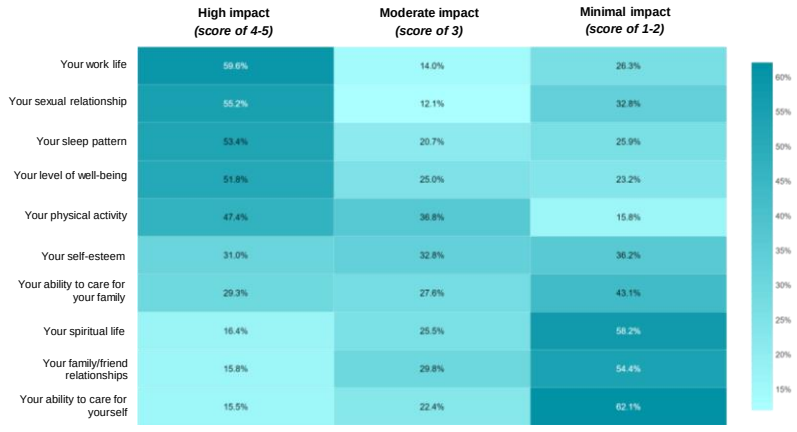
"Because of OVCA, I've lost the ability to have children, been forced into menopause in my thirties. I haven't been able to work for the last three years, which has impacted my income significantly and has set me back in my career. I'm plagued by chronic fatigue and bowel issues due to treatments, neuropathy and edema."

"I have been off work for over a year now since my first recurrence. My personal life is affected because I can't rely on my job financially so therefore it affects my self-esteem…I can't do so many normal things I used to do before such as just gardening, helping with home projects. Mentally I try to be positive but it's not always easy when you are constantly having chemo. It's challenging in so many ways. But I get through it."

"In 2013, 44 years old, mother of 2 little girls 10 and 3 years old. My life has completely capsized, 360 degrees in a fraction of a second. The first-line treatment made me extremely sick… first recurrence in 2014, 2nd line of chemotherapy 2nd recurrence in 2015 tamoxofin [sic]. Finally 3rd recurrence in 2017, operating protocol plus 20 treatment of radios… I have high frequency intestinal obstructions often hospitalized, I feel extreme fatigue with which I have to live. But what most hampers my life in my opinion, is the obsession with recidivism. For me, this is the hardest to live with."

"You can look at it like what have you lost and what have you gained. I tend to sort of look at it that way. In terms of loss, I've lost my job, I've lost my health, I've lost body parts, I've lost my strength and physical fitness that I used to have at one time...and [I've] lost a lot of cognitive function I think. So all of these things can translate into a bit of a loss of confidence… And then if I think about what I have gained in terms of the community, the connection with people and with other women…it is so beautiful and meaningful and important for everyone…"

Figure 1: The Impact of Ovarian Cancer, OCC



Women were asked to rate how their diagnosis has impacted different aspects of their life, using a 5-point scale (1=no impact, 2=mild impact, 3=moderate impact, 4=high impact, 5=extremely negative impact).
Percentage of women indicating a high, moderate, or minimal impact for each aspect is shown (N=58 responses).

3.1.2 Patients' Experiences with Current Therapy

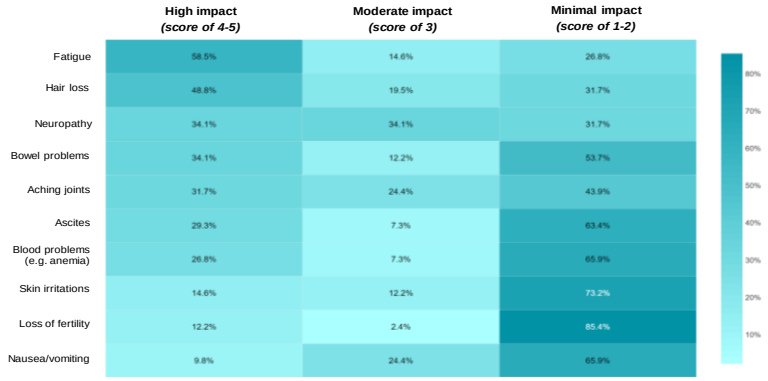
Of the 61 respondents, the majority had received chemotherapy (n=39; 93%) followed by a PARP inhibitor (n=14; 33%); namely, 11 women had been treated with olaparib (n=8) or rucaparib (n=3) with 1 receiving both. Radiation and hormone therapy were only

reported by 14% (n=6) and 2% (n=1) of respondents, respectively. Respondents' QoL were most highly impacted (score of 4-5) by fatigue (58.5%) and hair loss (48.8%) followed by neuropathy, bowel problems, and aching joints from current ovarian cancer treatments (Figure 2). As stated by 1 patient: *"I live with perpetual fatigue, perpetual stiffness, joint pain and muscle pain…I am essentially a poster child for side effects… I am almost physically unrecognizable to myself now, how I look and how I feel…(it is the) reality of taking this medication that is keeping my disease stable."* Most respondents had mixed feelings about the effectiveness of current treatments (not including niraparib). The following quotations detail the patients' experiences with current treatment(s) (not including niraparib) to manage ovarian cancer. Namely, 1 respondent noted that their cancer came back.

"While I experienced a reduction in CA125 and visible disease, I did not experience the same degree of success when compared to my first round of treatment. I left my second round of treatment with stable disease only."

"In August the doctor told me I was in remission…last fall I was rebuilding and I felt fantastic… life begins again. Then when I was told I had a recurrence in February I was devastated. I was hoping to get more than 6 or 7 months."

Figure 2: Impact of Treatment Side Effects on QoL, OCC



Women were asked to rate how side effects of their ovarian cancer treatment affected their quality of life, using a 5-point scale (1=no effect, 2=mild, 3=moderate, 4=high, 5=extremely negative effect). The percentage of women indicating a high, moderate, or minimal impact for each side effect is shown (N=41 responses).

3.1.3 Impact on Caregivers

There were 5 caregivers who responded to OCC's online survey. Three caregivers reported being a spouse or partner of a patient, 1 reported being the mother of a patient, and 1 did not report their relationship. Three had been providing care for 1 to 3 year(s) and 2 had been providing care for more than 4 years, with the majority spending 1 to 3 hours each day completing tasks associated with caregiving. Work life and sleep patterns were most negatively impacted by the caregiver role—as depicted in their own words.

"Have had to retire work early causing some financial issues. Take my wife to all her appointments and feel the anxiety she goes though each time. I take care of daily chores and try to make her life 'normal'."

"Quit my job to help care for my sister, as she lives alone...became very depressed - trouble sleeping, constantly feeling anxious about 'when' the ovarian cancer will recur, as the doctor said it will."

3.2 Information about the Drug Being Reviewed

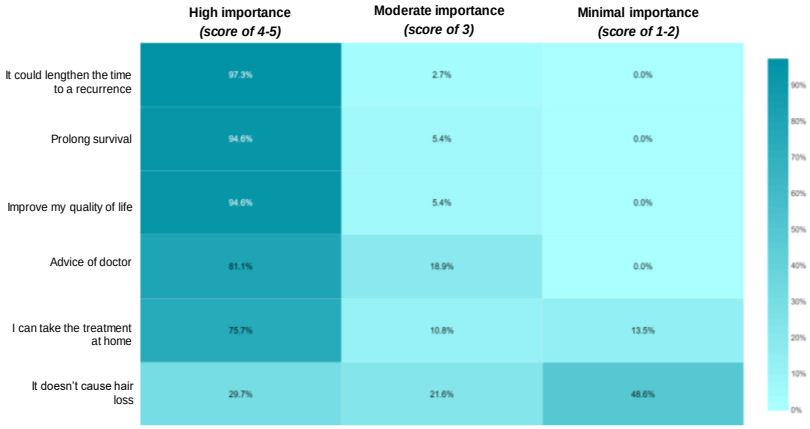
3.2.1 Patient Expectations for New Therapies

OCC noted that there was great interest in niraparib as a treatment option; namely, 65% of 37 women who had not been treated with niraparib considered taking it. Some respondents had not considered treatment with niraparib because they thought it was not relevant to their disease type (e.g., low-grade serous carcinoma). More women required a mild or moderate improvement versus a high improvement in their ovarian cancer when considering niraparib as a treatment (65% versus 35% of 34 respondents, respectively). Further, majority of women (>90%) emphasized the possibility of lengthening the time to recurrence, prolonging survival, and improving their QoL as the most important factors when considering niraparib. Namely, most respondents rated the following factors to be of high importance (score of 4 to 5): lengthening the time to recurrence (97.3%), prolonging survival (94.6%),

and improving their QoL (94.6%) (Figure 3). OCC noted these ratings aligned with more general treatment values explored in semi-structured interviews, which highlighted QoL (100%), possibility of a cure (89%), and prolonging life (89%) as the most important factors that would affect decisions to choose a new treatment. Factors such as hair loss, potential side effects, and method/frequency of drug administration were felt to be of less importance.

Most respondents were willing to tolerate a long list of physical side effects in hopes that niraparib would improve their overall daily functioning and/or prognosis; 79% of 34 respondents felt that the potential benefits of niraparib would outweigh the risks. Of note, respondents indicated their willingness to tolerate specific side effects from a list created by OCC. Patients were willing to tolerate side effects including taste changes/decreased appetite (88%), tiredness/weakness/fatigue (82%), and headaches (62%). Alternatively, no respondents were willing to tolerate bone marrow problems or blood cancer as potential side effects of niraparib and a small percentage of patients were willing to tolerate respiratory problems (12%) and high blood pressure (21%). Most respondents indicated their willingness to tolerate side effects in order to potentially prolong life and avoid chemotherapy for a longer period of time.

Figure 3: Factors in Considering Niraparib as a Treatment Option, OCC



Women were asked to rate how important the following factors would be in considering niraparib as a treatment option for ovarian cancer, using a 5-point scale (1=not important, 2=mild, 3=moderate, 4=high, 5=extremely important negative impact). The percentage of women indicating a high, moderate, or minimal importance for each factor is indicated, based on 37 responses.

3.2.2 Patient Experiences to Date

OCC gathered input from 4 women who had experience with niraparib through semi-structured interviews. All 4 had high-grade serous ovarian cancer; 2 were diagnosed at stage III and 2 were diagnosed at stage IV between 2005 to 2019; and 2 had the BRCA 1/2 mutation. All the patients had undergone genetic testing for BRCA1/2 and/or other ovarian cancer genes as part of their original diagnostic work-up (i.e., not as a condition of taking niraparib). All women were taking niraparib at the time of the interview for 2 to 4 months. One patient received niraparib as first-line maintenance treatment in a clinical trial setting; whereas the other 3 received niraparib as recurrent treatment accessed through their insurance plan. There was 1 patient each from Alberta, Saskatchewan, Ontario, and Quebec. All patients had experienced at least 1 side effect while on niraparib. Namely, tiredness/weakness/fatigue, bowel problems, and high blood pressure were most commonly experienced (each by 3 patients); taste changes/ decreased appetite and insomnia (each by 2 patients); and pain and respiratory problems (each by 1 patient). No patients reported experiencing anemia, bruising/ bleeding easily, infections due to low white blood cell count, headaches/dizziness, bone marrow problems, or blood cancer as a result of niraparib. Two of the patients indicated that they could accept all the side effects that they had experienced. The other 2 patients expressed that while none of the side effects were 'acceptable,' most were managed through additional medications. Despite these side effects and a relatively short time on niraparib, 3 of the 4 patients indicated that niraparib had improved their QoL. As stated by 1 of the women: *"It means the world to me, it's hope, it's my life. I was always very positive and doing everything I could so when I had the reoccurrence I was pretty devastated...when the oncologist told me about Zejula I felt so grateful, I had hope again. The whole idea of preventing or delaying reoccurrence is huge for me. It means the world to me."* Moreover, responses were

overwhelmingly positive and hopeful when OCC asked these patients what it means to them if granted the promise of gaining access to a PARP inhibitor without the requirement of a BRCA1/2 mutation status.

3.3 Companion Diagnostic Testing

Testing for mutations such as BRCA1/2 may be conducted for the diagnosis of ovarian cancer but is not required for niraparib.

3.4 Additional Information

OCC expressed their own excitement regarding the possibility of women gaining access to niraparib, in their own words, "*as an organization dedicated to improving the lives of all women living with ovarian cancer, we are very excited about the possibility of women gaining access to a PARP inhibitor in the first-line, regardless of BRCA1/2 mutation status.*" Namely, they highlighted the accessibility of niraparib specifying that treatment with niraparib is not dependent on *BRCA* status and would be accessible to the majority of women with ovarian cancer. OCC also asked patients "*What does the promise of getting access to a PARP inhibitor without needing a BRCA1/2 mutation mean to you?*" from which, a common sentiment is the frustration regarding the lack of new treatment options for women in the *BRCA-negative* population.

- *"A lack of treatment for non-BRCA patients, like me, continues to be very frustrating. Access to PARP inhibitors is vitally important and something I hope to receive."*
- *"Very upsetting that PARP inhibitors are currently only funded if you are BRCA positive. The ordinary person cannot afford it on their own and patient assistance programs hardly cover anything."*
- *"Lynparza is already approved and is free for those with BRCA. But another med like Zejula might benefit people without [a] mutation.*
- *"A potential cure...I think every ovarian cancer patient deserves a chance to live, because at the end of the day…we are all in the same abysmal reality of survival rates…we all deserve to have our realities changed, to be given hope in our lives…that we may be able to live in a different way, without cancer."*
- *"[it means] the world…I don't know why they haven't done more research on women who are BRCA negative…it doesn't seem fair."*
- *"It is important because anyone with ovarian cancer is facing the same risks."*
- *"It's a matter of life and death."*
- *"It is nice to have access across the board, because you never know who may benefit."*
- *"A recognition that my disease counts as much as anyone else with ovarian cancer."*

Additionally, OCC provided the following comments from the *Target Ovarian Cancer (UK) patient report of the Scottish Medicines Consortium consultation on niraparib* that highlight the benefit of niraparib.

- **Impact on QoL:** the threat of recurrent disease looms large over the lives of women with ovarian cancer; the emotional, practical, and physical implications for patients and their family are significant. As a result, it is difficult for women to plan events and activities that would have a positive impact on their QoL.
- **Benefits of new treatment:** niraparib has the potential to extend the time between chemotherapy treatments and potentially prolong the use of platinum-based chemotherapy without the requirement for patients to have the BRCA1/2 mutation. Thus, women and their families have more opportunities to focus on the emotional and physical recovery.
- **Mode of delivery:** Niraparib is given in tablet form allowing women to easily continue treatment in their own home. Therefore, it greatly reduces the need for hospital visits and the need to plan their life around appointments and treatment administration.

4 Summary of Provincial Advisory Group (PAG) Input

The PAG 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 9 provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Numerous clinical eligibility criteria
- Criteria for discontinuation of therapy
- Re-treatment with a PARP inhibitor

Economic factors:

- Tests for monitoring safety and effectiveness during maintenance
- Large patient population

4.1 Currently Funded Treatments

The standard of care for patients diagnosed with advanced ovarian cancer is cytoreductive surgery and platinum-based chemotherapy. For patients with high risk of relapse, bevacizumab may be added to chemotherapy. However, it is infrequently prescribed in Canada and does not have an approved indication in this setting. Following complete or partial response to upfront chemotherapy, patients can be on active surveillance or continuation maintenance with bevacizumab (if used in conjunction with chemotherapy). Olaparib is under provincial consideration for this indication but only in patients who are positive for a BRCAmut.

PAG noted that the PRIMA trial compared niraparib to placebo. PAG seeks additional comparison of niraparib with bevacizumab and with olaparib for BRCA-mutated tumours.

4.2 Eligible Patient Population

The reimbursement request of niraparib is as maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy. In view of the characteristics of the patient population and exclusion criteria in the PRIMA trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with niraparib:

- ECOG performance score ≥2.
- Patients who could not receive first-line platinum chemotherapy and received an alternative chemotherapy regimen instead.
- Patients who have not completed at least 6 cycles of platinum-based or alternate chemotherapy.
- Patient with mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer.
- Patient having undergone more than 2 debulking surgeries.
- Patients with intolerance of olaparib.
- PAG seeks an estimate of the maximum time between completion of chemotherapy and commencement of niraparib.

PAG seeks clarity on the role of CA-125 testing prior to initiation of niraparib, as patients in the trial had to have either CA-125 in the normal range or a CA-125 decrease by more than 90% during their frontline therapy that is stable for at least 7 days (i.e., no increase >15%) prior to starting niraparib. PAG identified additional eligibility criteria in the study, notably a partial or complete tumour

response and no measurable disease of more than 2 cm at the time of study entry. PAG would like to know if all these criteria need to be met for eligibility to niraparib reimbursement.

If niraparib were recommended for reimbursement, PAG noted that patients currently on bevacizumab maintenance or observation would need to be addressed on a time-limited basis.

PAG noted potential indication creep of niraparib to patients who did not achieve a clinical complete response or partial response following upfront chemotherapy, to patients who progressed on olaparib, to patients with platinum-sensitive disease following first-line platinum treatment, and to patients with other ovarian cancer histologies.

4.3 Implementation Factors

The recommended dose of niraparib is 200 mg (2 x 100-mg capsules) taken orally once daily. For patients who weigh ≥77 kg (170 lbs) and have baseline platelet count ≥150,000/μL, the recommended starting dose of niraparib is 300 mg (3 x 100-mg capsules) taken orally once daily. Treatment should be continued until disease progression or unacceptable toxicity. PAG seeks a clear definition of disease progression and advice on criteria for treatment discontinuation. PAG noted that oral capsules allow for easy dose adjustment and reduction of wastage, although they may be a burden to some. PAG added that weight-based dosing and the need for a platelet count complicates drug dispensation.

PAG has concerns that the high rate of grade 3 and 4 anemia observed with niraparib therapy could impact QoL significantly and would require resources to manage. PAG noted that resources (frequent clinic visits, nursing and lab time) will be required to perform blood work for monitoring cytopenias and to conduct blood transfusions for severe anemia. Familiarity with olaparib, another PARP inhibitor used in ovarian cancer, can help anticipate and manage these effects. PAG seeks guidance on potentially stopping niraparib to manage toxicity and then re-starting the therapy. Furthermore, PAG seeks advice on the frequency and type of monitoring during maintenance therapy (e.g., CA-125 testing, CT scans).

For patients with non-BRCA-mutated disease, niraparib would be an additional therapy as it is for maintenance and does not replace chemotherapy. PAG remarked that extra pharmacy, laboratory, and nursing resources for dispensing and monitoring would be required, as patients would otherwise be on observation. Nevertheless, PAG identified the oral route of administration as an enabler to implementation. It was noted that niraparib 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.

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 and sequencing with niraparib including the scenarios below:

- Circumstances where niraparib would be preferable to olaparib should both options be available.
- Options after failure of niraparib including potential re-treatment with a PARP inhibitor for maintenance in the relapsed/refractory setting.
- Switching between niraparib and olaparib (if BRCA-mutated) or vice versa in cases of unacceptable toxicity.
- Re-treatment with niraparib following platinum chemotherapy in patients who discontinued maintenance treatment for reasons other than progression.

4.5 Companion Diagnostic Testing

PAG did not identify a companion diagnostic test required for eligibility to niraparib. However, BRCA mutation results may help inform choice of therapy between niraparib and olaparib. PAG is seeking confirmation if BRCA and HRD testing are required.

4.6 Additional Information

PAG highlighted the large target population should reimbursement for both non-BRCA and BRCA-mutated patients be recommended. This may translate into substantial budget impact for the drug programs.

5 Summary of Registered Clinician Input

A total of 5 registered clinician inputs were provided: 3 from individual oncologists (1 each from Ontario, BC, and Saskatchewan) and 2 group inputs on behalf of Ontario Health (OH) [Cancer Care Ontario (CCO)] Gynecologic Cancers Drug Advisory Committee (GC DAC) (2 clinicians) and the National BRCA Collaborative through the Society of Gynecologic Oncology of Canada (GOC) (5 clinicians) for the review of niraparib as maintenance treatment of adult patients with advanced epithelial ovarian cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

Current treatments specified by the National BRCA Collaborative-GOC and OH (CCO) GC DAC clinicians included bevacizumab for high-risk patients (sub-optimally debulked stage III or IV patients) and olaparib for first-line maintenance treatment for patients with a BRCAmut (decision to fund is currently under negotiation). Some high-risk patients receive bevacizumab as maintenance therapy; however, it is not universally adopted due to toxicities, resources, and a modest benefit. Further, across Canada, there is no available or consistent treatment for BRCA-negative) patients; thus, they may be on active surveillance. Most clinicians indicated there is an unmet need. Overall, the inclusion and exclusion criteria of the pivotal trial were deemed suitable for clinical practice and were noted to capture a broad range of patients except for those who are platinum-resistant, patients with refractory disease (who would be unlikely to benefit), and patients with a worse performance status (only ECOG 0/1 included). For BRCA-mutated patients, clinicians noted that niraparib has similar efficacy and tolerability (with the exception of thrombocytopenia and hypertension) compared to olaparib. Compared to bevacizumab, clinicians noted niraparib is more tolerated and has a better safety profile and requires less clinic visits as it is an oral drug, which allows patients to be monitored virtually and with blood work. Overall, niraparib was noted to be well tolerated with minimal safety concerns and demonstrated significant efficacy among different endpoints of the pivotal trial.

All clinicians indicated they would administer niraparib in the patient population included in the pivotal trial (stage III or IV cancers in patients who have a complete or partial response to platinum-based chemotherapy). In addition, both groups suggested niraparib also be used in patients with stage III disease who had undergone primary debulking and did not have residual disease after surgery. The National BRCA Collaborative-GOC clinicians stated given there is no validated HRD test available and a modest PFS benefit was found for patients without HRD (as assessed by myChoice©) or a BRCAmut, consideration could be given to administering niraparib to all high-risk, high-grade serous/endometrioid ovarian cancer patients who are not platinum-resistant or refractory. Both groups noted that for the BRCA-mutated population, niraparib will be another option (in addition to olaparib if funded). For the high-risk population (bevacizumab candidates in Ontario), niraparib would be an option to replace bevacizumab potentially allowing for bevacizumab to be reserved for platinum-resistant disease. However, the individual clinician from Ontario stated that niraparib could replace olaparib for BRCA-mutated patients, HRD patients, or all ovarian cancer patients. Further, the individual clinicians from Ontario and BC noted that the pivotal trial demonstrated benefit in all patients; therefore, niraparib should not be limited to any subgroup and they would use niraparib in BRCA-negative patients.

The clinicians expressed different preferences for niraparib over olaparib in BRCA-mutated patients; however, clinicians highlighted the decision would be based on patient tolerance, availability, clinician preference, and the shorter treatment duration of olaparib. The individual clinicians from Ontario and Saskatchewan noted a preference for niraparib except when anemia is of concern. Most clinicians preferred niraparib over bevacizumab following first-line platinum-based chemotherapy in ovarian cancer patients with a high risk of relapse and would prefer to reserve the use of bevacizumab in the platinum-resistant setting when patients have limited treatment options. They also cited the patient convenience associated with niraparib, and efficacy and safety concerns associated with bevacizumab. There were similar opinions among clinicians regarding which assessments to conduct to assess disease progression in patients treated with niraparib (e.g., CA-125 assessments, clinical exams, and CT); however, there were varying opinions regarding the frequency of assessment. All clinicians indicated there is evidence or a rationale for testing BRCA status in all patients who are on front-line therapy for advanced ovarian cancer as germline BRCAmut (gBRCAmut) testing allows for identification of hereditary risk and somatic BRCAmut (sBRCAmut) testing may guide the use or selection of PARP inhibitors. The clinicians noted that HRD testing is not currently funded or part of standard care across Canada including the Myriad myChoice© assay used in the pivotal trial.

Please see below for details from the clinician inputs.

5.1 Current Treatments

The National BRCA Collaborative-GOC and OH (CCO) GC DAC clinicians stated that current treatments include bevacizumab for high-risk patients (sub-optimally debulked stage III or IV patients) and olaparib (PARP inhibitor) for first-line maintenance treatment for women with a gBRCAmut or sBRCAmut specified to account for about 25% of all ovarian cancer patients). The decision to fund olaparib is currently under negotiation; thus, patients have accessed olaparib through a manufacturer-supported compassionate access program. Across Canada, there is no available or consistent treatment for BRCA-negative (i.e., BRCAwt) patients; thus, they may be on active surveillance following completion of first-line chemotherapy. The BC clinician specified there is no appropriate comparator for BRCA-negative patients.

5.2 Eligible Patient Population

The National BRCA Collaborative-GOC and OH (CCO) GC DAC clinicians and the individual clinicians from BC and Saskatchewan indicated there is an unmet need as there is no first-line maintenance therapy for BRCA-negative patients. Accordingly, the clinicians noted that the patient population in the reimbursement request aligns with the need in their clinical practice. The individual clinician from BC specified that the patient population in the reimbursement request represents 75-80% of all patients. Some high-risk patients receive bevacizumab as maintenance therapy; however, it is not universally adopted due to toxicities, resources (bevacizumab requires IV infusion every 3 weeks for a year), and a modest benefit even in the high-risk population.

The National BRCA Collaborative-GOC clinicians noted that the inclusion and exclusion criteria of the pivotal trial (PRIMA) are suitable for clinical practice. Both groups indicated that the pivotal trial criteria included advanced cancer of the ovary, peritoneum, or fallopian tube; high-grade serous or endometrioid carcinoma (over 90% of patients); and stage III or IV cancers with partial or complete response to chemotherapy in the frontline setting. Additionally, it was noted that the pivotal trial criteria included a broad range of patients except for platinum resistant patients, patients with refractory disease (who would be unlikely to benefit), and patients with a worse performance status (only ECOG 0/1 included). It was noted that the pivotal trial included all HRD patients regardless of histology and were identified by the Myriad myChoice© test assay. The individual clinician from BC noted they would use this treatment for BRCA-negative patients who have demonstrated a complete or partial response to first-line platinum-based chemotherapy. They specified that these patients enter a period of active surveillance following completion of first-line chemotherapy, and there is a 70% or greater chance of disease recurrence or progression. The individual clinicians from BC and Ontario noted that the pivotal trial demonstrated benefit and efficacy in all patients (including HRP patients); therefore, niraparib should not be limited to any particular subgroup.

5.3 Relevance to Clinical Practice

The National BRCA Collaborative-GOC and OH (CCO) GC DAC clinicians and the individual clinician from BC reported having experience with niraparib. The individual clinicians from Ontario and Saskatchewan did not report if they had experience administering niraparib. All clinicians indicated that they would administer niraparib in the patient population included in the pivotal trial (stage III or IV cancers in patients who have had a complete or partial response to platinum-based chemotherapy). Both groups suggested the use of niraparib in patients with stage III disease who had undergone primary debulking and did not have residual disease; the OH (CCO) GC DAC clinicians elaborated that these patients would be expected to derive the same benefit from niraparib based on biology. Further, they noted that PARP inhibitors are currently not available for the HRD patient population. The individual clinician from Ontario noted that patients with germline or somatic BRCAmut would be eligible for niraparib; and the individual clinicians from Ontario, Saskatchewan and BC all indicated they would use niraparib in BRCA-negative patients. Additionally, the Saskatchewan clinician would administer niraparib in patients who experience toxicities to other PARP inhibitors.

The National BRCA Collaborative-GOC and OH (CCO) GC DAC clinicians noted that for BRCA-mutated patients, niraparib has similar efficacy and tolerability (with the exception of thrombocytopenia and hypertension) compared to olaparib. Additionally, they noted that treatment with niraparib is slightly longer (3 years for niraparib versus 2 years for olaparib), which adds costs to the healthcare system and may inconvenience patients. The individual clinician from Ontario stated that it is unclear if efficacy is similar across PARP inhibitors but noted that the side effects are different. The National BRCA Collaborative-GOC clinicians highlighted that the BRCA-negative, HRD patients (defined by myChoice© assay threshold) derived benefit (HR = 0.5) and the BRCA-negative

(BRCAwt)/HRP patients experienced a more modest benefit. The interim OS analysis showed an estimated probability of survival at 24 months of 81% in the niraparib group and 59% in the placebo group (HR=0.51; 95% CI, 0.27 to 0.97) for the BRCA-negative (BRCAwt)/HRP population. Additionally, they noted that the median PFS benefit for high-risk patients treated with bevacizumab was 4.1 months, and while this may seem slightly better than the PFS benefit associated with niraparib for the BRCA-negative (BRCAwt)/HRP patients, bevacizumab is associated with higher toxicity rates and requires IV infusion (i.e., niraparib exhibits a better safety profile and tolerability compared to bevacizumab). The individual clinician from BC noted from their experience of administering niraparib in the clinical trial setting that most patients tolerate niraparib with minimal safety concerns. The OH (CCO) GC DAC clinicians stated that niraparib is an alternate treatment option in patients who have contraindications or intolerance to bevacizumab for the high-risk BRCA-negative (BRCAwt) population. The National BRCA Collaborative-GOC clinicians would recommend limiting niraparib to the BRCA-mutated and HRD patient populations if HRD testing was available. Overall, the clinicians noted that niraparib is better tolerated and is an oral take-home drug; thus, patients can be monitored virtually with less required visits to the hospital/treatment centre. Nevertheless, a discussion with patients is warranted regarding the risks and benefits as niraparib is associated with certain toxicities.

5.3.1 What is the evidence and what is the clinician opinion of how frequently patients on niraparib should be assessed for disease progression? What assessments should be conducted (e.g., CA-125, diagnostic imaging, clinical, etc.)?

The individual clinician from Ontario stated that no definitive data exists to guide how frequently patients on niraparib should be assessed for disease progression. The individual clinician from BC stated that prior data have demonstrated that routine use of a CA-125 assessment to monitor for recurrence does not result in improved patient outcomes; thus, investigations should be done at the time patients have symptoms and the frequency of assessing for progression is up to the treating clinician. The clinicians indicated similar opinions on which assessments should be conducted (e.g., CA-125 assessments, clinical examinations, and CT imaging); however, there were varying opinions in the frequency of assessments for disease progression. The National BRCA Collaborative-GOC clinicians stated that patients should be assessed approximately every 3 months for the first 2 years and CA-125 assessments and diagnostic imaging should be conducted. The OH (CCO) GC DAC clinicians noted that more frequent bloodwork would be required to monitor niraparib-related toxicities compared to those not on maintenance therapy. Namely, CA-125 assessments every 4 weeks with labs and CT scans conducted every 3 months or less frequently if CA-125 levels remain normal or stable. Both groups noted that disease recurrence would be managed according to standard of care. The individual clinician from Ontario stated that it is common practice to conduct clinical, CA-125, and CT assessments every 3 to 4 months. The individual clinician from BC stated they use a mix of CA-125 assessments and clinical monitoring; however, there is no prescribed follow-up method or algorithm that is recommended. Regarding frequency, clinicians expressed that patients should be assessed clinically on a monthly basis, mainly to monitor for tolerability and toxicity of niraparib. The individual clinician from Saskatchewan stated that imaging should be conducted as clinically relevant after baseline and every 3 months for CA-125 assessments.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The National BRCA Collaborative-GOC clinicians specified that for HRD, BRCA-negative (BRCAwt) patients, niraparib should be made available as there are no other available treatments. They noted that if a test were available to identify patients' homologous recombination status, they would not recommend administering niraparib in HRP patients. However, given there is no available validated test and a modest PFS benefit was found for HRP patients (as assessed by the myChoice© assay), consideration could be given to administering niraparib to all high-risk, high-grade serous/endometrioid ovarian cancer patients who are not platinum resistant or refractory. For BRCA-mutated patients, both clinician groups noted that niraparib should be available as another PARP inhibitor option based on the assumption that olaparib will be funded (the National BRCA Collaborative-GOC clinicians specified this for HRD, BRCA-mutated patients). However, the individual clinician from Ontario stated that niraparib could replace olaparib for BRCA-mutated patients, HRD patients, or all ovarian cancer patients. The OH (CCO) GC DAC clinicians stated that for the high-risk population (bevacizumab candidates in Ontario), niraparib would be an option to replace bevacizumab potentially allowing for bevacizumab to be reserved for platinum-resistant disease in the future.

5.4.1 Is there evidence and/or preference for bevacizumab vs. niraparib following first-line platinum-based chemotherapy in patients with ovarian cancer with a high risk of relapse?

Overall, most clinicians preferred the use of niraparib following first-line platinum-based chemotherapy in ovarian cancer patients with a high risk of relapse. The groups stated that assuming there is a similar or better OS benefit, there is preference to administer niraparib based on patient convenience and a more favourable toxicity profile. The National BRCA Collaborative-GOC clinicians provided evidence from various clinical trials to support their preference. In the subgroup of patients at high-risk of relapse (ICON7 trial), the magnitude of benefit of bevacizumab was an OS improvement of 4.8 months (39.3 months versus 34.5 months) and PFS improvement of 4.1 months (20 months versus 15.9 months). In the high-risk subgroup of the pivotal trial (PRIMA), the magnitude of benefit for "all-comers" (HRD and HRP) was a PFS improvement of 5.7 months (13.9 months versus 8.2 months). They noted that benefits were larger in the BRCA-mutated and HRD subgroups as the median PFS benefit was only 2.7 months for HRP patients (compared to placebo). The individual clinician from Ontario stated niraparib would be better suited as first-line maintenance therapy; bevacizumab is not commonly used in the first-line setting as it is used mostly in patients with very poor prognostic criteria (e.g., sub-optimally debulked, stage III, or stage IV patients). The individual clinicians from Ontario and BC noted that many clinicians reserve bevacizumab for patients with resistance to platinum-based chemotherapy given their limited treatment options and due to the efficacy and safety concerns of bevacizumab. The BC clinician further noted that the data that have been published thus far from trials that have investigated the use of bevacizumab, have evaluated bevacizumab combined with a PARP inhibitor, which brings into question whether bevacizumab is actually necessary. Accordingly, the clinician noted comparing any new maintenance therapy option in the first-line setting to bevacizumab is not appropriate, and thus there is no preference for bevacizumab over a PARP inhibitor such as niraparib. The individual clinician from Saskatchewan stated that PARP inhibitors would be used in the majority of cases without bevacizumab.

5.4.2 Is there evidence or in what situations would niraparib be preferred over olaparib if BRCA-mutated?

There were different preferences regarding the use of niraparib over olaparib in BRCA-mutated patients. Namely, the BC clinician stated that there is no evidence that one PARP inhibitor would be favoured over the other, rather preference would be based on clinician choice. However, similar to the clinician groups, the clinician highlighted the shorter treatment duration of olaparib (2 and 3 years for olaparib and niraparib, respectively). The clinician groups indicated a preference for olaparib because of the shorter treatment duration but also mentioned that patient tolerance and availability would contribute to clinician preference. The individual clinician from Ontario expressed certainty that the data suggests efficacy of niraparib in HRD, HRP, and BRCA-mutated patients; thus, niraparib would be preferred in the majority of ovarian cancer patients. The individual clinician from Saskatchewan noted clinician experience and anemia as considerations for preference between niraparib and olaparib in BRCA-mutated patients.

5.4.3 Is there evidence to inform whether CA-125 response or stability should be confirmed prior to initiating niraparib?

There were differing opinions regarding whether CA-125 response or stability should be confirmed prior to initiating niraparib. However, most clinicians suggested the use of multiple assessments such as radiographic imaging (e.g. CT) and clinical examinations (most commonly mentioned) in addition to assessing CA-125 levels. The National BRCA Collaborative-GOC clinicians stated that evidence for niraparib is based on patients who have demonstrated a partial or complete response to first-line platinum chemotherapy, according to investigator assessment (as per the pivotal trial). They highlighted this is not specifically defined but it is assumed this means that CA-125 has either normalized or stabilized. Therefore, based on the inclusion criteria of the pivotal trial, it seems reasonable to expect a CA-125 response or stability prior to starting niraparib. Further, they noted there are some data (ASCO 2020) to suggest that CA-125 may be less reliable in predicting recurrence for women on PARP inhibitors compared to those on surveillance. Thus, there would be a low clinical threshold for instigating imaging in a patient receiving a PARP inhibitor. Similarly, the OH (CCO) GC DAC clinicians stated that CT imaging is likely more informative as CA-125 levels may not be a useful marker in some patients and noted to follow the approach used in the pivotal trial. The individual clinician from Ontario stated that the evidence is not well documented; however, the most compelling approach would be to use imaging plus clinical assessment while considering CA-125 levels. The individual clinician from BC stated that there is no evidence that suggests CA-125 is useful to confirm response or stability. Clinicians would rely on imaging, a clinical exam, and findings from either primary or interval debulking surgery. CA-125 can be used as an adjunct tool but is not useful on its own. The individual clinician from Saskatchewan stated trimodal assessments should be performed prior to initiating niraparib (i.e., lab work, clinical assessments, and radiographically).

5.5 Companion Diagnostic Testing

The National BRCA Collaborative-GOC and the OH (CCO) GC DAC clinicians noted that HRD testing is not currently publicly funded or part of standard care. Therefore, testing may be outsourced to validated laboratories and some tertiary care centres are developing in-house testing. The clinicians highlighted that the availability of HRD testing could inform the use of niraparib in patients who are HRP as a small benefit of less than 3 months was observed in the clinical trial. The individual clinician from Ontario noted that if the indication for the treatment under review is for HRP patients then testing would be irrelevant. The individual clinician from BC stated that given the pivotal trial demonstrated niraparib efficacy in all comers, there is no need for a companion diagnostic test at this time. Further, there is no single validated test to determine homologous recombinant status nor is the interpretation of HRD based on available tests consistent.

5.5.1 Is there evidence or rationale for testing BRCA in all patients who are on front-line therapy for advanced ovarian cancer?

All clinicians indicated there is evidence or a rationale for testing BRCA status in all patients who are on front-line therapy for advanced ovarian cancer. Both groups noted that germline BRCA testing allows for identification of hereditary risk, which has important implications for unaffected family members, and somatic BRCA testing may guide treatment selection such as the use of PARP inhibitors. The individual clinician from Ontario highlighted that if all patients are going to be treated with a PARP inhibitor then the only value in BRCA testing at present would be for familial risk. However, they currently only test in high-grade serous cases due to the higher incidence of BRCAmut in these patients, and further specified there is a lower but definitive rate of BRCAmut in endometrioid and clear cell cases and a very low rate for low-grade serous and mucinous cases. The individual clinician from BC stated they already test all ovarian cancer patients for gBRCAmut mutations, which is in line with national and international guidelines. They noted that many jurisdictions across Canada will soon also begin to routinely test all women for sBRCAmut. The individual clinician from Saskatchewan noted that all patients should be tested for the BRCA mutation and this is performed at a rate of 80% in their jurisdiction.

5.7 Additional Information

None to report.

6 Systematic Review

6.1 Objectives

The primary objective of this systematic review is to evaluate the efficacy and safety of niraparib as monotherapy compared to standard of care (e.g., active surveillance/observation, or olaparib for patients with a BRCAmut) for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

A supplemental question relevant to the CADTH review and to the PAG were identified while developing the review protocol and is outlined in Section 7.

- Summary and critical appraisal of a feasibility study of a NMA and unanchored PAIC of niraparib, olaparib, and bevacizumab as maintenance therapies in patients with newly diagnosed advanced ovarian cancer

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 Table 4. 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 4: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes

Published or unpublished RCTs
 	
In the absence of RCTs, fully published clinical trials investigating the safety and efficacy of niraparib should be included
	Female adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy
	
	Subgroups of interest:
	• HRD status
	• BRCAmut status
	  ○ Somatic BRCAmut status
	  ○ Germline BRCAmut status
		Niraparib	• Olaparib (for gBRCAmut)
			• Bevacizumab (for high-risk patients as per the ICON-7 trial)[a]
			• Observation/active surveillance
			• Best supportive care
			• Placebo
				• **PFS**
				• **OS**
				• PFS-2[b]
				• TFST
				• **HRQoL**
				• AEs
				• AEs of special interest include: MDS/AML, myelosuppression, hypertension, thrombocytopenia, and nausea

AE = adverse event; AML = acute myeloid leukemia; BRCA = breast cancer susceptibility gene; CA-125 = cancer antigen-125; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; HRD = homologous recombination deficiency; HRQoL – health-related quality of life; MDS = myelodysplastic syndrome; mut = mutation; OS = overall survival; PFS = progression-free survival; PFS-2 = progression-free survival on next line of therapy; PR = partial response; RCT = randomized controlled trial; TFST = time-to-first subsequent therapy.

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

[a] High-risk as per the ICON-7 trial was defined as International Federation of Gynecology and Obstetrics stage IV disease, inoperable stage III disease, or sub-optimally debulked (>1 cm) stage III disease.[35]

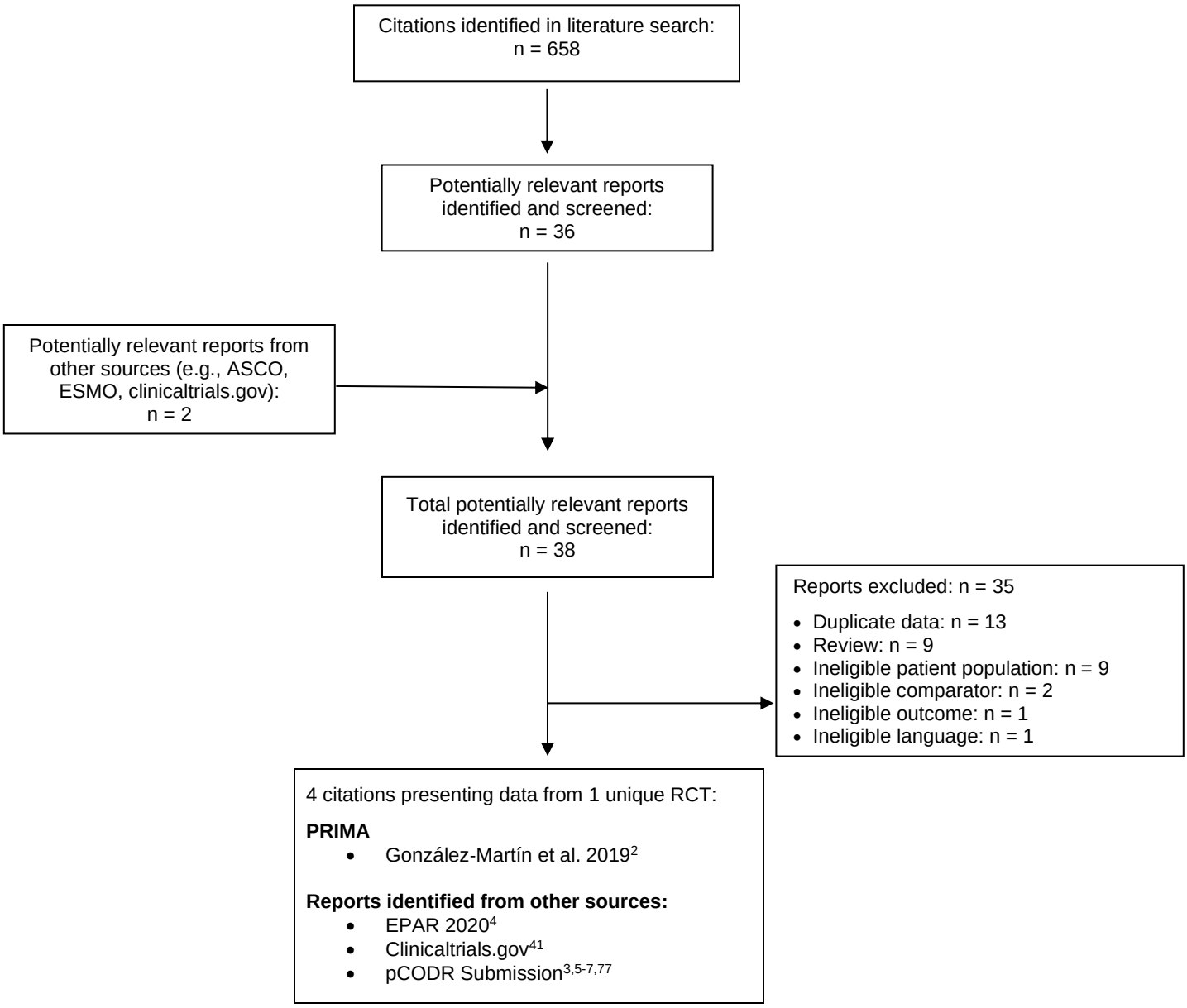
[b] Time to progression or death on the next line of therapy.

6.3 Results

6.3.1 Literature Search Results

Of the 38 potentially relevant reports identified, 3 reports representing 1 unique phase III RCT (PRIMA) were included in the CADTH systematic review[2,4,41] and 35 studies were excluded. Studies were excluded because they contained duplicate data,[42-54] were a review,[55-63] included an ineligible patient population,[64-72] reported data for an ineligible comparator,[73,74] assessed ineligible study outcomes,[75] or were not reported in English.[76]

Figure 4: Flow Diagram for Study Selection



Note: Additional data related to the PRIMA trial were also obtained through requests to the sponsor by CADTH. [3,5-7,77]

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

One RCT, PRIMA, met the selection criteria of the systematic review. Key characteristics of the PRIMA trial including study design, eligibility criteria, interventions, and trial outcomes, are summarized in Table 5.

Table 5: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion/Exclusion Criteria	Intervention and Comparator	Trial Outcomes

PRIMA/ENGOT-OV26/GOG-3012 NCT02655016
 	
Characteristics:
Phase III, double-blind, randomized (2:1), placebo-controlled
• n randomized = 733 (niraparib: n = 487; placebo: n = 246)
 	
• n treated = 728 (niraparib: n = 484; placebo: n = 244)
 	
Setting:
181 sites in 20 countries (Belgium, Canada, Czechia, Denmark, Finland, France, Germany, Hungary, Israel, Ireland, Italy, Norway, Poland, Russia, Spain, Sweden, Switzerland, Ukraine, United Kingdom, and United States)
 	
Patient Enrolment Dates:
July 2016 to June 2018
 	
Primary Analysis Data cut-off date:
May 17, 2019
 	
Status:
	Key Inclusion Criteria:
	• Female patients ≥ 18 years of age
	• ECOG PS 0 to 1
	• Newly diagnosed, histologically confirmed, advanced cancer of the ovary, peritoneum, or fallopian tube with high-grade serous or endometrioid features that were classified as stage III or IV according to FIGO criteria. Namely, the following stage III and/or IV patients were eligible:
	  ○ Inoperable stage III disease
	  ○ Stage III with visible residual disease after primary debulking surgery
	  ○ Any stage IV disease
	  ○ Stage III or IV patients who were treated with neoadjuvant chemotherapy
	• Received 6 to 9 cycles of first-line platinum-based chemotherapy which resulted in an investigator-assessed CR or PR after 3 or more cycles.
	  ○ Receipt of intraperitoneal chemotherapy is eligible
	  ○ Must have had ≥ 2 post-operative cycles of platinum-based therapy following interval debulking surgery
	• Randomized within 12 weeks of the first day of the last cycle of chemotherapy
	• CA-125 values either within the normal range or a CA-125 decrease of more than 90% during front-line therapy that was stable for at least 7 days
	• Agreement to undergo HRD testing
	  ○ Central HRD test had to be available for randomization; however, patients with documented gBRCA 1, gBRCA 2, or sBRCA 1/2 mutations could be randomized without HRD test status results
	  ○ A tumour sample for HRD testing could be submitted prior to the screening period if it appears likely for the patient to meet other eligibility requirements
		Intervention:
		Niraparib once daily in 28-day cycles for 36 months or until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up
		
		Comparator:
		Placebo once daily in 28-day cycles for 36 months or until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up
			Primary:
			• PFS
			
			Secondary:
			• OS
			• TFST
			• PFS-2
			• Time to CA-125 progression
			• Safety outcomes
			• PROs (FOSI, EQ-5D-5L, EORTC-QLQ-C30, EORTC-QLQ-OV28)
			
			Exploratory:
			• PK analyses
			• Biomarkers in relation to ovarian cancer and PARP inhibition
			• Relationship between HRD status and platinum sensitivity in ovarian cancer patients who have initial response to front-line platinum therapy

Trial Design	Inclusion/Exclusion Criteria	Intervention and Comparator	Trial Outcomes
Ongoing for patient follow-up **Funding** Tesaro/GlaxoSmithKline Inc.	○ Patients with known HRD status from commercially available tests were eligible; however, central HRD testing for the trial had to be performed and the central HRD test results had to be available prior to randomization for stratification ○ Patients with a HRD test result that is 'not determined' are not required to undergo repeat HRD testing **Key Exclusion Criteria:** • Mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma, or undifferentiated ovarian cancer • Stage III cancer with complete cytoreduction after primary debulking surgery • More than 2 debulking surgeries for the study disease • Patient received bevacizumab as maintenance therapy (if a patient received bevacizumab as part of first-line therapy but were unable to receive bevacizumab as part of maintenance therapy for any reason, the patient was not excluded as long as the last dose of bevacizumab was taken ≥28 days prior to signing informed consent) • Condition or laboratory abnormality that might confound the study results or interfere with participation for the full duration of the study (including having received a transfusion or colony-stimulating factors within 2 weeks of the first dose of study treatment) • Pregnant, breast feeding, or expecting to conceive while on study treatment or up to 180 days after the last study treatment dose • Known hypersensitivity to the components of niraparib • Received investigational therapy administered within 4 weeks or within a time interval less than at least 5 half-lives of the investigational agent (whichever is longest) prior to the first scheduled day of scheduled dosing of the PRIMA trial • Any known ≥grade 3 anemia, neutropenia, or thrombocytopenia due to prior chemotherapy that persisted more than 4 weeks • Invasive cancer other than ovarian cancer less than 5 years prior to study enrollment (except definitively treated uterine cervical or urinary tract carcinoma in situ, non-melanomatous skin cancer or ductal carcinoma in situ of the breast) • Prior treatment with a known PARP inhibitor		

BRCA = breast cancer susceptibility gene; CA-125 = cancer antigen 125; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC-QLQ- C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer 30; EORTC-QLQ- OV28 = European Organisation for Research and

Treatment of Cancer Quality of Life Questionnaire – Ovarian Cancer Module - OV28; EQ-5D-5L: European Quality of Life scale, 5-Dimensions; FIGO = International Federation of Gynecology and Obstetrics; FOSI = Functional Assessment of Cancer Therapy - Ovarian Symptom Index; gBRCAmut = germline BRCA mutation; OS = overall survival; PARP = poly(adenosine diphosphate [ADP]–ribose) polymerase; PK = pharmacokinetics; PFS = progression-free survival; PFS-2 = progression-free survival on next line of therapy; PR = partial response; PRO = patient-reported outcome; sBRCAmut = somatic BRCA mutation; TFST = time-to-first subsequent therapy.

Data sources: González-Martín 2019,[2] Clinicaltrials.gov,[41] Clinical Study Protocol,[3] Checkpoint Questions 2020.[6]

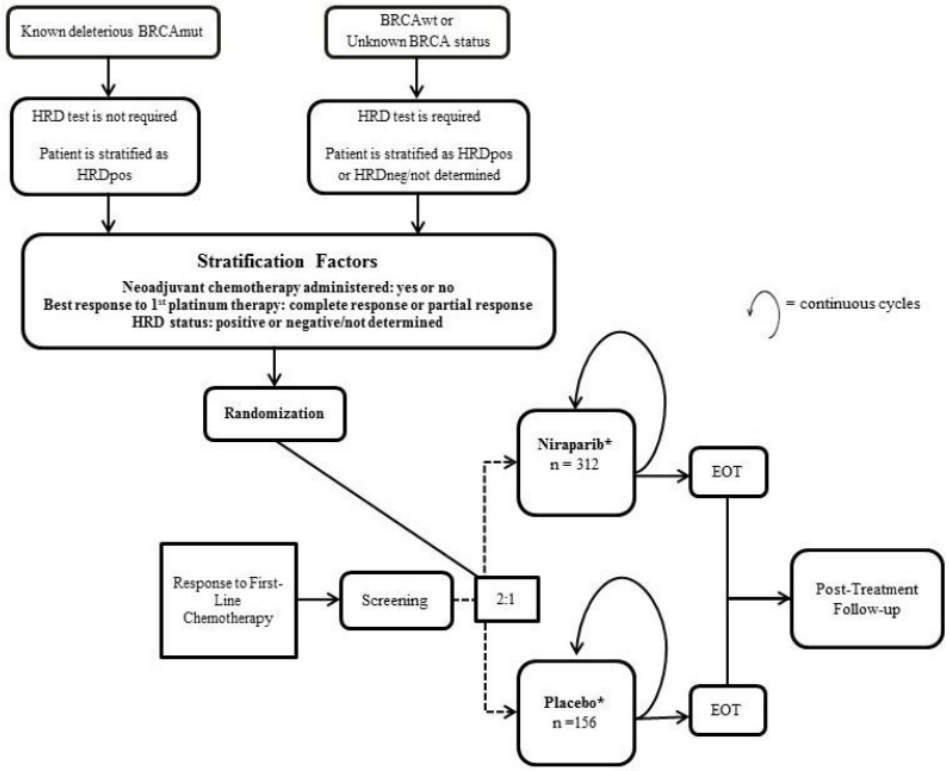
a) Trial

PRIMA is an ongoing, international, double-blind, placebo-controlled, phase III RCT that evaluated the efficacy and safety of niraparib compared to placebo as maintenance treatment in adult patients with newly diagnosed advanced ovarian cancer.[2] The trial was conducted in 181 sites in 20 countries that included 10 sites in Canada from which 87 patients were randomized (refer to Table 5 for a list of participating countries).

Trial Design

The PRIMA study design is depicted in Figure 5 and the key eligibility criteria are outlined in Table 5.

Figure 5: PRIMA Study Design



Abbreviations: EOT = end-of-treatment; PFS = progression-free survival
* The starting dose of study treatment will be based upon the patient's baseline body weight or baseline platelet count. Patients with a baseline body weight ≥ 77 kg **and** baseline platelet count ≥150,000 µL will receive 300 mg; patients with a baseline body weight <77 kg **or** baseline platelet count <150,000 µL will receive 200 mg.
Note: Treatment is continuous (in 28-day cycles) until patient discontinues treatment. Post-treatment follow-up is continuous (every 12 weeks) until patient discontinues study.

Data source: Clinical Study Protocol[3]

Eligibility Criteria, Screening, and Randomization

In brief, eligible patients had newly diagnosed, histologically confirmed advanced ovarian cancer with high-grade serous or endometrioid features that were classified as stage III or IV according to FIGO criteria. The following stage III and/or IV patients were eligible for inclusion:

- Stage III with visible residual disease after primary debulking surgery (patients with complete cytoreduction with NVRD after primary debulking surgery were excluded)
- Inoperable stage III disease
- Any stage IV disease
- Stage III or IV patients who were treated with neoadjuvant chemotherapy (patients with NVRD after interval debulking surgery were included)

Refer to Table 6 for detailed inclusion criteria related to treatment response after surgery and chemotherapy.

Enrolled patients had to have received 6 to 9 cycles of first-line platinum-based chemotherapy that resulted in an investigator-assessed CR or PR after 3 or more cycles.[2,3] Any residual disease following chemotherapy must have been less than 2 cm, and CA-125 values had to be either within the normal range or show a decrease of more than 90%. Patients were randomized within 12 weeks after completing the last dose of platinum-based chemotherapy administered on the first day of the last cycle.

Table 6: Inclusion Criteria about Treatment Response to Chemotherapy

Chemotherapy	Residual Tumour after Surgery[a]	Residual Tumour after Chemotherapy[b]	Eligible for PRIMA Trial
Stage III Patients			
Neoadjuvant	No constraint	≤ 2 cm	Yes
Neoadjuvant	No constraint	> 2 cm	No[b]
Adjuvant/Front-line	> 0 cm	≤ 2 cm	Yes
Adjuvant/Front-line	> 0 cm	> 2 cm	No[b]
Adjuvant/Front-line	0 cm	Not applicable	No[a]
Stage IV Patients			
Any	No surgery-related criterion	≤ 2 cm	Yes
Any	No surgery-related criterion	≥ 2 cm	No[b]

[a] Based on the criteria: Stage III patients who had undergone debulking surgery must have had residual disease after debulking surgery unless the patient received neoadjuvant therapy.
[b] Based on the criteria: Patients must have achieved a complete or partial (no measurable lesion >2 cm) tumour response to platinum-based regimen per RECIST criteria.

Data source: Clinical Study Protocol[3]

Tumour samples underwent central testing for homologous recombinant status using the myChoice© HRD test by Myriad Genetics.[2] Test scores range from 1 to 100 with higher scores indicating a greater number of genomic abnormalities on the basis of loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions. Any tumour that had a score greater than or equal to 42 or had a deleterious or suspected deleterious BRCA1/2 mutation was considered HRD (i.e., HRD-positive). Prior to Protocol Amendment 1 (described below in Table 8), enrollment was restricted to patients considered to be HRD-positive. Following this amendment, the eligibility criterion requiring HRD-positivity was removed and homologous recombination status became a stratification factor during randomization. Patients with an undetermined homologous recombinant status were eligible to participate in the trial. Tumour samples could be sent prior to the protocol-defined screening period after patients had signed the consent form.

The definitions for the biomarker test results used in the trial for BRCA and homologous recombination status are summarized in Table 7.

Table 7: Terminology of Biomarker Test Results used in the PRIMA trial

Terminology	Definition and details
gBRCAmut	A germline BRCA mutation is an inherited deleterious mutation in either a BRCA1 or BRCA2 tumour suppressor gene. Harmful mutations in either of these genes may produce a hereditary breast-ovarian cancer syndrome in affected persons. Cells with deleterious or suspected deleterious germline BRCA1 or BRCA2 mutations have a defect in the repair of DNA breaks by the error-free mechanism of homologous recombination. This defect results in the repair of such lesions by error-prone mutagenic pathways, such as single-strand annealing and nonhomologous end joining, leading to genomic instability. Women with harmful germline mutations in either BRCA1 or gBRCA2 have a risk of breast cancer that is approximately 5 times the normal risk, and a risk of ovarian cancer that is about 10 to 30 times normal.
Somatic BRCA mutation (sBRCAmut)	A somatic BRCA mutation is a deleterious or suspected deleterious alteration in the BRCA1 or BRCA2 genes that is acquired after conception (not hereditary). Somatic mutations can occur in any cell of the body except the germ cells (sperm and egg) and therefore are not passed on to children. A somatic BRCA mutation may also confer increased risk of cancer in affected cells. These mutations are not present in the germline.
BRCA wild type (BRCAwt)	A tumour which does not possess either a deleterious or suspected deleterious germline or a somatic BRCA mutation.
Homologous recombination deficiency (HRD)	Unlike the BRCA1 and BRCA2 mutation test, homologous recombination deficiency score is not based on individual gene mutations but represents dysregulation in the homologous recombination pathway (due to genetic mutations or alterations) leading to an inability to efficiently repair damaged DNA. Cells deficient in homologous recombination are more susceptible to the effects of DNA-damaging agents such as platinum agents or PARP inhibitors.
Homologous recombination deficient (HRD-positive)	Homologous recombination deficiency status was determined by the myChoice© HRD test. Any tumour that had a score ≥42 or had a deleterious or suspected deleterious BRCA1/2 mutation was considered homologous recombination deficient.
Homologous recombination proficient (HRP or HRD-negative)	Homologous recombination proficiency status was determined by the myChoice© HRD test. Any tumour that scored <42 and did not possess a deleterious or suspected deleterious BRCA1/2 mutation was considered homologous recombination proficient.

BRCA = breast cancer susceptibility gene; gBRCAmut = germline BRCA mutation; HRD = homologous recombination deficient; HRP = homologous recombination proficient; PARP = poly(adenosine diphosphate [ADP]–ribose) polymerase; sBRCA = somatic BRCA mutation.

Data source: González-Martín 2019[2]

Patients were randomized in a 2:1 ratio to receive niraparib or placebo using a central interactive web response system.[3] Randomization was stratified according to clinical response after first-line platinum-based chemotherapy (CR or PR), receipt of neoadjuvant chemotherapy (yes or no), and tumour homologous recombination status (deficient vs. proficient or not determined).[2] Unless gBRCAmut or sBRCAmut status was known, randomization could not occur prior to receiving on-study HRD test results. If a patient had a documented deleterious gBRCAmut or sBRCAmut by local testing results, randomization could occur prior to receipt of the myChoice© HRD test results; accordingly, the patient's tumour was considered HRD-positive for the purpose of stratification (these tumours were subsequently tested with the myChoice© HRD test). Patients were to receive the first dose of study treatment either on the day of randomization or within 7 days if possible. Laboratory tests were repeated if they were performed more than 7 days prior to the first dose of study treatment.

Patients, investigators, study staff, and the sponsor study team were blinded to the treatment assignment and tumour homologous recombination status of patients from the time of randomization to the database lock.[3] Study staff entered the stratification factors for clinical response after first-line platinum-based chemotherapy and receipt of neoadjuvant chemotherapy into the electronic data capture system; subsequently, an unblinded sponsor employee without affiliation to the study team entered the homologous recombination status for the final stratification factor for randomization. Patients and investigators could be unblinded for cases associated with important medical reasons as determined by the investigator and for specific non-urgent medical events. Patients who required unblinding were discontinued from study treatment but remained in the study until PD, death, withdrawal of consent, or loss to follow-up.

Protocol Amendments

The key amendments to the PRIMA trial protocol are summarized in Table 8.[3] The notable changes to the protocol included the addition of neoadjuvant chemotherapy and homologous recombination status as stratification factors; the revision of the inclusion criteria to specify high-grade and predominantly serous or endometroid ovarian cancers; provision of further guidance on the surgical and chemotherapy inclusion criteria; and revisions to the dosing scheme of niraparib to include both a fixed dose option and an individualized dose option based on patients' weight and/or platelet count (more details provided on this amendment in the *Interventions* section below).

Table 8: Summary of Key Protocol Amendments in the PRIMA trial

Amendment Number (Date)	Amendment Summary
Amendment 1 (December 1, 2016)	• TFST and next anti-cancer therapy following study treatment were added as secondary outcomes. • The relationship between homologous recombination status and platinum sensitivity for patients with ovarian cancer with an initial response to front-line platinum therapy was added as an exploratory outcome. • The administration of neoadjuvant chemotherapy and homologous recombination status were added as stratification factors. • The inclusion criteria were revised to specify high-grade and predominantly serous or endometroid ovarian cancers and to provide further guidance on the surgical and chemotherapy inclusion criteria. The exclusion criteria were also revised to provide more specific guidance. • MDS/AML were specified as AEs of special interest.
Amendment 2 (November 16, 2017)	• The dosing scheme was revised to include both a fixed dose option and an individualized dose option based on a patient's weight and/or platelet count (more details provided in the *Interventions* section below). Dose modification rules were also clarified due to this revised dosing scheme. • The sample size was revised from 330 patients to 468 patients based on a longer median PFS assumption for the placebo arm in both the HRD-positive population and the overall population.
Amendment 3 (February 12, 2018)	• The sample size was revised from 468 patients to 620 patients based on a longer median PFS assumption for patients with a BRCAmut in the placebo arm, which lead to a longer median PFS assumption for the placebo arm in both the HRD-positive population and the overall population.

AE = adverse event; AML = acute myeloid leukemia; BRCA = breast cancer susceptibility gene; BRCAmut = BRCA mutation; HRD = homologous recombination deficiency; MDS = myelodysplastic syndrome; PFS = progression-free survival; TFST = time-to-first subsequent therapy.

Data source: Clinical Study Protocol[3]

Study Assessments

Clinical visits occurred every cycle (28 ± 3 days).[2] Tumour assessments to assess for PD were performed by CT or MRI of the abdomen/pelvis at screening and then every 12 weeks ± 7 days until disease progression. Disease progression was assessed by BICR according to RECIST, version 1.1. Patients who discontinued treatment for a reason other than PD, death, withdrawal of consent or loss to follow-up, continued with assessments at the specified intervals. All patients were followed for OS and other secondary outcomes. Post-treatment assessment of survival status and the use of subsequent anti-cancer therapies were performed every 12 ± 2 weeks. If a patient discontinued treatment for progression that was not confirmed by BICR, scans and CA-125 testing were to continue every 12 ± 2 weeks until progression was confirmed. Clinical progression was reviewed if an increased CA-125 level was accompanied by histologic proof or clinical symptoms. The following data were collected in the electronic case report form for the next anticancer therapy following study treatment: name of drug (and/or class), start and stop date, progression date, dose limiting toxicities, and best response.[77]

CA-125 testing was conducted at screening, at day 1 of each treatment cycle, and at the EOT (within 7 days of last dose or discontinuation), and every 12 weeks post-treatment.[3] Progression of CA-125 was assessed according to the Gynecological Cancer InterGroup (GCIG) criteria. Physical examinations, vital sign measurements, and clinical laboratory tests were conducted on days 1 and 15 of the first treatment cycle, and on day 1 of each following cycle. Additionally, complete blood cell counts (CBCs) were conducted on days 8 and 22 of the first cycle.

Data on AEs and serious adverse events (SAEs) were collected from time of signing the consent form through to treatment discontinuation.[2] Collection of SAE data continued for 30 days after treatment discontinuation. Safety data could be reported by the patient or discovered by study staff (during physical examinations or by asking open-ended, non-leading questions) and were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and assessed for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Study Endpoints and Statistical Analyses

Efficacy Outcomes

Efficacy outcomes were assessed according to the ITT principle, defined as all patients who underwent randomization.[3] The primary endpoint of the trial was PFS assessed by BICR, which was evaluated hierarchically in patients with HRD-positive tumours and then in the overall patient population (i.e., all trial patients).[2] PFS was defined as the time from treatment randomization after completion of platinum-based chemotherapy to the earliest date of objective PD on imaging according to RECIST version 1.1 or death from any cause. PD was defined as meeting at least 1 of the following criteria:[3]

1) tumour progression according to RECIST version 1.1 assessed by CT or MRI
2) identification of new lesions or determination that existing lesions qualified for unequivocal PD (using additional diagnostic tests such as, histology/cytology, ultrasound techniques, endoscopy, and positron emission tomography), and CA-125 progression according to GCIG criteria
3) definitive clinical signs and symptoms of PD unrelated to non-malignant or iatrogenic causes such as intractable cancer-related pain, malignant bowel obstruction/worsening dysfunction, or unequivocal symptomatic worsening of ascites or pleural effusion, and CA-125 progression according to GCIG criteria

Note: An increase in CA-125 alone was not considered as meeting PD criteria.

The secondary outcomes assessed in the trial included the following:[2,3]

- OS defined as the time of randomization to the date of death by any cause
- TFST defined as the time from the date of randomization to date of the first subsequent anticancer therapy or death
- PFS-2 defined as the time from treatment randomization to the earlier date of assessment of progression on the next anti-cancer therapy following study treatment or death by any cause
- Time to CA-125 progression

Additionally, the following exploratory outcomes were also analysed but were not included in this report:[3]

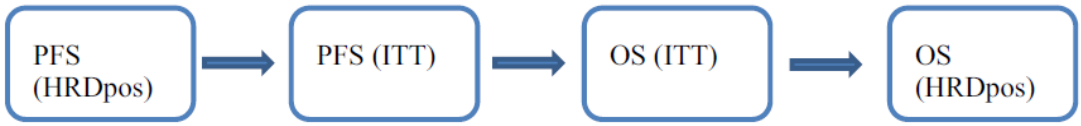
- Pharmacokinetics analyses
- Biomarkers in relation to ovarian cancer and PARP inhibition
- Relationship between homologous recombination status and platinum sensitivity in ovarian cancer patients who have initial response to front-line platinum therapy

All time-to-event outcomes (i.e., PFS, OS, TFST, and PFS-2) were analyzed using Kaplan-Meier (KM) methods and a 1-sided stratified log-rank test.[3] HRs and 2-sided 95% CIs were estimated using a Cox proportional-hazards model stratified by randomization factors. The type 1 error rate for PFS was controlled at a 1-sided 0.025 significance level.

For the assessment of PFS and OS, a hierarchical-testing procedure was used to control for the overall type 1 error (Figure 6). If the results for an outcome were positive (i.e., statistically significant) the next outcome in the hierarchy was assessed in the following order:[2]

- PFS in patients with HRD-positive tumours
- PFS in the overall population
- OS (interim analysis) at the time of final PFS analysis in the overall population and in patients with HRD-positive tumours
- OS analysis when the number of OS events is reached (future analysis when a data maturity of 60% is achieved)[6]

Figure 6: Hierarchical Testing Procedure in the PRIMA Trial



Data source: Statistical Analysis Plan[77]

To assess the consistency of the treatment effect, subgroup analyses of PFS (and OS, although these were not reported) were prespecified and performed in the following subgroups of patients: age, race, ECOG PS, disease stage, primary tumour site, geographic region, HRD status, BRCA status, baseline CA-125 level, use of neoadjuvant chemotherapy, and best response to first platinum regimen .[3] Cox proportional hazards models were used to estimate the HR (95% CI) for each subgroup.[77] Following Protocol Amendment 2, an individualized dose option (i.e., 300 mg or 200 mg of niraparib) based on a patient's baseline weight and or platelet count (more details provided in the *Interventions* section below) was implemented; thus, subgroup analyses based on the fixed and individualized starting dose options were planned.

Sample Size

Following Protocol Amendments 2 and 3 described above, the target enrollment for the PRIMA trial was 620 patients (including 310 patients who were HRD-positive).[2,3] The required sample size was calculated to provide 90% power to detect a difference in PFS between niraparib and placebo at a 1-sided significance level of 0.025. The target sample size corresponded to a HR of 0.50 for niraparib relative to placebo in the HRD-positive population, and a HR of 0.65 in the overall population. The target sample size estimation was based on the median duration of PFS in patients with ovarian cancer and a BRCAmut who received placebo, which was 21 months in in the HRD-positive population and 14 months in the overall population. Based on these assumptions, approximately 270 PFS events were expected for the final analysis of PFS in the overall population.

Interim Analysis

No interim analysis for PFS was planned.[3] An interim analysis of OS was planned to occur at the time of the PFS analysis.[2,3]

Sensitivity Analyses

To assess the robustness of the primary efficacy analysis results, several sensitivity analyses of PFS were pre-planned in both the HRD-positive and overall population (all using a stratified log-rank test and Cox model):[3]

- Investigator data to assess informative censoring
- BICR data using alternative censoring rules to assess attrition bias
- BICR data using stratification factors from the electronic case report form to assess stratification bias
- BICR data where progressions were not at the protocol-scheduled scan timepoints to assess evaluation-time bias
- BICR data using radiology only
- BICR data in the per-protocol population
- BICR data assessing subsequent anti-cancer therapy bias
- BICR data using only best response to platinum therapy and HRD status as stratification factors

Safety Outcomes

Safety outcomes were analyzed in the safety population, which was defined as all patients who had received at least 1 dose of study medication.[3] Patients were analyzed as treated. Safety data were summarized using descriptive statistics and no inferential statistical analyses were planned.

Patient Reported Outcomes - FOSI, EORTC-QLQ-C30, EORTC-QLQ-OV28, and EQ-5D-5L

PROs related to HRQoL were assessed using the FOSI, EORTC-QLQ-C30, EORTC-QLQ-OV28, and EQ-5D-5L questionnaires.[2] The questionnaires were administered every 8 weeks ± 7 days for 56 weeks beginning on Cycle 1 Day 1, then every 12 weeks ± 7 days thereafter while patients received study treatment. Once a patient discontinued treatment, PRO data were collected at the time of treatment discontinuation and at 4, 8, 12, and 24 weeks (± 1 week for each timepoint) following the end of treatment regardless of the receipt of subsequent treatment. PROs were completed in the patient's native language and were to be administered prior to the conduct of any other procedure at each study assessment.

Patient compliance for completing questionnaires was summarized by visit and was calculated as the number of patients with an evaluable form at each visit, divided by the number of patients expected to complete the form at that visit.[2] PROs were analyzed descriptively by measuring changes from baseline in overall score, sub-scores, and individual items when applicable.[3] A mixed-effects model for repeated measures was performed to compare between-treatment group differences adjusted for correlations across multiple time points within a patient and controlling for the baseline value.[2] The model was used to analyze data on treatment visits, EOT, and week 12 and 24 visits after EOT. The model included patient, treatment, analysis visit, and treatment-by-visit interaction as explanatory variables, and the baseline value as a covariate along with the baseline-by-visit interaction. Treatment, visit, and treatment-by-visit interactions were fixed effects in the model, and patient was treated as a random effect.[77] The adjusted mean difference and 95% CI were presented to illustrate the effect of treatment; and adjusted means and standard error bars were plotted over time.

The individual questionnaires are further described below. In general, there were no substitutions made to accommodate missing data points, however methods for handling incomplete PRO instruments were performed according to their scoring manuals.[3]

FOSI

The FOSI is a validated 8-item questionnaire that assesses symptoms of ovarian cancer related to pain, fatigue, nausea, vomiting, bloating, cramping, worry, and QoL, and is based on a subset of questions from the Functional Assessment of Cancer Therapy - Ovarian questionnaire.[3] Patients report their symptoms over 7 days on a Likert scale (score range: 0=not at all to 4=very much). The FOSI score was calculated in accordance with the FOSI scoring manual.[2] The average score was calculated as the average of the 8 individual item scores.[3] The total symptom index score was calculated as the total of the 8 individual item scores where scores range from 0 (severely symptomatic) to 32 (asymptomatic)) and a higher score indicates a better QoL.

If responses to items were missing and at least 50% of the items were answered (if less than 50% of the items were answered, the scale was regarded as missing), the subscale scores were prorated by multiplying the sum of the subscale by the number of items in

the subscale, then dividing by the number of items actually answered.[2] A change in score of 2 points was considered the MCID.[3] Changes in score from baseline were categorized as follows: 1) improved: change from baseline of ≥ 2 points, 2) stable: -2 < change from baseline < 2, or 3) worsening: change from baseline ≤ -2 or 'patient was too ill' was listed as the reason for a patient not completing the FOSI form. For reporting the proportion of patients with a FOSI response of 'improved', 'stable', or 'worsening', the denominator was the number of all the patients with non-missing FOSI scores at baseline and at each corresponding visit. The time-to-symptom worsening on the FOSI score was analyzed using time-to-event methodology and was defined as the time from the date of randomization to the date of first worsened FOSI score (i.e., change from baseline ≤ -2).

EORTC-QLQ-C30 and EORTC-QLQ-OV28

The EORTC-QLQ-C30 is a validated 30-item HRQoL instrument consisting of 3 domains that was developed to assess a wide variety of interventions on a common scale.[2] The first domain requires patients to rate their need for assistance with or difficulty completing certain activities (such as walking and lifting) and daily self-care tasks. The second domain requires patients to rate their previous week for their limitations on work/hobbies, family life, social activities, and finances; shortness of breath; need for rest/tiredness; pain and its interference with activity; ability to sleep; weakness; appetite; symptoms of nausea, vomiting, constipation, and diarrhea; ability to concentrate/remember; and emotions (irritability and depression). The third domain requires patients to rate their overall health and overall QoL. The first and second domains use a 5-point Likert scale (score range: 0=not at all to 4=very much), and the third domain uses a 7-point Likert scale (score range: 1=very poor to 7=excellent). The EORTC-QLQ-OV28 is an ovarian cancer-specific instrument, which assesses ovarian cancer patients' abdominal/gastrointestinal symptoms, other chemotherapy side effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment, and sexual functioning.[2]

Scale scores were calculated by averaging the items within scales and transforming the average scores linearly, producing a scale with a range from 0 to 100.[3] A high score on a functional scale represents a high level of function, while a high score on a symptom scale represents a high level of symptoms/problems. If responses to items were missing for a scale and more than 50% of the items were answered (if less than 50% of the items were answered, the scale was regarded as missing), the scale score was calculated on the completed items.

A change in score of 10 points from baseline was considered the MCID.[3] Changes in score from baseline were categorized as follows for the global health status/QoL and the functional scales: 1) improved: change from baseline of ≥ 10 points, 2) stable: - 10 < change from baseline < 10, or 3) worsening: change from baseline ≤ - 10 or 'patient was too ill' was listed as the reason for a patient not completing the form. The changes from baseline were categorized as the following for the symptoms scales: 1) improved: change from baseline of ≤ - 10 points, 2) stable: - 10 < change from baseline < 10, or 3) worsening: change from baseline ≥ 10 or 'patient was too ill' was listed as the reason for a patient not completing the form. For reporting the proportion of patients with a response of 'improved', 'stable', or 'worsening', the denominator was the number of all the patients with non-missing scores at baseline and at each corresponding visit. The time-to-symptom worsening on the EORTC-QLQ-OV28 abdominal/GI score was analyzed using time-to-event methodology and was defined as the time from the date of randomization to the date of first worsened EORTC-QLQ-OV28 abdominal/GI score (i.e., change from baseline ≥ 10).

EQ-5D-5L

The EQ-5D-5L is a general preference-based HRQoL scale consisting of 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with 5 levels of response in each dimension (level 1=no problems to level 5=extreme problems).[2] The EQ-5D-5L scores were determined from health states using the US value set. The EQ-5D-5L descriptive system was calculated by mapping the 5L descriptive system data onto the 3L valuation set (an older version of the EQ-5D) using the EQ-5D-5L crosswalk value set.[3] An index value of 1 equates to full health and the closer the value is to 1, the better the health of the patient; therefore, a higher index value indicates a better QoL. The EQ-5D-5L VAS was used to obtain an assessment of the patient's perception of their overall health status; scores range on a scale from 0 (worst imaginable health) to 100 (best imaginable health). The index value was considered as missing when responses for 1 or more of the 5 dimensions was missing.

Funding

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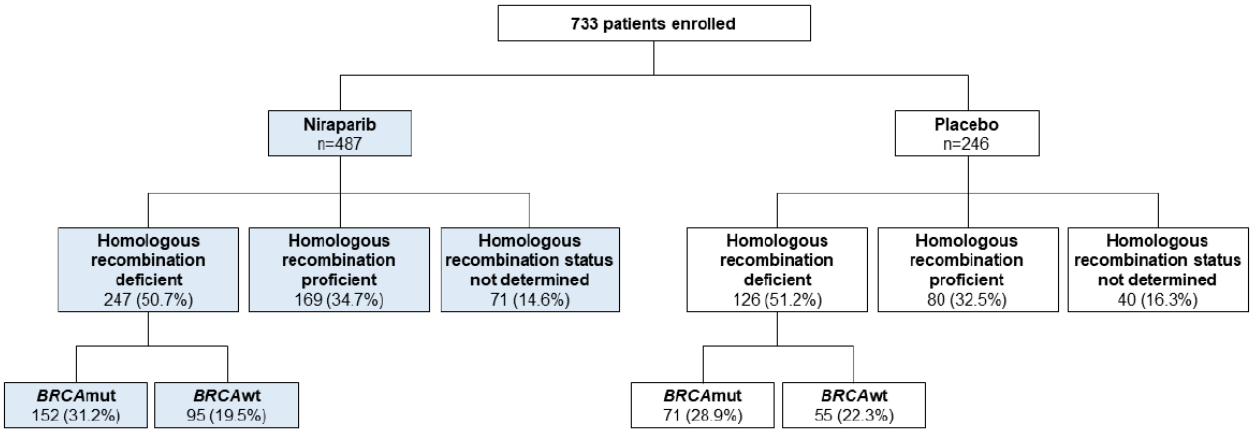
trial conduct which included the collection, analysis, and interpretation of trial data. Statistical analyses were performed by a clinical research organization, Veristat LLC, and wee overseen by the sponsor according to the statistical analysis plan. All analyses were independently reviewed and approved by a statistician from the Nordic Society of Gynecological Oncology (European Network of Gynaecological Oncological Trial Groups lead group). One of the authors of the manuscript was directly employed by the sponsors.

b) Populations

Biomarker populations

The biomarker populations in the PRIMA trial are summarized in Figure 7.[2] A total of 733 patients were enrolled in the trial, with 487 patients randomized to the niraparib group and 246 patients randomized to the placebo group. In the niraparib group, 247 (50.7%) patients had HRD-positive tumours of whom 152 (31.2%) had a BRCAmut and 95 (19.5%) were BRCAwt, 169 (34.7%) patients had HRP tumours (i.e., HRD-negative), and the homologous recombination status was not determined for 71 (14.6%) patients. In the placebo group, 126 (51.2%) patients had HRD-positive tumours of whom 71 (28.9%) had a BRCAmut and 55 (22.3%) were BRCAwt, 80 (32.5%) patients had HRP tumours, and the homologous recombination status was not determined for 40 (16.3%) patients.

Figure 7: Biomarker Populations in the PRIMA trial



BRCA = breast cancer susceptibility gene; BRCAmut = BRCA mutated; BRCAwt = BRCA wild type.

Figure source: From the New England Journal of Medicine, Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer, Volume No: 381(25), Suppl. Appendix, Page No: 40. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[2]

Demographic Characteristics

The baseline demographic and clinical characteristics of the PRIMA trial population for both the overall population and the HRD-positive population are summarized in Table 9.

In the overall population, 487 patients were randomized to receive niraparib and 246 patients were randomized to receive placebo.[2] The median age was 62 years in both groups. The majority of patients were 'White' (niraparib group: 89.5%; placebo group: 89.0%)[4] and had an ECOG PS of 0 (niraparib group: 69.2%; placebo group: 70.7%).[2] The median weight of patients in the niraparib and placebo groups was 66.00 kg and 65.55 kg, respectively.[4]

In the HRD-positive population, 247 patients were randomized to receive niraparib and 126 patients were randomized to receive placebo.[2] The median age was 58 years in both groups. The majority of patients were 'White' (niraparib group: 88.3%; placebo group: 85.7%)[4] and had an ECOG PS of 0 (niraparib group: 73.7%; placebo group: 77.0%).[2] The median weight of patients in the niraparib and placebo groups was 65.30 kg and 65.10 kg, respectively.[4]

Disease Characteristics

The disease characteristics of the PRIMA trial population for both the overall population and the HRD-positive population are summarized in Table 9.

In the overall population, baseline disease characteristics were generally well balanced between the treatment groups. The primary tumour sites (niraparib group versus the placebo group) were ovarian (79.7% versus 81.7%), fallopian tube (13.3% versus 13.0%) and peritoneum (7.0% versus 5.3%) and histological subtypes were serous (95.5% versus 93.5%), endometrioid (2.3% versus 3.7%), and 'other' (2.3% versus 2.4%). Most patients in each treatment group had International FIGO stage III cancer (65.3% versus 64.2%), received neoadjuvant chemotherapy (66.1% versus 67.9%), and had achieved a CR after their platinum-based chemotherapy (69.2% versus 70.0%).[2] Among patients who received neoadjuvant chemotherapy, 26% had NVRD after interval debulking surgery.[4] Most patients were BRCAwt (63.7% versus 66.3%) and the median time from diagnosis to first dose of study treatment was 7.68 months in the niraparib group and 7.74 months in the placebo group.[4]

In the HRD-positive population, baseline disease characteristics were generally well balanced between the treatment groups and similar to the overall population. The primary tumour sites (niraparib group versus the placebo group) were ovarian (81.4% versus 83.3%), fallopian tube (13.0% versus 10.3%), and peritoneum (5.7% versus 6.3%); and histological subtypes were serous (94.7% versus 92.1%), endometrioid (2.0% versus 4.8%), and 'other' (3.2% versus 3.2%). Most patients in each treatment group had International FIGO stage III cancer (65.2% versus 61.9%), received neoadjuvant chemotherapy (63.2% versus 63.5%), and had achieved a CR after their platinum-based chemotherapy (74.9% versus 73.8%).[2] The median time from diagnosis to first dose was 7.68 months in the niraparib group and 7.44 months in the placebo group.[4]

Patients' prior history of myelosuppression (including thrombocytopenia, anemia, leukopenia, and neutropenia) was relatively balanced between the populations and treatment groups.[5]

Table 9: Baseline Demographic and Clinical Characteristics of Patients in the PRIMA trial (ITT population)

Characteristic	HRD-positive Population (n=373)		Overall Population (n=733)	
	Niraparib (n=247)	Placebo (n=126)	Niraparib (n=487)	Placebo (n=246)
Median age (range) – years	58 (32-83)	58 (33-82)	62 (32-85)	62 (33-88)
International FIGO stage – n (%)				
III	161 (65.2)	78 (61.9)	318 (65.3)	158 (64.2)
A	4 (1.6)	1 (0.8)	7 (1.4)	4 (1.6)
B	10 (4.0)	9 (7.1)	16 (3.3)	12 (4.9)
C	140 (56.7)	67 (53.2)	285 (58.5)	138 (56.1)
Not specified	7 (2.8)	1 (0.8)	10 (2.1)	4 (1.6)
IV	86 (34.8)	48 (38.1)	169 (34.7)	88 (35.8)
ECOG PS – n (%)				
0	182 (73.7)	97 (77.0)	337 (69.2)	174 (70.7)
1	65 (26.3)	29 (23.0)	150 (30.8)	72 (29.3)
Primary tumour site – n (%)				
Ovarian	201 (81.4)	105 (83.3)	388 (79.7)	201 (81.7)
Fallopian tube	32 (13.0)	13 (10.3)	65 (13.3)	32 (13.0)
Peritoneum	14 (5.7)	8 (6.3)	34 (7.0)	13 (5.3)

Characteristic	HRD-positive Population (n=373)		Overall Population (n=733)	
	Niraparib (n=247)	Placebo (n=126)	Niraparib (n=487)	Placebo (n=246)
Histological subtype – n (%)				
Serous	234 (94.7)	116 (92.1)	465 (95.5)	230 (93.5)
Endometroid	5 (2.0)	6 (4.8)	11 (2.3)	9 (3.7)
Other	8 (3.2)	4 (3.2)	11 (2.3)	6 (2.4)
Receipt of neoadjuvant chemotherapy - n (%)				
Yes	156 (63.2)	80 (63.5)	322 (66.1)	167 (67.9)
No	91 (36.8)	46 (36.5)	165 (33.9)	79 (32.1)
Clinical response after platinum-based chemotherapy — n (%)	185 (74.9)	93 (73.8)	337 (69.2)	172 (70.0)
CR	62 (25.1)	33 (26.2)	150 (30.8)	74 (30.0)
PR				
CA-125 level — n (%)				
≤ULN	236 (95.5)	120 (95.2)	450 (92.4)	226 (91.9)
>ULN	9 (3.6)	5 (4.0)	34 (7.0)	18 (7.3)
Missing data	2 (0.8)	1 (0.8)	3 (0.6)	2 (0.8)
Age – n (%) years				
18- <65	173 (70.0)	88 (69.8)	297 (61.0)	147 (59.8)
65 <75	49 (19.8)	32 (25.4)	136 (27.9)	77 (31.3)
≥65	74 (30.0)	38 (30.2)	190 (39.0)	99 (40.2)
≥75	25 (10.1)	6 (4.8)	54 (11.1)	22 (8.9)
Weight – kg				
Median	65.30	65.10	66.00	65.55
Min, Max	38.0 to 137.0	38.5 to 136.5	38.0 to 137.0	37.8 to 146.5
Race – n (%)				
White	218 (88.3)	108 (85.7)	436 (89.5)	219 (89.0)
Black	5 (2.0)	1 (0.8)	10 (2.1)	2 (0.8)
Asian	10 (4.0)	8 (6.3)	14 (2.9)	11 (4.5)
American Indian or Alaskan Native	1 (0.4)	0	1 (0.2)	0
Native Hawaiian or Other Pacific Islander	1 (0.4)	0	1 (0.2)	0
Unknown	5 (2.0)	0	6 (1.2)	1 (0.4)
Not reported	7 (2.8)	9 (7.1)	19 (3.9)	13 (5.3)
Ethnicity – n (%)				
Hispanic or Latino	18 (7.3)	5 (4.0)	28 (5.7)	10 (4.1)
Not Hispanic or Latino	220 (89.1)	114 (90.5)	432 (88.7)	223 (90.7)
Unknown	6 (2.4)	5 (4.0)	17 (3.5)	9 (3.7)
Not reported	3 (1.2)	2 (1.6)	10 (2.1)	4 (1.6)
Region – n (%)				
US and Canada	ND	ND	218 (44.8)	115 (46.7)
Eastern Europe	ND	ND	61 (12.5)	27 (11.0)
Western Europe	ND	ND	192 (39.4)	96 (39.0)

Characteristic	HRD-positive Population (n=373)		Overall Population (n=733)	
	Niraparib (n=247)	Placebo (n=126)	Niraparib (n=487)	Placebo (n=246)
Reproductive Status				
Childbearing Potential	1 (0.4)	0	2 (0.4)	0
Mom-childbearing potential	246 (99.6)	126 (100)	485 (99.6)	246 (100)
Time from diagnosis to first dose, median months	7.680	7.440	7.680	7.740
BRCA status – n (%)				
BRCAmut	NR	NR	152 (31.2)	71 (28.9)
BRCA1	NR	NR	105 (21.6)	43 (17.5)
BRCA2	NR	NR	47 (9.7)	28 (11.4)
BRCAwt	NR	NR	310 (63.7)	163 (66.3)
BRCA not determined	NR	NR	25 (5.1)	12 (4.9)
HRD status – n (%)				
HRD-positive	NR	NR	247 (50.7)	126 (51.2)
tBRCAmut	NR	NR	152 (31.2)	71 (28.9)
non-tBRCAmut and HRDpos	NR	NR	95 (19.5)	55 (22.4)
HRD-negative	NR	NR	169 (34.7)	80 (32.5)
HRD not determined	NR	NR	71 (14.6)	40 (16.3)

BRCA = breast cancer susceptibility gene; BRCAmut = BRCA mutation; BRCAwt = BRCA wild type; CA-125 = cancer antigen 125; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; FIGO = International Federation of Gynecology and Obstetrics; gBRCAmut = germline BRCA mutation; HRD = homologous recombination deficiency; ITT = intention-to-treat; ND = not determined; NR = not reported; PR = partial response; SD = standard deviation; tBRCAmut = tumour tested BRCA mutation; ULN = upper limit of normal.

Data source: González-Martín ET Al 2019,[2] EPAR[4]

Previous Therapies

Trial patients' prior treatment history for ovarian cancer is summarized in Table 10. As per the trial eligibility requirements, all enrolled patients had received 1 prior line of platinum-based chemotherapy.[2] Overall, previous surgical and radiotherapy treatments for ovarian cancer were similar between the treatment groups and by patient population (Table 10).

In the overall population (niraparib versus placebo), the number of cycles of first-line platinum-based chemotherapy received by patients was balanced between the treatment groups; the majority of patients had received 6 cycles (68.4% versus 69.1%).[4] Most patients had received a taxane (97.7% versus 96.3%) and/or prior carboplatin (96.3% versus 95.5%) and the median duration of time from completion of platinum therapy to randomization was 8.00 weeks in the niraparib group and 8.14 weeks in the placebo group. Most patients had 1 previous surgery for their cancer (69.6% versus 67.9%) and had not received radiotherapy prior to trial enrollment (97.5% versus 97.2%).

Similarly, in the HRD-positive population (niraparib versus placebo), the number of cycles of first-line platinum-based chemotherapy was balanced between the treatment groups; the majority of patients had received 6 cycles (66.8% versus 66.7%).[4] Most patients had received a taxane (97.2% versus 96.8%) and/or prior carboplatin (94.7% versus 94.4%) and the median duration of time from completion of platinum therapy to randomization was 8.43 weeks in the niraparib group and 7.93 weeks in the placebo group. Most patients (niraparib versus placebo) had 1 previous surgery for their cancer (72.5% versus 68.3%) and had not received radiotherapy prior to trial enrollment (96.8% versus 97.6%).

Table 10: Patients' Prior Treatment for Ovarian Cancer (ITT Population)

Cancer Treatment n (%)	HRD-positive Population (n=373)		Overall Population (n=733)	
	Niraparib (n=247)	Placebo (n=126)	Niraparib (n=487)	Placebo (n=246)
Any surgeries/procedures related to the study indication:				
Yes	247 (100)	126 (100)	481 (98.8)	245 (99.6)
No	0	0	6 (1.2)	1 (0.4)
Number of surgeries				
1	179 (72.5)	86 (68.3)	339 (69.6)	167 (67.9)
2	62 (25.1)	33 (26.2)	129 (26.5)	68 (27.6)
≥ 3[a]	6 (2.4)	7 (5.6)	13 (2.7)	10 (4.1)
Radiotherapy prior to enrollment[b]				
Yes	8 (3.2)	3 (2.4)	12 (2.5)	7 (2.8)
No	239 (96.8)	123 (97.6)	475 (97.5)	239 (97.2)
Duration (months) of first-line platinum therapy				
Mean (SD)	5.22 (1.461)	5.11 (1.365)	5.25 (1.400)	5.32 (1.475)
Median (min, max)	5.09 (1.2 to 10.7)	5.04 (3.1 to 10.8)	5.09 (1.2 to 10.7)	5.22 (3.1 to 10.8)
Total number of cycles in first-line platinum therapy				
6	165 (66.8)	84 (66.7)	333 (68.4)	170 (69.1)
7	24 (9.7)	15 (11.9)	57 (11.7)	31 (12.6)
8	17 (6.9)	8 (6.3)	46 (9.4)	24 (9.8)
9	11 (4.5)	5 (4.0)	21 (4.3)	7 (2.8)
Missing[c]	30 (12.1)	14 (11.1)	30 (6.2)	14 (5.7)
Duration (weeks) from end date of first-line platinum therapy to date of randomization				
Mean (SD)	8.70 (3.648)	8.29 (3.763)	8.41 (3.209)	8.22 (3.340)
Median (min, max)	8.43 (0.3 to 28.0)	7.93 (1.1 to 26.1)	8.00 (0.3 to 28.0)	8.14 (1.1 to 26.1)
Other prior treatments				
Prior taxane	240 (97.2)	122 (96.8)	476 (97.7)	237 (96.3)
Prior carboplatin	234 (94.7)	119 (94.4)	469 (96.3)	235 (95.5)
Prior cisplatin	23 (9.3)	16 (12.7)	34 (7.0)	22 (8.9)
Prior doxorubicin	5 (2.0)	1 (0.8)	7 (1.4)	2 (0.8)
Prior gemcitabine	2 (0.8)	2 (1.6)	6 (1.2)	3 (1.2)
Prior bevacizumab	5 (2.0)	0	6 (1.2)	1 (0.4)
Prior cyclophosphamide	4 (1.6)	1 (0.8)	5 (1.0)	3 (1.2)
Prior other	6 (2.4)	1 (0.8)	11 (2.3)	3 (1.2)

HRD = homologous recombination deficiency; SD = standard deviation.

Notes:

a Per protocol, ≥3 debulking surgeries were prohibited. The inconsistency is due to all types of surgeries/procedures being recorded/counted instead of only the debulking surgeries.

b Prior radiotherapy included treatment for ovarian cancer and/or other indications in subjects' medical history.

c Per original protocol, with only subjects with HR-deficient status were enrolled, the number of cycles was not collected, but was estimated from start and end date of chemotherapy for eligibility review.

Data source: EPAR[4]

c) Interventions

Treatment

Patients were randomized 2:1 to receive either niraparib or placebo once daily in 28-day cycles for 36 months or until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up.[2,3] Crossover to niraparib was not allowed in the PRIMA trial for patients randomized to placebo.[2] Prior to Protocol Amendment 2 on November 16, 2017, patients received a fixed-dose of 300 mg daily (3 x 100 mg niraparib capsules or 3 placebo capsules matched in appearance to niraparib); however, following the amendment, an individualized dose option based on a patient's weight and/or platelet count was implemented. Patients with a baseline body weight of less than 77kg and/or a baseline platelet count of less than 150 000 µL were administered a 200 mg dose once daily (2 x 100 mg niraparib capsules or 2 placebo capsules matched in appearance to niraparib).[3] The original dose of 300 mg was chosen based on results from a phase I dose-escalation study,[78] and the protocol amendment instituting the individualized dose option was informed by the results of the NOVA trial (a phase III RCT that evaluated the efficacy and safety of niraparib compared to placebo as maintenance treatment in adult patients with platinum-sensitive, recurrent ovarian cancer).[40] In the NOVA trial, most patients in the niraparib group required dose modification due to TEAEs; however, these dose modifications did not affect treatment efficacy.[40] Exploratory analyses of the NOVA trial data demonstrated that baseline body weight and platelet count were associated with an increased risk of TEAEs, particularly grade 3/4 thrombocytopenia. These findings were subsequently confirmed in a separate study population.[79] Thus, a starting dose of 200 mg was considered in patients with body weight less than 77 kg and platelet count less than 150,000/µL to decrease the incidence of TEAEs.[77]

The use of other anti-cancer therapy was not permitted during the trial.[3] Palliative radiotherapy (excluding the pelvic region and/or palliative radiotherapy encompassing greater than 20% of the bone marrow within 1 week of the first dose of study treatment) was allowed for pre-existing small areas of painful metastases that could not be managed with local or systemic analgesics, as long as no evidence of disease progression was present. Prophylactic cytokines (granulocyte colony-stimulating factor) were not to be administered in the first cycle of the study but were permissible in subsequent cycles according to local guidelines.

Treatment/Dose Interruptions and Dose Reductions

Dose interruptions and/or reductions could be implemented at the investigator's discretion at any time in the trial for any grade toxicity that was considered intolerable by the patient.[2]

The guidelines used in the trial to manage dose reductions for non-hematological toxicities are summarized in Table 11.[2] Treatment interruptions were required for any non-hematological NCI CTCAE (version 4.03) grade 3 or 4 AE that the investigator considered to be treatment-related. If the toxicity was resolved to baseline or less than or equal to grade 1 within 28 days, treatment could be restarted at a reduced dose (either 200 mg once daily or 100 mg once daily depending on the starting dose) [first dose reduction]. If the toxicity recurred at a similar or worse grade, a second dose interruption was allowed in patients with an initial dose of 300 mg, followed by a further dose reduction to 100 mg once daily [second dose reduction]. If after the second dose reduction the toxicity was not resolved or recurred at a similar or worse grade toxicity recurred after 2 dose reductions, the patient was required to permanently discontinue treatment. No more than 2 dose reductions were permitted. For patients with an initial dose of 200 mg, only 1 dose reduction was allowed. No further dose reductions were permitted without discussion with a medical monitor. In all patients requiring a dose interruption, if the toxicity was not resolved to baseline or less than or equal to grade 1 within 28 days, and/or the patient had already undergone the maximum dose reductions, treatment was permanently discontinued.

Table 11: Dose Reduction Guidelines for Non-Hematological Toxicity used in the PRIMA trial

Dose level	Initial dose: 3 capsules per day	Initial dose: 2 capsules per day
Starting dose	3 capsules once daily (300 mg/day)	2 capsules once daily (200 mg/day)
First dose reduction	2 capsules once daily (200 mg/day)	1 capsule once daily (100 mg/day)
Second dose reduction	1 capsule once daily (100 mg/day)	Patient must discontinue treatment

Table source: From the New England Journal of Medicine, Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer, Volume No: 381(25), Suppl. Appendix, Page No: 23. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[2]

The guidelines used in the trial to manage dose modifications or reductions for hematologic toxicities are summarized in Table 12.[2] If dose modifications were required to manage hematological toxicity, weekly blood draws for CBC were required for 4 weeks after the AE had resolved to prespecified levels. If a patient did not return to prespecified levels within 4 weeks of the dose interruption or if the patient had already had maximum dose reductions as outlined for non-hematological toxicities, the patient permanently discontinued treatment. A patient requiring transfusion of platelets or red blood cells or hematopoietic growth factor support had their dose reduced if they were able to resume treatment. In cases where MDS/AML were confirmed by a hematologist, treatment was permanently discontinued.

Table 12: Dose Modification and Reduction Guidelines for Hematologic Toxicity used in the PRIMA trial

Monitor CBC until the AE resolves. To ensure safety of the new dose, CBC weekly blood draws were required for an additional 4 weeks after the AE resolves. Continue monitoring on day 1 of every cycle thereafter. If MDS/AML or secondary cancers (new malignancies other than MDS/AML) is confirmed, discontinue niraparib.	
Platelet count <100,000/μL	**First occurrence:** Withhold study treatment for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. For adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the medical monitor is required to resume niraparib. Resume study treatment at same or reduced dose per Table 11. If platelet count was <75,000/μL, resume at a reduced dose after recovery. **Second occurrence:** Withhold study treatment for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. For adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the medical monitor is required to resume niraparib. Resume niraparib at a reduced dose per Table 12. Discontinue study treatment if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period or if the patient has already undergone maximum dose reductions per Table 12.
Neutrophil count <1000/μL or hemoglobin <8 g/dL	Withhold study treatment for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1500/μL or hemoglobin returns to ≥9 g/dL. For adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the medical monitor is required to resume niraparib. Resume niraparib at a reduced dose per Table 12. Discontinue study treatment if neutrophil count or hemoglobin level has not returned to acceptable levels within 28 days of the dose interruption period or if the patient has already undergone maximum dose reductions per Table 12.
Hematologic adverse reaction requiring transfusion	For patients with a platelet count ≤10,000/μL, platelet transfusion should be considered. If there are other risk factors such as coadministration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. Resume study treatment at a reduced dose per Table 12.

AE = adverse event; AML = acute myeloid leukemia; CBC = complete blood cell count; MDS = myelodysplastic syndrome.

Table source: From the New England Journal of Medicine, Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer, Volume No: 381(25), Suppl. Appendix, Page No: 24. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[2]

Drug Exposure

Treatment exposure data from the PRIMA trial are summarized in Table 13. Patient exposure to study drug was reported in the safety population (defined as all patients who had received at least 1 dose of either niraparib or placebo)[2], which included a total of 728 patients in the overall population comprised of 484 patients in the niraparib group and 244 patients in the placebo group; and 370 patients in the HRD-positive population comprised of 245 patients in the niraparib group and 125 patients in the placebo group.

In the safety population, the median duration of treatment exposure from the first to last dose was 11.1 months in the niraparib group and 8.3 months in the placebo group, and the median time on study was 14.8 months and 14.7 months, respectively.[5] The median number of treatment cycles received by patients was 12.5 in the niraparib group and 9.0 in the placebo group with 50.0% and 39.8% of patients, respectively, starting more than 12 cycles. The median dose intensity in the niraparib group versus the placebo group was 181.3 mg/day versus 290.6 mg/day, respectively, and the median relative dose intensity was 62.6% versus 98.9%, respectively.

Overall, rats of dose interruption and dose reduction for any reason were higher in the niraparib group (79.5% and 74.8%, respectively) compared to the placebo group (23.8% and 12.3%, respectively).

Table 13: Overall Study Drug Exposure and Compliance in the PRIMA trial (Safety Population)

	HRDpos		Overall	
Compliance	**Niraparib (N=245)**	**Placebo (N=125)**	**Niraparib (N=484)**	**Placebo (N=244)**
Total number of capsules consumed[a]				
Mean (StD)	624.7 (446.48)	864.2 (545.72)	533.7 (410.40)	765.2 (522.32)
Median	537.0	753.0	443.0	626.5
Q1, Q3	327.0, 838.0	450.0, 1260.0	208.0, 751.0	373.0, 1173.0
Min, Max	9, 2574	33, 2485	9, 2574	30, 2485
Dose intensity (mg/day)[b]				
Mean (StD)	174.7 (69.81)	260.3 (51.66)	174.7 (67.31)	259.9 (50.66)
Median	182.2	293.9	181.3	290.6
Q1, Q3	106.6, 208.1	204.2, 299.3	108.9, 206.9	200.6, 299.3
Min, Max	31, 350	58, 308	31, 350	58, 327
Relative dose intensity[c]				
Mean (StD)	65.0 (25.19)	94.7 (14.15)	64.8 (24.81)	94.9 (13.74)
Median	62.8	99.1	62.6	98.9
Q1, Q3	42.3, 89.8	95.1, 100.0	42.3, 90.6	95.3, 100.0
Min, Max	16, 175	19, 143	16, 175	19, 144

HRDpos = homologous recombination deficiency positive; StD = standard deviation.

Data source: Clinical Study Report[5]

Prior to the amendment of the dosing schedule, a total of 473 patients in the overall population, including 315 in the niraparib treatment group, had received the fixed starting dose of 300 mg.[4] After implementation of the revised dosing scheme, a total of 238 patients (156 in the niraparib group; 82 in the placebo group) received either 200 mg or 300 mg in accordance with body weight and platelet count; of these patients, 122 (25.1%) in the niraparib group and 61 (24.7%) of patients in the placebo group received 200 mg as their individualized dose.[4]

The patients who received the individualized starting dose had a shorter follow-up time than patients enrolled before the amendment. Therefore, patients who received individualized dosing received fewer treatment cycles and less treatment exposure. A summary of the treatment exposure by dosing scheme is provided in Table 13. In the overall population, the median relative dose intensity was 66.4% in the niraparib group and 99.1% in the placebo group for patients who received the individualized starting dose, compared to 60.6% in the niraparib group and 98.8% in the placebo group who received the fixed starting dose. Treatment exposure by dosing scheme was similar in the HRD-positive population.

Table 14: Summary of Overall Exposure to Study Drug by Group and Dosing Scheme

Parameter	Niraparib			Placebo
	All	Individualized Starting Dose of 200 mg or 300 mg[e]	Fixed Starting Dose of 300 mg	All
Number of cycles started, n	484	169	315	244
Mean (SD)	11.7 (7.38)	9.8 (5.41)	12.7 (8.09)	10.8 (6.66)
Median	12.5	12.0	13.0	9.0
Min, max	1 to 31	1 to 18	1 to 32	1 to 31
Overall treatment duration (month)[a], n	484	169	315	244
Mean (SD)	10.3 (6.63)	8.6 (4.81)	11.3 (7.26)	9.5 (5.93)
Median	11.1	11.0	11.5	8.3
Min, max	0 to 19	0 to 16	0 to 19	0 to 28
Actual treatment duration (month)[b], n	484	169	315	244
Mean (SD)	9.7 (6.50)	8.2 (4.75)	10.6 (7.14)	9.4 (5.88)
Median	10.4	10.0	10.7	8.3
Min, max	0 to 29	0 to 16	0 to 29	0 to 28
Dose intensity (mg/day)[c], n	481	168	313	244
Mean (SD)	174.7 (67.31)	162.1 (57.98)	181.4 (70.99)	259.9 (50.66)
Median	181.3	178.6	181.8	290.6
Min, max	31 to 350	31 to 350	73 to 307	58 to 327
Relative dose intensity (%)[d], n	481	168	313	244
Mean (SD)	64.8 (24.81)	72.7 (24.99)	60.5 (23.66)	94.9 (13.74)
Median	62.6	66.4	60.6	98.9
Min, max	16 to 175	16 to 175	24 to 102	19 to 144

AE = adverse event; SD = standard deviation.
Notes:
[a] Overall treatment duration = last dose date – first dose date + 1.
[b] Actual treatment duration = last dose date – first dose date – duration of dose interruption(s) + 1.
[c] Dose intensity (mg/day) = sum of total daily doses actually consumed/ overall treatment duration
[d] Relative dose intensity (%) = dose intensity/assigned starting dose in mg)*100.
[e] Individualized starting dose (200 mg or 300mg /day) based on baseline weight and baseline platelet count level.

Data source: EPAR 2020[4]

d) Patient Disposition

The disposition of patients through the PRIMA trial is summarized in Table 15. Of the 989 patients who were assessed for eligibility, 256 were determined to be ineligible and 733 were randomized. Most screening failures were due to the patient not meeting the clinical or laboratory inclusion criteria, which was primarily attributed to a lack of having either CA-125 in the normal range or CA-125 decreased by more than 90% during front-line therapy that was not stable for more than 7 days.[2,4] In the overall population, a total of 5 patients (3 in the niraparib group and 2 in the placebo group) were randomized but did not receive assigned treatment. The 3 patients in the niraparib group did not receive treatment for the following reasons: one was no longer eligible due to a CA-125 increase of more than 15% from nadir at post-screening visit (HRD-positive patient); one was not able to attend the Cycle 1 Day 1 visit so all screening procedures were outside of window and the patient was not willing to repeat testing (HRD-positive patient); 1 patient decided not to participate 2 days after signing the informed consent form but before first dose (HRD-negative patient).[6] The 2

patients in the placebo group (2/246) did not receive treatment for the following reasons: 1 was randomized by error before eligibility screen failure was indicated (platelet count was not within eligible range; HRD-positive patient); 1 patient had laboratory tests at the Cycle 1 Day 1 visit that were worse than required at screening and this patient choose not to repeat the tests (HRD-negative patient).

In the overall population, a smaller proportion of patients had discontinued treatment in the niraparib group compared to the placebo group (63.0% versus 71.1%).[2] Compared to placebo, fewer patients in the niraparib group had discontinued treatment due to disease progression (44.8% versus 65.9%) and more patients had discontinued due to AEs (11.9% versus 2.0%). As of the primary data cut-off date (May 17, 2019), 246 patients (177 in the niraparib group and 69 in the placebo group) were still receiving treatment.

Similarly, in the HRD-positive population, a smaller proportion of patients had discontinued treatment in the niraparib group compared to the placebo group (50.2% versus 65.9%).[2] Compared to placebo, fewer patients in the niraparib group had discontinued treatment due to disease progression (32.4% versus 60.3%) and more patients had discontinued due to AEs (10.9% versus 1.6%). As of the primary analysis data cut-off date, 246 patients (121 in the niraparib group and 42 in the placebo group) were still receiving treatment.

Table 15: Patient Disposition and Analysis Populations in the PRIMA trial

Patient Disposition, n (%)	HRD-positive Population		Overall Population	
	Niraparib	Placebo	Niraparib	Placebo
Patients randomized	247 (100.0)	126 (100.0)	487 (100.0)	246 (100.0)
Received treatment	245 (99.2)	125 (99.2)	484 (99.4)	244 (99.2)
HRD-positive patients	NA	NA	245 (50.3)	125 (50.8)
HRD-negative patients	NA	NA	239 (49.1)	119 (48.4)
Discontinued study treatment	124 (50.2)	83 (65.9)	307 (63.0)	175 (71.1)
AEs	27 (10.9)	2 (1.6)	58 (11.9)	5 (2.0)
PD	80 (32.4)	76 (60.3)	218 (44.8)	162 (65.9)
Withdrew	8 (3.2)	0 (0.0)	12 (2.5)	1 (0.4)
Other	9 (3.6)	5 (4.0)	19 (3.9)	7 (2.8)
Ongoing treatment	121 (49.0)	42 (33.3)	177 (36.3)	69 (28.0)

AE = adverse event; HRD = homologous recombination deficiency; PD = progressive disease.

Data source: González-Martín 2019[2]

Protocol Deviations

The significant protocol deviations that occurred in the trial are summarized in Table 16. A protocol deviation was classified as significant if it was confirmed to adversely impact the completeness, accuracy, and/or reliability of the study data, or affect a patient's rights, safety, or well-being. Significant protocol deviations were reported in 43.1% (n=210) of patients in the niraparib group and 27.2% (n=67) of patients in the placebo group.[4] The higher number of protocol deviations in the niraparib group was primarily related to study visit/procedures (26.3% and 12.6%, respectively). Other significant protocol deviations were reported with similar frequency between the 2 groups, including study drug administration/study treatment (14.0% and 9.8%, respectively), and randomization (5.7% and 5.3%, respectively).

Overall, 1% (n=7) of trial patients had a significant protocol deviation that led to exclusion from the per protocol trial population; 4 patients in the niraparib group and 3 patients in the placebo group.[4] Among these patients, the 4 patients in the niraparib group and 2 patients in the placebo group had deviations related to study drug administration/ study treatment, and the remaining patient in the placebo group had a deviation related to disallowed medication. The protocol deviations that occurred during the trial are unlikely to

have impacted the results of efficacy analyses as the per-protocol analysis that was performed as a sensitivity analysis showed results consistent with the primary efficacy analysis.

Table 16: Summary of Significant Protocol Deviations in the PRIMA Trial

Protocol Deviation Classification/ Category, n (%)	Overall	
	Niraparib (n=487)	Placebo (n=246)
Subjects with at least 1 significant protocol deviation leading to exclusion of per-protocol population	4 (0.8)	3 (1.2)
AE/SAE	0	0
Disallowed Medication	0	1 (0.4)
Documentation	0	0
Inclusion/Exclusion Criteria	0	0
Informed Consent	0	0
IP Administration/Study Treatment	4 (0.8)	2 (0.8)
Randomization	0	0
Study Visits/Procedures	0	0
Withdrawal Criteria	0	0
Subjects with at least 1 significant protocol deviation	210 (43.1)	67 (27.2)
AE/SAE	19 (3.9)	4 (1.6)
Disallowed Medication	0	0
Documentation	2 (0.4)	1 (0.4)
Inclusion/Exclusion Criteria	8 (1.6)	5 (2.0)
Informed Consent	1 (0.2)	1 (0.4)
IP Administration/Study Treatment	68 (14.0)	24 (9.8)
Randomization	28 (5.7)	13 (5.3)
Study Visits/Procedures	128 (26.3)	31 (12.6)
Withdrawal Criteria	2 (0.4)	0

AE = adverse event; IP = investigational product; SAE = serious adverse event.

Data source: EPAR 2020[4]

e) Critical Appraisal: Limitations and Potential Sources of Bias

Overall, the PRIMA trial was well conducted. It is the first phase III trial to demonstrate a statistically significant and clinically meaningful PFS benefit in patients with newly diagnosed advanced ovarian cancer irrespective of BRCAmut status. The CADTH Methods Team identified the following limitations and potential sources of bias that should be considered when interpreting the trial results:

- The trial was double-blind with adequate generation of the sequence and concealment of treatment allocation methods; however, the higher incidence of AEs, dose interruptions, and dose reductions that occurred in the niraparib group had the potential to unmask patients to their assigned treatment. The extent to which spontaneous unblinding of patients and investigators occurred in the trial and the amount of bias that would be introduced is unknown, but the possible influence of this on subjective outcomes like safety and PROs should be considered.

- Although PFS and OS were assessed in the 2 efficacy populations using a hierarchical-testing procedure, there were multiple secondary efficacy outcomes assessed in the trial and numerous predefined subgroup analyses performed that were not adjusted to account for multiple comparison testing to control the risk of type 1 error. As the trial was not powered to test specific hypotheses in these outcomes and subgroups, the results of these analyses should be interpreted as exploratory in nature.
- Protocol Amendment 2 introduced a change to the dosing scheme of the trial that occurred after the enrollment of the majority trial patients (65%), who all received a fixed starting dose of 300 mg. The patients enrolled after the amendment received an individualized starting dose (200 mg or 300 mg according to patient weight and/or platelet count) and received fewer treatment cycles and thus less treatment exposure due to a shorter follow-up period. The results of subgroup analyses performed of PFS by dosing scheme suggest that starting dose did not affect treatment efficacy in either the HRD-positive or the overall population. Although the dosing scheme was changed during the trial, the study sample size was not increased to ensure adequate power to test for differences in outcome based on dosing scheme. In addition, patients were assigned to a dosing scheme based on weight and/or platelet count and not through randomization, so there is the possibility that any differences in baseline characteristics between groups could bias treatment effect estimates. These limitations introduce uncertainty into the analyses performed and therefore these subgroup results should be interpreted with caution. Lastly, the available data by dosing scheme from the trial do not reliably inform on the efficacy associated with the lower starting dose (200 mg) of niraparib.
- According to the CGP, HRD testing is not routinely performed in Canadian clinical practice because the test has not been clinically validated. Therefore, there is uncertainty in the reliability and validity of the trial results based only on HRD status.
- Patients were considered eligible for the trial if they had received 6 to 9 cycles of first-line platinum-based chemotherapy which resulted in an investigator-assessed CR or PR after 3 or more cycles, had visible residual disease of less than or equal to 2 cm (i.e., stage III or IV patients who had residual disease following primary debulking surgery and chemotherapy), and had CA-125 values either within the normal range or a decrease in CA-125 of more than 90% that was stable for at least 7 days. According to the CGP, these response criteria are more stringent than what would be considered a clinical response in a Canadian standard of care setting. The CGP indicated PR and CR are defined using RECIST criteria and not changes in tumour size or CA-125. These differences in criteria between the trial and what's routinely done in clinical practice may have implications in terms of external generalizability of the trial results.
- At the time of the primary efficacy analysis, the OS data were at approximately 10.8% maturity[2] and showed no statistically significant difference between the treatment groups in either the HRD-positive or overall patient population. The OS data were considered immature and not interpretable at the time of the interim analysis based on the low number of events; and therefore, longer-term survival data are required to assess the magnitude of an OS benefit. Patient crossover was not permitted in the trial; however, the longer-term OS data will be confounded by the use of post-trial treatments, which was high in the trial. In the HRD-positive population, 30.2% and 49.6% of patients in the niraparib and placebo groups, respectively, received a subsequent anti-cancer regimen post-progression; and the corresponding percentages in the overall population were 40.9% and 51.2%, respectively.[6]
- For the assessment of PROs, patient compliance rates were reported to be high (>80%) at all assessment timepoints, however, for all instruments, the increase in patients completing the EOT assessment indicated that a sizable proportion of patients did not complete PRO assessments at earlier timepoints particularly after Cycle 13. Thus, the number of patients included in the analyses of PROs at later assessment timepoints was reduced and the patients left in the trial who completed PRO assessments are likely not representative (i.e., have better HRQoL) of all patients randomized to each treatment group. In this scenario, data are not missing at random since patients who have left the trial are likely sicker (or have died), and therefore, the results at later timepoints are likely biased. This point is demonstrated by the lower mean adjusted scores for the EOT assessments for the FOSI and EQ-5D-5L utility index and VAS, which are based on a greater number of patients who completed questionnaires compared to preceding assessment timepoints. Time-to-event analysis of PROs mitigates some of the bias associated with analyses based on mean changes in scores from baseline because all available data are used in the analysis. In the trial, the time-to-worsening of symptoms analyses based on the MCIDs of the FOSI and EORTC-QLQ-OV28 showed no differences between the treatment groups with respect to the time-to- worsening of ovarian cancer symptoms.
- The sponsor Tesaro/GlaxoSmithKline Inc. funded the trial and was involved in all aspects of its conduct including design of the study, data collection, and performing and interpreting data analyses. The extent to which the sponsor's involvement may have influenced the results and reporting of the trial is unknown.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The results for the primary and secondary efficacy outcomes of the PRIMA trial are summarized in Table 17. As of the May 17, 2019 data cut-off date, the median duration of follow-up in the overall population was 13.8 months (range, <1.0 to 28.0),[2] and it was 13.9 months (95% CI, 13.8 to 16.0) and 13.8 months (95% CI, 13.6 to 14.1) in the niraparib and placebo groups, respectively.[5] In the HRD-positive population, the median follow-up was 13.9 months (95% CI, 13.7 to 16.4) in the niraparib group and 13.7 months (95% CI, 12.7 to 16.7) in the placebo group.

Table 17: Summary of Efficacy Outcomes in the PRIMA trial (ITT population)

Efficacy Outcomes	HRD-positive Population (n=373)		Overall Population (n=733)	
	Niraparib (n=247)	Placebo (n=126)	Niraparib (n=487)	Placebo (n=246)
PFS by BICR				
Median (95% CI) in months[a]	21.9 (19.3 to NE)	10.4 (8.1 to 12.1)	13.8 (11.5 to 14.9)	8.2 (7.3 to 8.5)
Censored observations, n (%)	166 (67.2)	53 (42.1)	255 (52.4)	91 (37.0)
Event rate, n (%)	81 (32.8)	73 (57.9)	232 (47.6)	155 (63.0)
HR (95% CI)[b]	0.43 (0.310 to 0.588)		0.62 (0.502 to 0.755)	
p-value[c]	<0.0001		<0.0001	
Survival distribution function, % (95% CI)				
6-months	86 (81 to 90)	68 (59 to 76)	73 (69 to 77)	60 (53 to 66)
12-months	72 (65 to 77)	42 (33 to 51)	53 (48 to 58)	35 (29 to 42)
18-months	59 (50 to 66)	35 (25 to 45)	42 (36 to 47)	28 (21 to 35)
24-months	47 (36 to 58)	26 (14 to 39)	32 (25 to 39)	23 (14 to 32)
30-months	47 (36 to 58)	26 (14 to 39)	32 (25 to 39)	23 (14 to 32)
OS				
Event rate, n (%)	16 (6.5)	10 (7.9)	48 (9.9)	31 (12.6)
Censored observations, n (%)	231 (93.5)	116 (92.1)	439 (90.1)	215 (87.4)
HR (95% CI)[b]	0.61 (0.265 to 1.388)		0.70 (0.442 to 1.106)	
p-value[c]	0.2323		0.1238	
24-month survival, % (95% CI)	91 (84 to 95)	85 (65 to 94)	84 (78 to 89)	77 (63 to 86)
TFST				
Median (95% CI) in months	NE (24.7 to NE)	13.7 (11.6 to 19.3)	18.6 (15.8 to 24.7)	12.0 (10.3 to 13.9)
Censored observations, n (%)	171 (69.2)	60 (47.6)	277 (56.9)	108 (43.9)
Event rate, n (%)	76 (30.8)	66 (52.4)	210 (43.1)	138 (56.1)
HR (95% CI)[b]	0.46 (0.330 to 0.640)		0.65 (0.521 to 0.802)	
PFS-2				

Efficacy Outcomes	HRD-positive Population (n=373)		Overall Population (n=733)	
	Niraparib (n=247)	Placebo (n=126)	Niraparib (n=487)	Placebo (n=246)
Median (95% CI) in months[a]	NE (25.3 to NE)	NE (NE to NE)	27.2 (25.3 to NE)	NE (NE to NE)
Event rate, n (%)	37 (15.0)	20 (15.9)	92 (18.9)	53 (21.5)
Censored observations, n (%)	210 (85.0)	106 (84.1)	395 (81.1)	193 (78.5)
HR (95% CI)[b]	0.84 (0.485 to 1.453)		0.81 (0.577 to 1.139)	

BRCA = breast cancer susceptibility gene; CI = confidence interval; HR = hazard ratio; HRD = homologous recombination deficiency; NE = not estimable; OS = overall survival; PFS = progression-free survival; PFS-2 = progression-free survival on next line of therapy; TFST = time-to-first subsequent therapy.
[a] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[b] Based on stratified Cox proportional hazards model using randomization stratification factors as above.
[c] Based on stratified log-rank test using randomization stratification factors: administration of neoadjuvant chemotherapy, best response to platinum therapy, and homologous recombination deficiency test result status (for overall population only).

Data sources: González-Martín 2019,[2] EPAR[4]

Primary Outcome: Progression-free Survival

At the time of data cut-off date, a total of 387 PFS events had occurred in the overall population; there were 232 events in the niraparib group and 155 events in the placebo group. In the HRD-positive population, 81 PFS events had occurred in the niraparib group and 73 PFS events had occurred in the placebo group.[2]

The PFS KM curves for the HRD-positive population and the overall population are displayed in Figure 8. The PRIMA trial met its primary endpoint, demonstrating a statistically significant longer duration of PFS in the niraparib group compared to the placebo group in both efficacy populations (HRD-positive population and the overall population).

In the HRD-positive population, the median PFS was 21.9 months in the niraparib group and 10.4 months in the placebo group corresponding to an absolute median PFS benefit of 11.5 months in the niraparib group (HR = 0.43; 95% CI, 0.31 to 0.59; P <0.001).[2] In the overall population, the median PFS was 13.8 months in the niraparib group and 8.2 months in the placebo group, corresponding to an absolute median PFS benefit of 5.6 months (HR = 0.62; 95% CI, 0.50 to 0.76; P <0.001). For both efficacy populations (HRD-positive and overall population), estimates of PFS at 6, 12, 18, and 24 months were higher in the niraparib group versus the placebo group at each time point (Table 17).[4]

Figure 8: Kaplan–Meier Estimates of PFS in the PRIMA trial

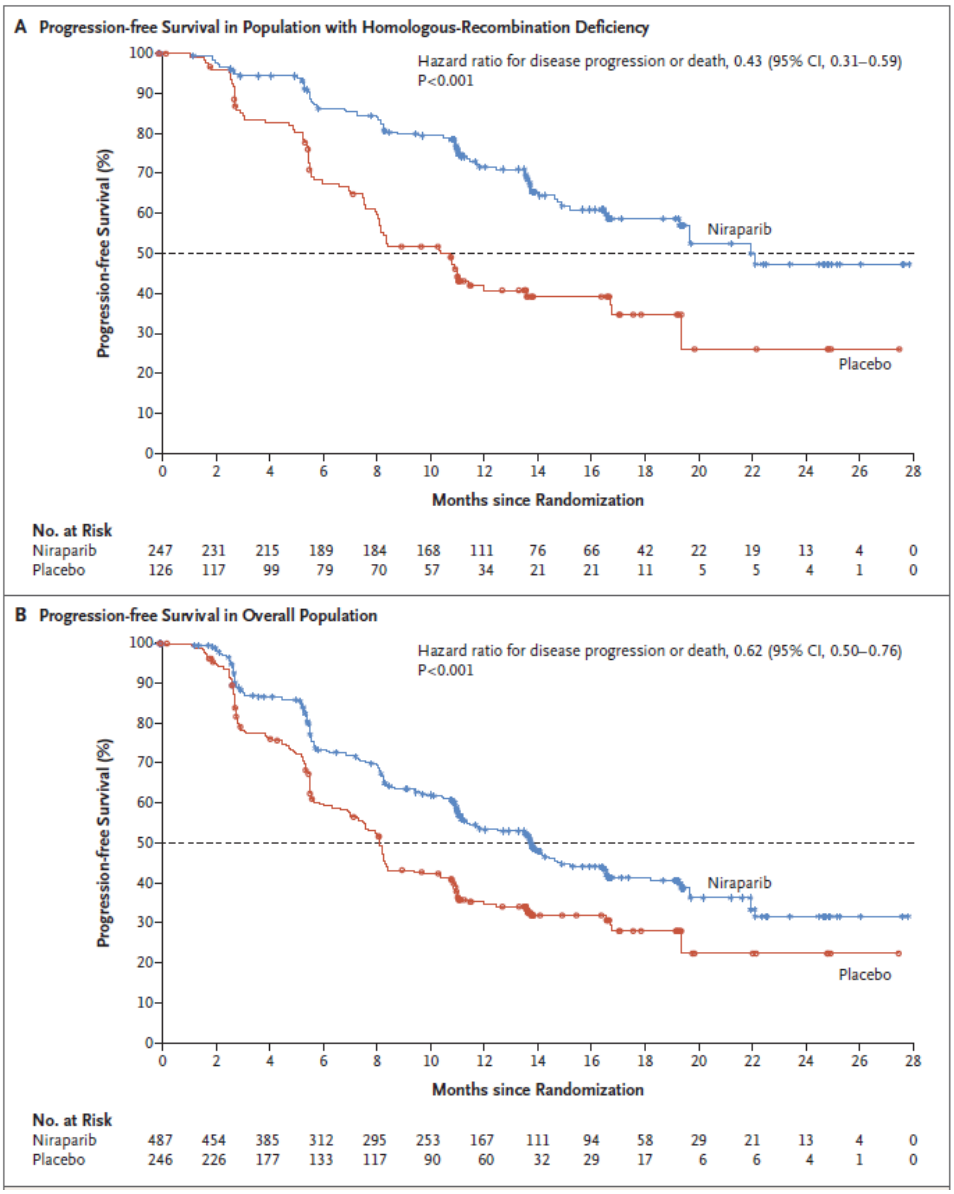


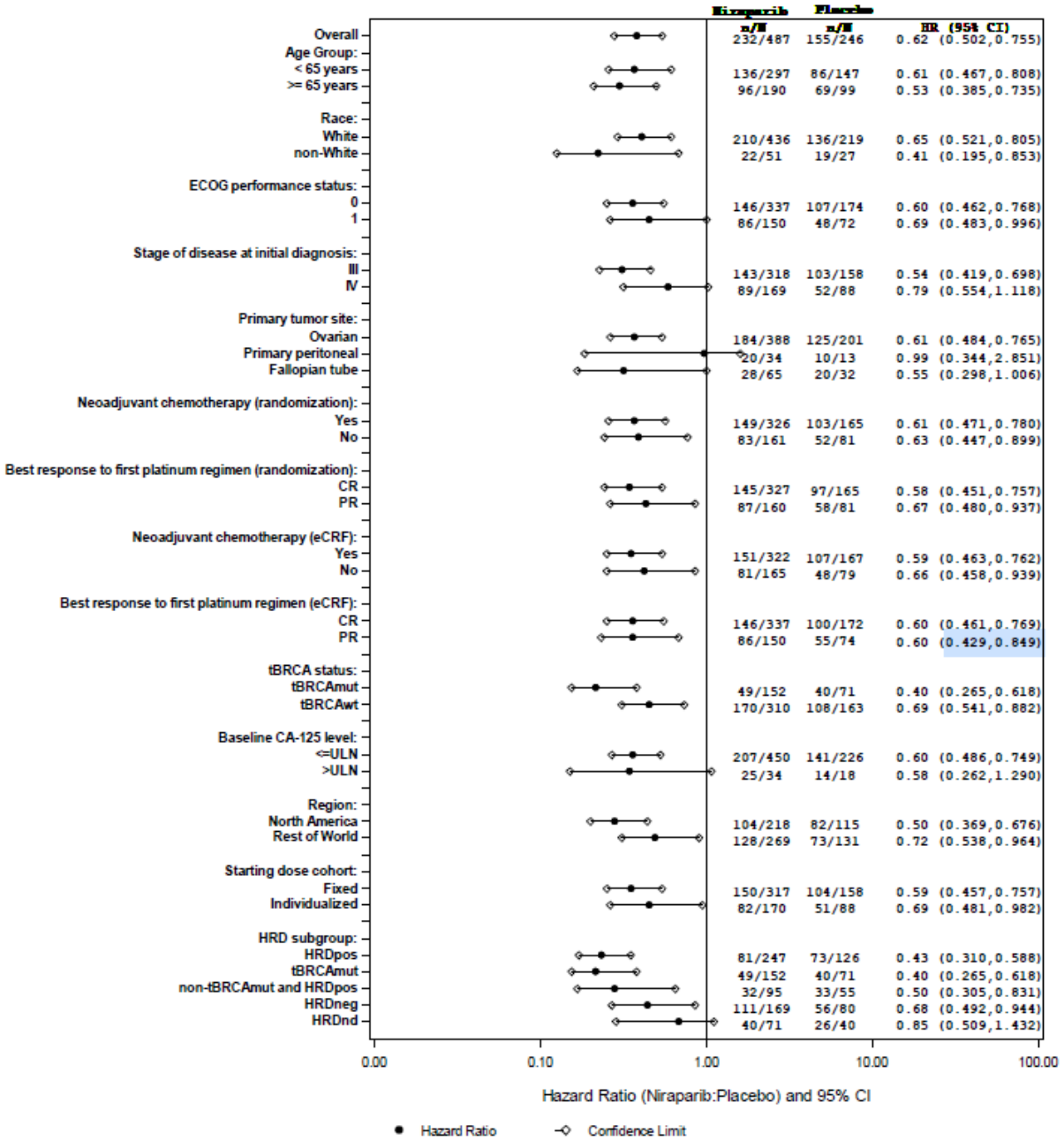
Figure source: From the New England Journal of Medicine, Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer, Volume No: 381(25), Page No: 2397. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[2]

Progression-free Survival in Prespecified Subgroups

The results of prespecified subgroup analyses of PFS in the overall population are presented in Figure 9.[2,4] The results of these analyses demonstrate that the PFS benefit associated with niraparib was consistent and observed in all patient subgroups with the exception of the following groups of patients: ECOG PS of 1, stage IV disease at initial diagnosis, primary peritoneal or fallopian tube as primary tumour site, baseline CA-125 level greater than the ULN, and HRD status undetermined. In these subgroups, all the treatment effect estimates favoured treatment with niraparib, but the 95% CI included the null value of 1, suggesting no difference in PFS between the treatment groups. These subgroup analyses were not powered to detect statistically significant differences in outcome between treatment groups and some analyses may have been limited by small sample size.

As previously mentioned, analyses were also performed based on patients receiving either the fixed or individualized starting dose (see Protocol Amendment 2 for more details) (Table 18).[4] The results of these analyses in both the overall population (fixed dose: HR = 0.59; 95% CI, 0.457 to 0.757; individualized dose: HR = 0.60;, 95% CI, 0.481 to 0.982) and the HRD-positive population (fixed dose: HR = 0.44; 95% CI, 0.298 to 0.638; individualized dose: HR = 0.39; 95% CI, 0.215 to 0.723) suggest that the treatment effect of niraparib was consistent for both dosing schemes. The results of the test of interaction in both patient populations were non-significant, suggesting that the different starting doses had no effect on treatment efficacy (fixed versus individualized). These analyses were exploratory and were not prespecified in the protocol.

Figure 9: Prespecified Subgroup Analyses of PFS in Overall Population (ITT Population)



BRCA = breast cancer susceptibility gene; CA-125 = cancer antigen 125; CI = confidence interval; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; HRD = homologous recombination deficiency; nd = not determined; PFS = progression-free survival; PR = partial response.

Data source: EPAR 2020[4]

Table 18: PFS by Starting Dose (ITT population)

Population Parameter Statistic	Fixed		Individualized	
	Niraparib	Placebo	Niraparib	Placebo
HRDpos				
N	160	83	87	43
PFS (months)[a,b]				
Median (95% CI)	22.1 (19.6, NE)	8.4 (7.6, 13.6)	14.0 (12.5, NE)	10.9 (6.1, NE)
Censored observations, n (%)	103 (64.4)	31 (37.3)	63 (72.4)	22 (51.2)
Event rate, n (%)	57 (35.6)	52 (62.7)	24 (27.6)	21 (48.8)
p-value[c]	<0.0001		0.0019	
Hazard ratio (95% CI)[d]	0.44 (0.298, 0.638)		0.39 (0.215, 0.723)	
Overall				
N	317	158	170	88
PFS (months)[a,b]				
Median (95% CI)	14.7 (13.6, 19.4)	8.2 (7.0, 9.8)	11.4 (9.7, 13.9)	8.2 (5.6, 10.9)
Censored observations, n (%)	167 (52.7)	54 (34.2)	88 (51.8)	37 (42.0)
Event rate, n (%)	150 (47.3)	104 (65.8)	82 (48.2)	51 (58.0)
p-value[c]	<0.0001		0.0389	
Hazard ratio (95% CI)[d]	0.59 (0.457, 0.757)		0.69 (0.481, 0.982)	

CI = confidence interval; HR = hazard ratio; HRDpos = homologous recombination deficiency positive; NE = not estimable; OS = overall survival; PFS = progression-free survival.
Notes:
[a] PFS is defined as the time in months from the date of randomization to progression or death.
[b] Quartile estimates from product-limit (KM) method. CIs from Brookmeyer and Crowley method with log-log transformation.
[c] Base on stratified log rank test using randomization stratification factors.
[d] Based on stratified Cox proportional hazards model using randomization stratification factors.

Data source: EPAR 2020[4]

Sensitivity Analyses

There were 8 sensitivity analyses performed to assess the robustness of the PFS results; these analyses considered various factors that included PFS by investigator assessment, PFS by BICR assessing alternative censoring rules, PFS by BICR using different stratification factors, and PFS by BICR using different progression criteria (refer to Section 6.3.2 for a more detailed description of these analyses). The results of these analyses in each of the efficacy populations (HRD-positive and overall populations) were consistent with the primary efficacy analysis results; whereby, there was a longer PFS in the niraparib group compared to the placebo group (HR range: 0.42 to 0.47 in the HRD-positive population and 0.60 to 0.64 in the overall population).[5]

Secondary Efficacy Outcomes

The results for the secondary efficacy outcomes assessed in the PRIMA trial are summarized in Table 17.

Overall Survival

At the time of the May 17, 2019 data cut-off date, the interim analysis of OS indicated that the survival data were immature based on a total of 79 deaths (10.8% maturity)[2] with data censored for over 87% of patients in both treatment groups.[4] Overall, the interim OS results showed treatment effect estimates that favoured niraparib compared to placebo but the differences in deaths between the treatment groups were not statistically significant.[2] In the HRD-positive population, 26 patients had died that included 16 deaths

(6.5%) in the niraparib group and 10 deaths (7.9%) in the placebo group (HR = 0.61; 95% CI, 0.27 to 1.39). In the overall population, 79 patients had died that included 48 (9.9%) in the niraparib group and 31 (12.6%) in the placebo group (HR = 0.70; 95% CI, 0.44 to 1.11). The median estimates of OS were not reported due to the low event rate and insufficient follow-up time.

Other Secondary Outcomes

At the time of the data cut-off date, the data for PFS-2 and TFST were considered immature at 20% and 47% maturity, respectively. Overall, the results for these outcomes were consistent with the primary outcome results and showed treatment effect estimates that favoured treatment with niraparib compared to placebo.[2]

Patient Reported Outcomes – FOSI, EORTC-QLQ-C30, EORTC-QLQ-OV28, and EQ-5D-5L

Patient compliance rates and the results for PROs were similar in the HRD-positive and overall populations, therefore the results for the overall patient population are presented below.

The patient completion rates for each of the PRO questionnaires are shown in Table 19. Overall, the compliance rates for each PRO questionnaire were similar between the niraparib and the placebo groups throughout the treatment period, and at the end of treatment.[2,5] In both treatment groups, completion rates were greater than 80% at all assessment timepoints, which was calculated based on the number of patients with an evaluable form at each visit, divided by the number of patients expected to complete the form at that visit. However, for all instruments, the increase in patients completing the EOT assessment indicates that a sizable proportion of patients did not complete PRO assessments at earlier timepoints particularly after Cycle 13.

Table 19: PRO Questionnaire Completion Rates by Visit

Completed Questionnaires, Number of evaluable forms/ number of expected forms (%)	Overall Population	
	Niraparib	Placebo
FOSI		
Baseline	483/487 (99.2)	242/246 (98.4)
Cycle 3	425/441 (96.4)	221/232 (95.3)
Cycle 5	352/375 (93.9)	185/196 (94.4)
Cycle 7	316/344 (91.9)	158/177 (89.3)
Cycle 9	286/299 (95.7)	125/138 (90.6)
Cycle 11	254/266 (95.5)	99/109 (90.8)
Cycle 13	231/249 (92.8)	97/98 (99.0)
Cycle 15	185/198 (93.4)	74/83 (89.2)
Cycle 18	100/109 (91.7)	38/39 (97.4)
Cycle 21	56/61 (91.8)	21/22 (95.5)
Cycle 24	30/33 (90.9)	8/8 (100.0)
Cycle 27	13/16 (81.3)	5/5 (100.0)
Cycle 30	5/6 (83.3)	4/4 (100.0)
End of treatment	262/309 (84.8)	158/177 (89.3)
EQ-5D-5L		
Baseline	481/487 (98.8)	245/246 (99.6)
Cycle 3	424/441 (96.1)	227/232 (97.8)
Cycle 5	358/375 (95.5)	186/196 (94.9)
Cycle 7	319/344 (92.7)	158/177 (89.3)
Cycle 9	287/299 (96.0)	128/138 (92.8)

Completed Questionnaires, Number of evaluable forms/ number of expected forms (%)	Overall Population	
	Niraparib	Placebo
Cycle 11	255/266 (95.9)	101/109 (92.7)
Cycle 13	235/249 (94.4)	96/98 (98.0)
Cycle 15	183/198 (92.4)	74/83 (89.2)
Cycle 18	102/109 (93.6)	38/39 (97.4)
Cycle 21	58/61 (95.1)	21/22 (95.5)
Cycle 24	30/33 (90.9)	8/8 (100.0)
Cycle 27	13/15 (86.7)	5/5 (100.0)
Cycle 30	5/6 (83.3)	4/4 (100.0)
End of treatment	265/309 (85.8)	159/177 (89.8)
EORTC-QLQ-C30		
Baseline	484/487 (99.4)	246/246 (100.0)
Cycle 3	430/441 (97.5)	229/232 (98.7)
Cycle 5	359/375 (95.7)	188/196 (95.9)
Cycle 7	322/344 (93.6)	161/177 (91.0)
Cycle 9	290/299 (97.0)	128/138 (92.8)
Cycle 11	256/266 (96.2)	102/109 (93.6)
Cycle 13	236/249 (94.8)	96/98 (98.0)
Cycle 15	185/198 (93.4)	74/83 (89.2)
Cycle 18	102/109 (93.6)	38/39 (97.4)
Cycle 21	58/61 (95.1)	21/22 (95.5)
Cycle 24	30/33 (90.9)	8/8 (100.0)
Cycle 27	13/15 (86.7)	5/5 (100.0)
Cycle 30	5/6 (83.3)	4/4 (100.0)
End of treatment	265/309 (85.8)	162/177 (91.5)
EORTC-QLQ-OV28		
Baseline	485/487 (99.6)	246/246 (100.0)
Cycle 3	428/441 (97.1)	228/232 (98.3)
Cycle 5	359/375 (95.7)	188/196 (95.9)
Cycle 7	322/344 (93.6)	161/177 (91.0)
Cycle 9	290/299 (97.0)	128/138 (92.8)
Cycle 11	256/266 (96.2)	102/109 (93.6)
Cycle 13	236/249 (94.8)	96/98 (98.0)
Cycle 15	185/198 (93.4)	74/83 (89.2)
Cycle 18	102/109 (93.6)	38/39 (97.4)
Cycle 21	58/61 (95.1)	21/22 (95.5)
Cycle 24	30/33 (90.9)	8/8 (100.0)
Cycle 27	13/15 (86.7)	5/5 (100.0)
Cycle 30	5/6 (83.3)	4/4 (100.0)
End of treatment	265/309 (85.5)	162/177 (91.5)

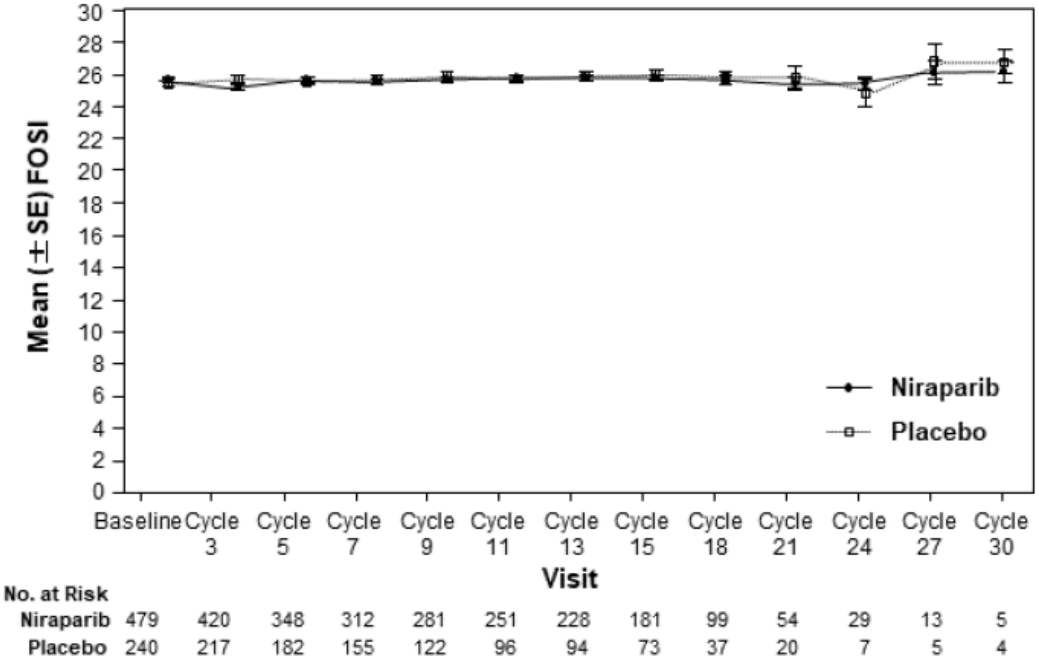
EORTC-QLQ- C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer 30; EORTC-QLQ- OV28 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Ovarian Cancer Module - OV28; EQ-5D-5L = European QOL 5-dimension 5-level questionnaire; FOSI= Functional Assessment of Cancer Therapy-Ovarian symptom index; NR = not reported.

Data source: Clinical Study Report[5]

FOSI

Mean [SD] FOSI scores were similar at baseline between the niraparib and placebo treatment groups in the overall population (niraparib: 25.6 [3.73]; placebo: 25.4 [3.51]) (Figure 10) and throughout the trial with no observed differences based on changes in score from baseline between the treatment groups during the treatment period, except for Cycle 3 where placebo had a higher value indicative of less symptoms and improved QoL.[5] The KM curve for time-to-symptom worsening, which factors all assessment timepoints into account, showed no difference between niraparib and placebo (HR = 1.10; 95% CI, 0.915 to 1.330) in the time-to-worsening of ovarian cancer symptoms based on the MCID of 2 points.

Figure 10: Adjusted FOSI Scores by Study Visit in the Overall Population



Data source: From the New England Journal of Medicine, Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer, Volume No: 381(25), Suppl. Appendix, Page No: 41. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[2]

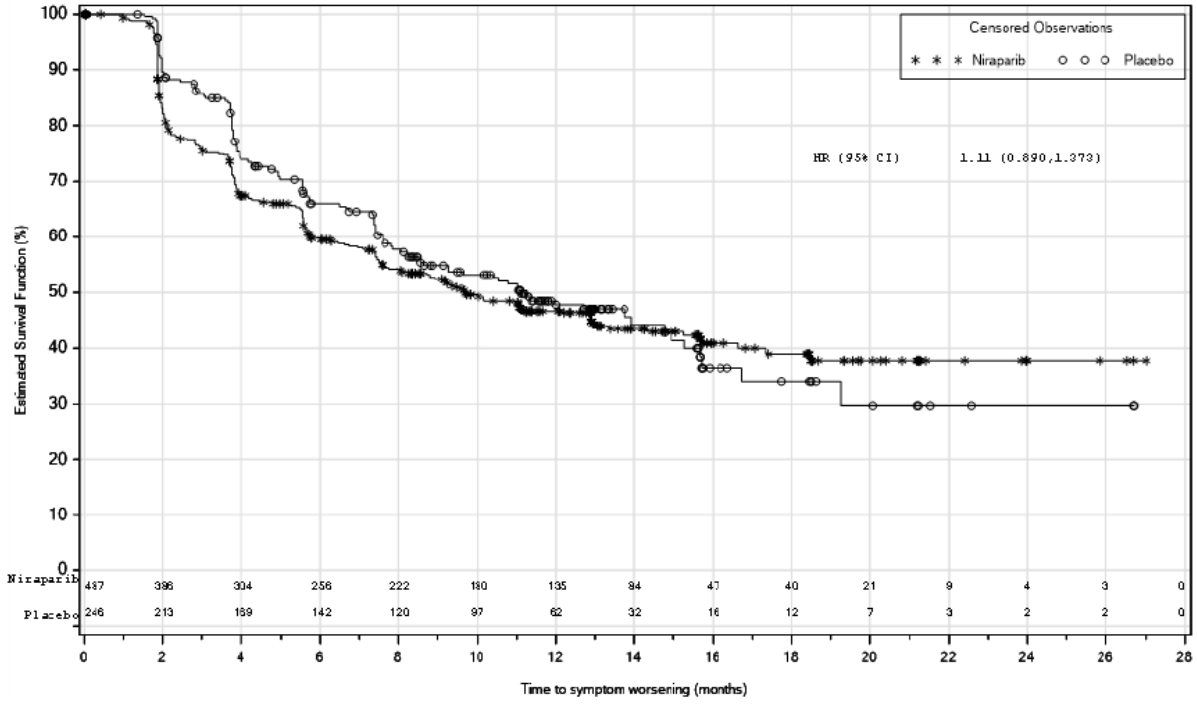
EORTC-QLQ-C30 and EORTC-QLQ-OV28

Mean [SD] scores for the global health status/QoL score of the EORTC-QLQ-C30 were similar at baseline between the niraparib and placebo treatment groups (niraparib: 71.5 [18.86]; placebo: 70.2 [18.66]) and throughout the trial; there were no differences based on changes in score from baseline between the treatment groups during treatment, except for gastrointestinal-related assessments. Constipation was worse in niraparib treated patients through Cycle 15 and again at Cycle 21 with similar trends in nausea/vomiting (through Cycle 9), appetite loss (Cycles 3, 5, and EOT), and dyspnea (Cycles 3 and 5). Conversely, diarrhea was reported as worse in placebo treated patients at Cycles 3, 5, 11, 15 and 24.

The EORTC-QLQ-OV28 did not demonstrate any consistent differences in QoL scores between the niraparib and placebo groups.[5] The KM curve for time-to-abdominal/gastrointestinal score worsening (Figure 11) demonstrated no difference between niraparib and

placebo (HR=1.11; 95% CI, 0.890 to 1.372), suggesting no difference between the groups in the time-to-worsening of abdominal and gastrointestinal-related symptoms based on the MCID of 10 points.

Figure 11: KM Curve for EORTC-QLQ-OV28 Abdominal/Gastrointestinal Score Worsening in the Overall Population (ITT Population)



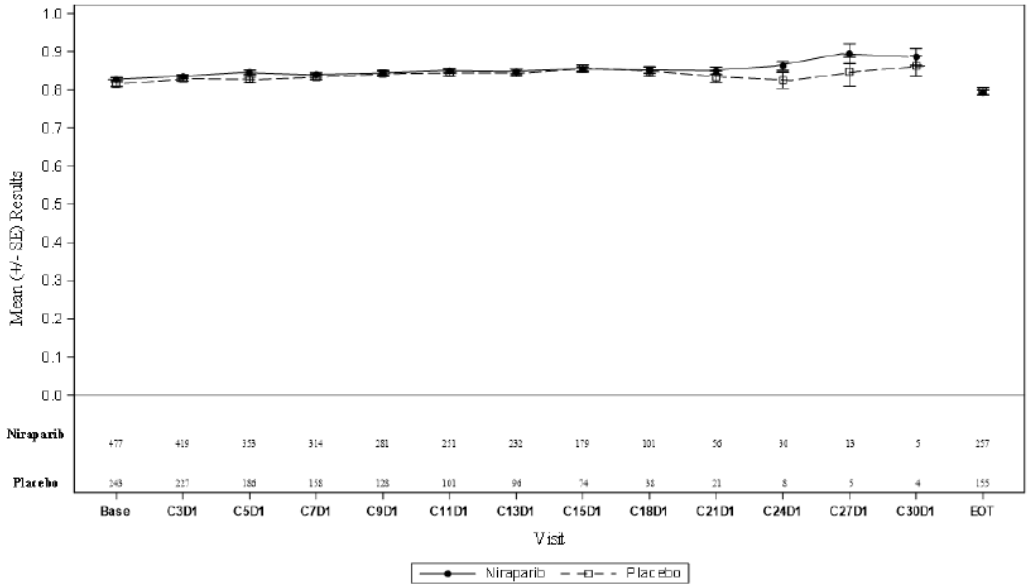
CI = confidence interval; EORTC-QLQ-OV28 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; GI = gastrointestinal; HR = hazard ratio; ITT = intent-to-treat KM = Kaplan-Meier.

Data source: Clinical Study Report[5]

EQ-5D-5L

Mean [SD] EQ-5D-5L index (niraparib: 0.827 [0.1229]; placebo: 0.817 [0.1245]) and VAS scores (niraparib: 75.5 [17.24]; placebo: 74.8 [17.10]) were similar between the niraparib and placebo treatment groups (utility index: Figure 12; VAS: Figure 13) at baseline[4] and throughout the study, with no observed differences based on changes in score from baseline during the treatment period, except for Cycle 5 where niraparib had a higher utility index value, indicative of better QoL at this time point.[5]

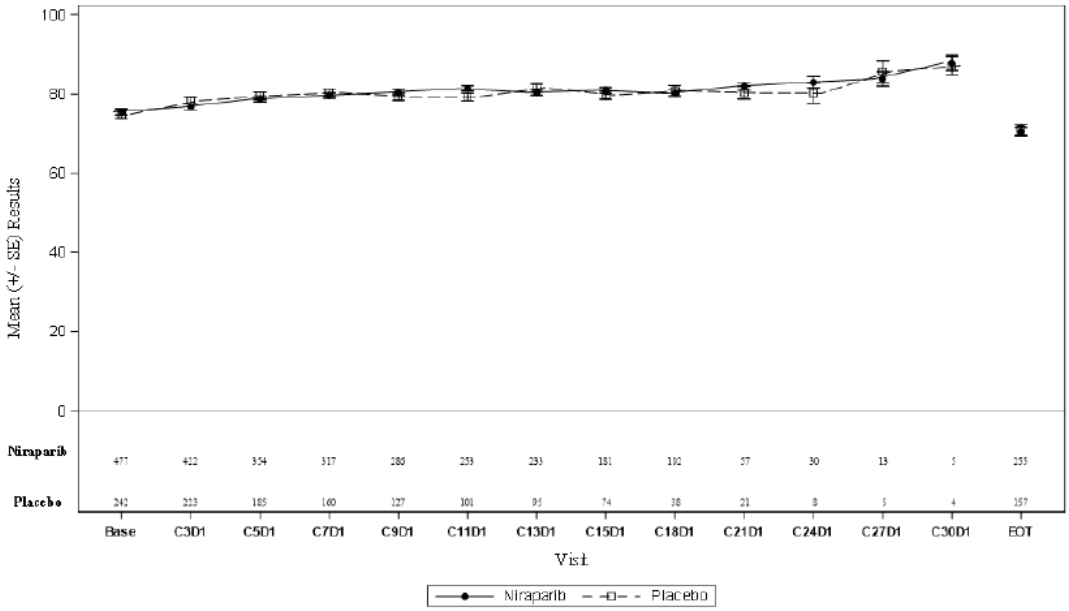
Figure 12: Adjusted EQ-5D-5L Index Scores by Study Visit in the Overall Population (ITT Population)



C = cycle; D = day; EQ-5D-5L = European Quality of Life scale, 5-Dimensions; ITT = Intent-to-treat; SE = standard error.

Data source: Clinical Study Report[5]

Figure 13: Adjusted EQ-5D-5L VAS Scores by Study Visit in the Overall (ITT Population)



C = cycle; D = day; EQ-5D-5L = European Quality of Life scale, 5-Dimensions; HRD = homologous recombinant deficiency; ITT = Intent-to-treat; SE = standard error.

Data source: Clinical Study Report[5]

Harms

Adverse Events

A summary of the incidence of AEs in the PRIMA trial is provided in Table 20.[2] At least 1 AE occurred in 98.8% of patients who received niraparib and in 91.8% of patients who received placebo; and at least 1 treatment-related AE (TRAE) occurred in 96.3% and 68.9% of patients, respectively. Overall, the incidence of all categories of AEs was higher in the niraparib group compared to the placebo group. There were no treatment-related deaths reported in the trial and 3 deaths were attributed to AEs (2 in the niraparib group and 1 in the placebo group). The 2 deaths in the niraparib group were related to pleural effusion and intestinal perforation. .[4]

Table 20: Summary of TEAEs in the PRIMA trial (Safety Population)

Reported – n (%)	Niraparib (n=484)	Placebo (n=244)
Any AE	478 (98.8)	224 (91.8)
Any Grade ≥3 AE	341 (70.5)	46 (18.9)
Any TRAE	466 (96.3)	168 (68.9)
Any Grade ≥3 TRAE	316 (65.3)	16 (6.6)
Any SAE	156 (32.2)	32 (13.1)
Any treatment-related SAE	118 (24.4)	6 (2.5)
Any AE Leading to Treatment Discontinuation	58 (12.0)	6 (2.5)
Any AE Leading to Dose Reduction	343 (70.9)	20 (8.2)
Any AE to Treatment Interruption	385 (79.5)	44 (18.0)
Any AE Leading to Death	2 (0.4)	1 (0.4)

AE = adverse event; SAE = serious adverse event; TRAE= treatment-related adverse event.
Data source: González-Martín 2019[2]

Table 21 provides a summary of the TEAEs that occurred in at least 10% of patients in each treatment group of the PRIMA trial.[2] The most common TEAEs of any grade that occurred in the niraparib group (versus the placebo group) were anemia (63.4% versus 17.6%), nausea (57.4% versus 27.5%), thrombocytopenia (45.9% versus 3.7%), constipation (39.0% versus 18.9%), fatigue (34.7% versus 29.5%), platelet count decreased (27.5% versus 1.2%), and neutropenia (26.4% versus 6.6%). The most common grade 3 or 4 TEAEs in the niraparib group (versus the placebo group) were anemia (31.0% versus 1.6%), thrombocytopenia (28.7% versus 0.4%), platelet count decreased (13.0% versus 0%), and neutropenia (12.8% versus 1.2%).

Table 21: TEAEs occurring it at least 10% of Patients in the PRIMA trial (Safety Population)

	Niraparib (n=484)		Placebo (n=244)	
MedDRA Preferred Term — no. (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	307 (63.4)	150 (31.0)	43 (17.6)	4 (1.6)
Nausea	278 (57.4)	6 (1.2)	67 (27.5)	2 (0.8)
Thrombocytopenia	222 (45.9)	139 (28.7)	9 (3.7)	1 (0.4)
Constipation	189 (39.0)	1 (0.2)	46 (18.9)	0
Fatigue	168 (34.7)	9 (1.9)	72 (29.5)	1 (0.4)
Platelet count decreased	133 (27.5)	63 (13.0)	3 (1.2)	0
Neutropenia	128 (26.4)	62 (12.8)	16 (6.6)	3 (1.2)
Headache	126 (26.0)	2 (0.4)	36 (14.8)	0
Insomnia	119 (24.6)	4 (0.8)	35 (14.3)	1 (0.4)
Vomiting	108 (22.3)	4 (0.8)	29 (11.9)	2 (0.8)
Abdominal pain	106 (21.9)	7 (1.4)	75 (30.7)	1 (0.4)
Decreased appetite	92 (19.0)	3 (0.6)	20 (8.2)	0
Diarrhea	91 (18.8)	3 (0.6)	55 (22.5)	1 (0.4)
Dyspnea	88 (18.2)	2 (0.4)	30 (12.3)	2 (0.8)
Arthralgia	85 (17.6)	2 (0.4)	47 (19.3)	0
Neutrophil count decreased	82 (16.9)	37 (7.6)	5 (2.0)	0
Hypertension	82 (16.9)	29 (6.0)	17 (7.0)	3 (1.2)
Asthenia	78 (16.1)	4 (0.8)	31 (12.7)	2 (0.8)
White blood cell count decreased	74 (15.3)	12 (2.5)	8 (3.3)	0
Cough	74 (15.3)	0	35 (14.3)	1 (0.4)
Dizziness	71 (14.7)	0	26 (10.7)	1 (0.4)
Back pain	64 (13.2)	0	24 (9.8)	0
Leukopenia	57 (11.8)	10 (2.1)	13 (5.3)	0
Blood creatinine increased	55 (11.4)	1 (0.2)	10 (4.1)	0
Hot flush	54 (11.2)	1 (0.2)	20 (8.2)	0
Viral upper respiratory tract infection	49 (10.1)	0	25 (10.2)	0
Abdominal distension	32 (6.6)	0	30 (12.3)	0

MedDRA, Medical Dictionary for Regulatory Activities.

Table source: From the New England Journal of Medicine, Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer, Volume No: 381(25), Suppl. Appendix, Page No: 35. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Table 22 provides a summary of the treatment-related TEAEs occurring in at least 10% of patients and/or ≥ grade 3 TEAEs occurring in at least 5% of patients in each treatment group of the safety population of the PRIMA trial.[5] The most common treatment-related TEAEs of any grade that occurred in the niraparib group (versus the placebo group) were anemia (60.5% versus 12.7%), nausea (50.6% versus 20.1%), thrombocytopenia (45.2% versus 3.3%), fatigue (29.8% versus 23.0%), platelet count decreased (26.9% versus 1.2%), neutropenia (26.0% versus 5.7%), and constipation (25.8% versus 5.7%). The most common grade 3 or higher treatment-related TEAEs in the niraparib group (versus the placebo group) were anemia (30.2% versus 0.4%), thrombocytopenia

(28.7% versus 0%), platelet count decreased (13.0% versus 0%), neutropenia (12.4% versus 0.8%), and neutrophil count decreased (7.6% versus 0%).

Table 22: Treatment-Related TEAEs occurring in at least 10% at any Grade and/or at least 5% at Grade 3 or Greater of Patients in the PRIMA trial (Safety Population)

MedDRA preferred term, n (%)	Treatment-Related AEs Reported in ≥10% of Subjects (Safety Population)		Treatment-Related AEs Reported in ≥5% of Subjects (Safety Population)	
	Any Grade		Grade ≥3	
	Niraparib (n=484)	Placebo (n=244)	Niraparib (n=484)	Placebo (n=244)
Any Related TEAE	466 (96.3)	168 (68.9)	316 (65.3)	16 (6.6)
Anemia	293 (60.5)	31 (12.7)	146 (30.2)	1 (0.4)
Nausea	245 (50.6)	49 (20.1)	NR	NR
Thrombocytopenia	219 (45.2)	8 (3.3)	139 (28.7)	0
Fatigue	144 (29.8)	56 (23.0)	NR	NR
Platelet count decreased	130 (26.9)	3 (1.2)	63 (13.0)	0
Neutropenia	126 (26.0)	14 (5.7)	60 (12.4)	2 (0.8)
Constipation	125 (25.8)	14 (5.7)	NR	NR
Headache	81 (16.7)	15 (6.1)	NR	NR
Neutrophil count decreased	80 (16.5)	5 (2.0)	37 (7.6)	0
White blood cell count decreased	71 (14.7)	8 (3.3)	NR	NR
Asthenia	72 (14.9)	27 (11.1)	NR	NR
Decreased appetite	71 (14.7)	14 (5.7)	NR	NR
Vomiting	70 (14.5)	8 (3.3)	NR	NR
Insomnia	65 (13.4)	12 (4.9)	NR	NR
Diarrhea	44 (9.1)	33 (13.5)	NR	NR

MedDRA = Medical Dictionary for Regulatory Activities; NR = not reported; TEAE = treatment-emergent adverse event.
Data source: Clinical Study Report[5]

A summary of the TEAEs based on the fixed versus individualized dosing schemes used in the trial is presented in Table 23 (all grade) and Table 24 (grade 3 or higher). The incidence of any grade and grade 3 or higher TEAEs was lower in patients who received the individualized starting dose of niraparib compared to the fixed starting dose of niraparib, with the exception of neutropenic sepsis, which occurred in 1 patient treated with an individualized starting dose of niraparib.[2] One (0.3%) patient who received the fixed starting dose of niraparib experienced MDS (grade 3 or higher), and no patients in either the individualized starting dose of niraparib or in the placebo group experienced MDS.

Table 23: All Grade TEAEs in Patients Receiving Fixed Versus Individualized Dosing in the PRIMA trial (Safety Population)

	Niraparib		Placebo	
MedDRA preferred term — no. (%)	Fixed Dose (n=315)	Individualized Dose (n=169)	Fixed Dose (n=158)	Individualized Dose (n=86)
Anemia	223 (70.8)	84 (49.7)	19 (12.0)	24 (27.9)
Thrombocytopenia	165 (52.4)	57 (33.7)	6 (3.8)	3 (3.5)
Platelet count decreased	95 (30.2)	38 (22.5)	2 (1.3)	1 (1.2)
Neutropenia	87 (27.6)	41 (24.3)	10 (6.3)	6 (7.0)
Neutrophil count decreased	61 (19.4)	21 (12.4)	3 (1.9)	2 (2.3)
Hemoglobin decreased	4 (1.3)	1 (0.6)	0	0
Febrile neutropenia	3 (1.0)	1 (0.6)	0	0
Myelodysplastic syndrome	1 (0.3)	0	0	0
Pancytopenia	1 (0.3)	0	0	0
Neutropenic sepsis	0	1 (0.6)	0	0

MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Table source: From the New England Journal of Medicine, Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer, Volume No: 381(25), Suppl. Appendix, Page No: 37. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[2]

Table 24: Grade ≥3 TEAEs in Patients Receiving Fixed Versus Individualized Dosing in the PRIMA trial (Safety Population)

	Niraparib		Placebo	
MedDRA preferred term — no. (%)	Fixed Dose (n=315)	Individualized Dose (n=169)	Fixed Dose (n=158)	Individualized Dose (n=86)
Thrombocytopenia	114 (36.2)	25 (14.8)	0	1 (1.2)
Anemia	112 (35.6)	38 (22.5)	3 (1.9)	1 (1.2)
Platelet count decreased	51 (16.2)	12 (7.1)	0	0
Neutropenia	46 (14.6)	16 (9.5)	2 (1.3)	1 (1.2)
Neutrophil count decreased	28 (8.9)	9 (5.3)	0	0
Febrile neutropenia	3 (1.0)	1 (0.6)	0	0
Myelodysplastic syndrome	1 (0.3)	0	0	0
Pancytopenia	1 (0.3)	0	0	0
Neutropenic sepsis	0	1 (0.6)	0	0

MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Table source: From the New England Journal of Medicine, Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer, Volume No: 381(25), Suppl. Appendix ,Page No: 38. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[2]

Adverse Events of Special Interest

The treatment emergent myelosuppression events that occurred in the trial are summarized in Table 25. The most common myelosuppression TEAEs in the niraparib group (versus the placebo group) were thrombocytopenia (66.3% versus 4.9%), anemia (64.3% versus 17.6%), leukopenia (49.8% versus 13.1%), and neutropenia (42.4% versus 7.8%).[4] Thrombocytopenia was the most common myelosuppression TEAE in the niraparib group leading to a dose interruption (55.6%), dose reduction (47.3%), or a dose discontinuation (4.3%).

Table 25: Treatment-Emergent Myelosuppression Events Occurring in the PRIMA trial (Safety Population)

TEAE – n (%)	Niraparib (n=484)	Placebo (n=244)
Thrombocytopenia Event		
Overall	321 (66.3)	12 (4.9)
Grade 3 or 4	188 (38.8)	1 (0.4)
SAE	79 (16.3)	0
Dose Interruption	269 (55.6)	0
Dose Reduction	229 (47.3)	0
Dose Discontinuation	21 (4.3)	0

TEAE – n (%)	Niraparib (n=484)	Placebo (n=244)
Anemia Event		
Overall	311 (64.3)	43 (17.6)
Grade 3 or 4	150 (31.0)	4 (1.6)
SAE	27 (5.6)	0
Dose Interruption	152 (31.4)	2 (0.8)
Dose Reduction	131 (27.1)	2 (0.8)
Dose Discontinuation	9 (1.9)	0
Leukopenia Event		
Overall	241 (49.8)	32 (13.1)
Grade 3 or 4	105 (21.7)	4 (1.6)
SAE	11 (2.3)	0
Dose Interruption	97 (20.0)	2 (0.8)
Dose Reduction	68 (14.0)	3 (1.2)
Dose Discontinuation	10 (2.1)	0
Neutropenia Event		
Overall	205 (42.4)	19 (7.8)
Grade 3 or 4	100 (20.7)	3 (1.2)
SAE	11 (2.3)	0
Dose Interruption	93 (19.2)	2 (0.8)
Dose Reduction	65 (13.4)	3 (1.2)
Dose Discontinuation	9 (1.9)	0
Pancytopenia Event[a]		
Overall	2 (0.4)	0
Grade 3 or 4	2 (0.4)	0
SAE	2 (0.4)	0
Dose Interruption	1 (0.2)	0
Dose Reduction	1 (0.2)	0
Dose Discontinuation	0	0
Thromboembolic Event		
Overall	3 (0.6)	1 (0.4)
Grade 3 or 4	3 (0.6)	0
SAE	1 (0.2)	0
Dose Interruption	0	0
Dose Reduction	0	0
Dose Discontinuation	0	0

SAE = serious adverse event; TEAE = treatment-emergent adverse events.
Notes:
[a] Reported pancytopenia events included 1 TEAE report of MDS.
Data source: EPAR[4]

The treatment-emergent hypertension events that occurred in the trial are summarized in Table 26. Overall, 18.0% of patients in the niraparib group and 7.0% of patients in the placebo group experienced treatment-emergent hypertension events. None of the events lead to dose discontinuation.[5]

Table 26: Treatment-Emergent Hypertension Events Occurring in the PRIMA trial (Safety Population)

n (%)	Niraparib (n=484)	Placebo (n=244)
Overall	87 (18.0)	17 (7.0)
Grade 3 or 4	30 (6.2)	3 (1.2)
SAE	1 (0.2)	0
Dose Interruption	8 (1.7)	1 (0.4)
Dose Reduction	4 (0.8)	0
Dose Discontinuation	0	0

SAE = serious adverse event.
Data source: Clinical Study Report[5]

Subsequent Cancer Treatments Received Post-Progression

A summary of the anti-cancer treatments patients received in the PRIMA trial post-progression is provided in Table 27. In the HRD-positive population, 30.2% and 49.6% of patients in the niraparib and placebo groups, respectively, received a subsequent anti-cancer regimen post-progression;[6] and the corresponding percentages in the overall population were 40.9% and 51.2% of patients, respectively. In both populations, platinum-based chemotherapy (including carboplatin, cisplatin, oxaliplatin) was the most common post-progression treatment received by patients in each treatment group followed by doxorubicin (including adriamycin, liposomal doxorubicin). Of note, 2.9% and 5.6% of patients in the niraparib and placebo groups of the HRD-positive population, respectively, and 1.4% and 4.5% of patients in the niraparib and placebo groups of the overall population, respectively, received a PARP inhibitor post-progression.

Table 27: Subsequent Anti-cancer Treatments Received by Patients Post-Progression in the PRIMA trial (ITT Population)

n (%)	HRD-positive Population		Overall Population	
	Niraparib (n = 245)	Placebo (n = 125)	Niraparib (n = 484)	Placebo (n = 244)
Post-progression regimen	74 (30.2)	62 (49.6)	198 (40.9)	125 (51.2)
Platinum (carboplatin, cisplatin, oxaliplatin)	62 (25.3)	46 (36.8)	152 (31.4)	96 (39.3)
Doxorubicin (adriamycin, liposomal doxorubicin)	41 (16.7)	26 (20.8)	99 (20.5)	66 (27.0)
Gemcitabine	32 (13.1)	18 (14.4)	76 (15.7)	44 (18.0)
Taxane (paclitaxel, docetaxel, nab-paclitaxel)	17 (6.9)	13 (10.4)	62 (12.8)	30 (12.3)
Bevacizumab	12 (4.9)	9 (7.2)	39 (8.1)	31 (12.7)
PARP inhibitors	7 (2.9)	7 (5.6)	7 (1.4)	11 (4.5)
Other	10 (4.1)	5 (4.0)	28 (5.8)	9 (3.7)

HRD = homologous recombination deficiency; ITT = intention-to-treat; PARP = Poly (ADP-ribose) polymerase.
Note:
Patients could receive ≥1 therapy.
Data source: Checkpoint Responses 2020[6]

6.4 Ongoing Trials

Table 28: Ongoing Trials of Niraparib Maintenance Therapy in Adult Patients with Newly Diagnosed Advanced Ovarian Cancer

Trial Design	Inclusion/ Exclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: NCT03709316 **Characteristics:** Phase III, double-blind, randomized (2:1) placebo-controlled trial n (estimated) = 381 **Setting:** 30 sites in China **Patient Enrolment Start Date:** June 30, 2018 **Data cut-off:** Estimated primary completion date – June 29, 2021 **Sponsor:** Zai Lab (Shanghai) Co., Ltd.	**Key Inclusion Criteria:** • Female patients ≥ 18 years of age • Histologically confirmed high-grade serous/endometrioid or dominantly high-grade serous/endometrioid epithelial ovarian cancer, fallopian tube carcinoma or primary peritoneal carcinoma (no histological restriction for patients carrying germline BRCA mutations) • FIGO Stage III or IV patients • ECOG PS 0-1 • Patients have completed at least 6 cycles yet no more than 9 cycles of first-line platinum-containing chemotherapy • Investigator-assessed CR or PR after first-line platinum-containing chemotherapy. Efficacy assessment should be performed after the end of at least 3 cycles of chemotherapy • CA-125 level within the normal range after the end of chemotherapy or has decreased by more than 90% during the course of first-line chemotherapy and remains so for at least 7 days **Key Exclusion Criteria:** • Patients with mucinous, clear cell subtypes of epithelial ovarian cancer, carcinosarcoma, or undifferentiated ovarian cancer • Patients with Stage III disease who have undergone primary tumour reductive surgery with postoperative status of R0-complete resection (with no residual lesion) • Patients who have undergone tumour reductive surgery more than twice • Patients who plan to or have used bevacizumab as maintenance therapy after first-line platinum-containing chemotherapy.	**Intervention:** Niraparib (200 or 300 mg daily based on patient's weight or baseline platelet count) **Comparator:** Placebo (matched dose to niraparib; 200 or 300 mg daily based on patient's weight or baseline platelet count)	**Primary:** • PFS **Secondary:** • OS • TFST • PFS and OS in patients with HRD

BRCA = breast cancer susceptibility gene; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; HRD = homologous recombination deficiency; PFS = progression-free survival; PR = partial response; OS = overall survival; TFST = time to first subsequent therapy.
Data source: Clinicaltrials.gov[80]

7 Supplemental Questions

The following supplemental question was identified during the development of the review protocol as relevant to the CADTH review of niraparib for the maintenance treatment of adult patients with advanced epithelial ovarian cancer who are in a complete or partial response to first-line platinum-based chemotherapy:

- Summary and critical appraisal of a feasibility study of a NMA and unanchored PAIC of niraparib, olaparib, and bevacizumab as maintenance therapies in patients with newly diagnosed advanced ovarian cancer

Olaparib is currently an approved treatment in Canada for patients with newly diagnosed ovarian cancer and a BRCAmut (somatic or germline). Patients may also receive bevacizumab as part of their maintenance therapy if it was used in conjunction with chemotherapy. Accordingly, PAG requested data on the comparative efficacy of niraparib to olaparib and/or bevacizumab. The systematic review performed by CADTH (refer to section 6) did not identify any trials that directly compared niraparib to olaparib and/or bevacizumab.

In the absence of direct evidence, the sponsor submitted to CADTH the results of a feasibility assessment for conducting an ITC between niraparib and other maintenance therapies for newly diagnosed advanced ovarian cancer. As the sponsor's submitted feasibility report remains unpublished, a summary of the methods and results of the feasibility assessment are summarized below based on published conference sources provided by the sponsor.[7]

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Summary and Critical Appraisal of a Feasibility Study of a NMA and Unanchored PAIC of Niraparib, Olaparib, and Bevacizumab as Maintenance Therapies in Patients with Newly Diagnosed Advanced Ovarian Cancer

Methods

The objective of the study was to assess the feasibility of performing, 1) a NMA for estimating the comparative efficacy of niraparib monotherapy, following first-line chemotherapy in patients with advanced ovarian cancer, compared with other maintenance therapies; and 2) an unanchored PAIC of niraparib monotherapy with olaparib plus bevacizumab.[7]

The feasibility assessment was based on a systematic literature review (SLR) which aimed to review efficacy and safety outcomes in clinical trials of first-line maintenance therapies for advanced ovarian cancer.[7] The following databases were searched on February 27th, 2020 with no restriction on publication date: EMBASE, Medline and Medline In-Process (EMBASE interface - 1947 to present), Cochrane Central Register of Controlled Trials Centre (Cochrane library), Centre for Reviews and Dissemination Health Technology Assessment Database (1989 to present), Centre for Reviews and Dissemination National Health Service Economic Evaluation Database, ScHARRHUD (2006 to present), and EuroQol database (1970 to present). Grey literature was searched from April 2017 onwards in Google Scholar, clinicaltrials.gov, searches of the manufacturer's repository of evidence, websites of manufacturers of comparator products, bibliographic searching of any SLRs identified during screening, and relevant congresses over the previous 3 years. The main inclusion criteria of the SLR were as follows:

- population – patients with ovarian cancer who have received 1 line of previous chemotherapy treatment
- intervention/comparator – any maintenance therapy for ovarian cancer
- outcomes – efficacy (e.g., PFS, OS, TTD, duration of treatment, time to next treatment, time to first second treatment, stable disease, recurrence-free survival, PFS-2, platinum-free interval, response rate, HRQoL) and safety (e.g., AEs)
- study design – RCTs, non-RCTs, and observational studies (including patient registries)
- publication type – article, conference abstract, conference paper, and article in press

The SLR results were first screened based on title and abstract and potentially eligible reports underwent full-text review. Data extraction was performed for studies that met the inclusion criteria. All screening and data extraction were completed by 2 reviewers, with disagreements arbitrated by a third reviewer when required.

The level of heterogeneity across included studies, in terms of study design, population characteristics, treatment arms, and outcome measures, was assessed based on guidelines from the Cochrane Handbook for Systematic Reviews of Interventions. The feasibility of performing a NMA and unanchored PAIC was assessed based on assumptions using guidance by the Decision Support Unit in NICE DSU Technical Support Document 18.[81] The identification of all potential treatment effect modifiers and prognostic variables and the availability of data on these factors in the included studies was the key consideration for the feasibility assessment.

PFS was the key outcome of interest. The treatment effect modifiers and prognostic factors considered in the feasibility assessment included the following: age (mean), tumour histology (% serous histology), ECOG PS (% status 0), FIGO stage (% stage IV), history of cytoreductive surgery/best response to most recent platinum-based chemotherapy (% partial response), BRCAmut status (% positive), HRD status (% positive), prior treatment exposure alongside chemotherapy (% received bevacizumab), receipt of neoadjuvant chemotherapy (% receiving), and CA-125 ≤ ULN (%).It was not clear how these factors were identified as relevant; however, it was stated that clinical experts identified visible residual disease based on history of cytoreductive surgery as a key treatment effect modifier that would influence PFS.

Results

SLR: The SLR identified 8631 unique references, from which 50 full text articles representing 12 RCTs and 6 non-RCTs met the inclusion criteria. The 12 RCTs were included in the NMA feasibility assessment and are detailed in Table 29. Of the 12 RCTs, 4 evaluated PARP inhibitors (PRIMA, SOLO-1, PAOLA-1, and VELIA/GOG-3005), 5 evaluated anti-angiogenic therapies (AGO-OVAR16, NCT01227928, ICON-7, GOG-0218, and TRINOVA-3), and 1 trial each investigated anti-idiopathic therapies (MIMOSA), tyrosine protein kinase inhibitors (AGO-OVAR12), and aromatase inhibitors (CHIVA/GINECO). Of note, the safety outcomes for the 12 RCTs were not reported individually or separately from the non-RCTs.

Table 29: Summary of the RCTs included in the NMA Feasibility Assessment

Trial	Key Paper	Drug Class	Treatment Arms[a]	Efficacy Outcome Summary[b]
SOLO-1 [c] (NCT01844986)	Moore 2018	PARP inhibitors	Olaparib *versus* placebo	PFS: Favours olaparib (statistically significant) OS: Favours olaparib (not statistically significant)
PAOLA-1 (NCT02477644)	Ray-Coquard 2019	PARP inhibitors	Chemotherapy + bevacizumab, followed by olaparib + bevacizumab *versus* bevacizumab alone in maintenance	PFS: Favours olaparib + bevacizumab (statistically significant) OS: Outcome NR
PRIMA (NCT02655015)	González-Martín 2019	PARP inhibitors	Niraparib *versus* placebo	PFS: Favours niraparib (statistically significant) OS: Favours niraparib (not statistically significant)
VELIA/GOG-3005 (NCT02470585)	Coleman 2020	PARP inhibitors	Chemotherapy + veliparib in active treatment, followed by veliparib maintenance *versus* chemotherapy + veliparib in active treatment, followed by placebo maintenance *versus* chemotherapy + placebo in active treatment, followed by placebo maintenance	PFS: Favours chemotherapy plus veliparib plus veliparib maintenance (statistically significant) OS: Outcome NR
AGO-OVAR16 (NCT00866697); plus East Asian sub-study (NCT01227928)	Du Bois 2014 Vergote 2018 Kim 2018	Anti-angiogenic therapies	Pazopanib *versus* placebo	PFS: Favours pazopanib (statistically significant) in overall study; favours placebo (not statistically significant) in East Asian sub-study OS: Favours pazopanib (not statistically significant) in overall study; outcome NR in East Asian sub-study

Trial	Key Paper	Drug Class	Treatment Arms[a]	Efficacy Outcome Summary[b]
NCT01227928	Zang 2013	Anti-angiogenic therapies	Pazopanib *versus* placebo	PFS: Favours pazopanib (not statistically significant) OS: Outcome NR
ICON-7 (NCT00483782)	Oza 2015	Anti-angiogenic therapies	Chemotherapy in active treatment, followed by surveillance *versus* chemotherapy + bevacizumab in active treatment, followed by bevacizumab maintenance	PFS: Favours chemotherapy plus surveillance (not statistically significant) OS: Favours chemotherapy plus surveillance (not statistically significant)
GOG-0218 (NCT00262847)	Burger 2011	Anti-angiogenic therapies	Chemotherapy ± bevacizumab in active treatment, followed by placebo maintenance *versus* chemotherapy + bevacizumab in active treatment, followed by bevacizumab maintenance	PFS: Favours chemotherapy plus bevacizumab plus bevacizumab maintenance (statistically significant) OS: Favours chemotherapy plus bevacizumab plus bevacizumab maintenance (statistically significant)
TRINOVA-3 (NCT01493505)	Vergote 2019	Anti-angiogenic therapies	Chemotherapy + trebananib in active treatment, followed by trebananib maintenance *versus* CT in active treatment, followed by PBO maintenance	PFS: Favours chemotherapy plus trebananib plus trebananib maintenance (not statistically significant) OS: Favours chemotherapy plus trebananib plus trebananib maintenance (not statistically significant
MIMOSA (NCT00418574)	Sabbatini 2013	Anti-idiopathic therapies	Abagovomab *versus* placebo	PFS: Favours placebo (not statistically significant) OS: Favours placebo (not statistically significant)
AGO-OVAR12 (NCT01015118)	Ray-Coquard 2017	Tyrosine protein kinase inhibitors	Chemotherapy + nintendanib in active treatment, followed by nintendanib maintenance *versus* chemotherapy in active treatment, followed by placebo maintenance	PFS: Outcome NR OS: Favours chemotherapy plus nintendanib plus nintendanib maintenance (not statistically significant)
CHIVA/GINECO (NCT01583322)	Feron 2019	Aromatase inhibitors	Neoadjuvant chemotherapy + nintendanib in active treatment, followed by nintendanib maintenance *versus* neoadjuvant chemotherapy in active treatment, followed by placebo maintenance	PFS: Favours neoadjuvant chemotherapy plus placebo plus placebo maintenance (statistically significant) OS: Favours neoadjuvant chemotherapy plus placebo maintenance (statistically significant)

NR = not reported; OS = overall survival; PARP = poly(ADP-ribose) polymerase; PFS = progression-free survival. Notes:
[a] Treatments were in the maintenance phase following 1L CT unless otherwise specified.
[b] Determination of statistical significance in the table based on whether the confidence intervals displayed in the conference poster cross 1 (Guy et al, ESGO-SOA, 2020; poster number 373; Figure 2 [PFS] and Figure 3 [OS]). Results are for the ITT population (SOLO-1 included BRCAmut patients only).
[c] Trial included BRCAmut patients only.

Data source: Checkpoint Meeting Response, 2020[7]

NMA: The 12 RCTs identified by the SLR were excluded from a potential NMA with the PRIMA trial.[7] The reasons individual trials were excluded is summarized in Table 30 and can be categorized as follows: a) the lack of a common comparator with the PRIMA trial required to form a connected network (ICON-7, GOG-0218, PAOLA-1, CHIVA/GINECO, TRINOVA-3, VELIA/GOG-3005, and AGO-OVAR12); b) inclusion of stage III patients with NVRD following primary debulking surgery (SOLO-1, MIMOSA, AGO-OVAR16, NCT01227928, PAOLA-1, CHIVA/GINECO, TRINOVA-3, and VELIA/GOG-3005); c) interim or immature OS data (SOLO-1, MIMOSA, PAOLA-1, CHIVA/GINECO, and VELIA/GOG-3005); d) differing measurement of PFS and OS starting time point due to trial design (ICON-7, GOG-0218, CHIVA/GINECO, TRINOVA-3, VELIA/GOG-3005, and AGO-OVAR12); and e) disparity between disease biomarker (SOLO-1).

Table 30: Reasons Trials Excluded from Potential NMA with PRIMA

Trial	Reasons for excluding trials from a potential NMA with PRIMA
SOLO-1	• Inclusion of patients with NVRD following primary debulking surgery • Disparity between disease biomarker status • Interim or immature OS data
ICON-7	• Lack of common comparator within the network • Differing measurement of PFS and OS starting time point due to trial design
MIMOSA	• Inclusion of patients with NVRD following primary debulking surgery • PFS was not assessed • Interim or immature OS data
AGO-OVAR16	• Inclusion of patients with NVRD following primary debulking surgery
NCT01227928	• Inclusion of patients with NVRD following primary debulking surgery
GOG-0218	• Lack of common comparator within the network • Differing measurement of PFS and OS starting time point due to trial design
PAOLA-1	• Lack of common comparator within the network • Inclusion of patients with NVRD following primary debulking surgery • Interim or immature OS data
CHIVA/GINECO	• Lack of common comparator within the network • Inclusion of patients with NVRD following primary debulking surgery • Interim or immature OS data • Differing measurement of PFS and OS starting time point due to trial design
TRINOVA-3	• Lack of common comparator within the network • Inclusion of patients with NVRD following primary debulking surgery • Differing measurement of PFS and OS starting time point due to trial design
VELIA/GOG-3005	• Lack of common comparator within the network • Inclusion of patients with NVRD following primary debulking surgery • Interim or immature OS data • Differing measurement of PFS and OS starting time point due to trial design
AGO-OVAR12	• Lack of common comparator within the network • Differing measurement of PFS and OS starting time point due to trial design

ITC = indirect treatment comparison; NVRD = no visible residual disease; OS = overall survival; PFS = progression-free survival.

Data source: Checkpoint Meeting Response, 2020[7]

In summary, a NMA was considered not feasible by the authors for the following reasons:

Study design heterogeneity

- Therapies that were evaluated as maintenance therapies initiated alongside first-line chemotherapy, followed by a maintenance phase, could not be compared to PRIMA due to the inability to determine the treatment effect associated with the maintenance phase of the agent that was used alongside the first-line chemotherapy.
- Time on treatment could vary (e.g., 24 months in the PAOLA-1 trial versus 36 months in PRIMA) based on the maximum treatment duration specified in treatment discontinuation rules.

- If a large proportion of patients terminated therapy prior to PD, the outcome of PFS may have been impacted by the shorter treatment time. Compared to PRIMA, the maximum treatment durations were substantially shorter for some trials (i.e., AGO-OVAR16, NCT01227928, and TRINOVA-3 compared with PRIMA) and much longer for others (ICON-7, SOLO-1, PAOLA-1, and TRINOVA-3).
- One trial (MIMOSA) was excluded as treatment in the trial was discontinued based on recurrence (defined as the appearance of any lesion or development of tumour-related symptoms evaluated by medical examination that must be confirmed by a documented CT-scan) rather than disease progression (per RECIST version 1.1) as used in PRIMA.
- Trials were excluded if the patients received an active chemotherapy as part of the control arm (i.e., ICON-7, GOG-0218, CHIVA/GINECO, TRINOVA-3, VELIA/GOG-3005, and AGO-OVAR12).

Patient population heterogeneity

- When considering heterogeneity within the ITT patient population at baseline, all RCTs had confounding factors.
- Differences were noted in the patient populations that can lead to an imbalance in treatment effect modifiers (e.g., the inclusion of only patients with BRCAmut in the SOLO-1 trial; the inclusion of patients with NVRD following debulking surgery as per the MIMOSA, AGO-OVAR16, PAOLA-1, SOLO-1, VELIA/GOG-3005, NCT01227928, CHIVA/GINECO and TRINOVA-3 trials).

Outcome heterogeneity

- Outcome heterogeneity was noted for the assessment of PFS in all trials (e.g., BICR versus investigator-assessment, PFS not assessed or insufficient data, and/or PFS included the time patients were receiving standard chemotherapy, and as such, the PFS timings were not consistent).
- Outcome heterogeneity was noted for the assessment of OS in all trials (e.g., some studies included the time period when patients received first-line chemotherapy and/or data were immature at the time of the analysis).

PAIC: For the feasibility of performing a PAIC of niraparib monotherapy (PRIMA trial) compared with olaparib plus bevacizumab (PAOLA-1 trial), the following differences between the trials were identified:

- Inclusion criteria related to residual disease were wider in PAOLA-1 (which included patients' cytoreductive surgery history and best response to most recent platinum-based therapy; and patients with stage III disease and NVRD following primary debulking surgery) representing a patient population of better prognosis compared to the PRIMA trial patient population. This difference in patient populations in terms of prognosis violates the conditional constancy of absolute effects assumption for performing an unanchored PAIC.
- Receipt of neoadjuvant chemotherapy was identified as a confounding factor that would bias a PAIC, since patients who receive neoadjuvant chemotherapy have worse prognosis.
- Patients in PAOLA-1 received bevacizumab treatment in combination with their platinum-based chemotherapy prior to study entry and continued treatment with bevacizumab as a maintenance therapy with or without olaparib. As there were few patients in the PRIMA trial who received bevacizumab, bevacizumab treatment was considered a potential confounding factor and thus a source of bias.
- Discrepancies were identified between the trials related to the assessment method and frequency of measurement of PFS (primary endpoint for PRIMA was PFS by BICR and primary endpoint for PAOLA-1 was investigator-assessed PFS; more frequent scanning intervals in PRIMA, leading to the potential for a shorter median PFS estimate) that could bias comparisons.

Conclusions

Based on the results of the each feasibility assessment, the authors concluded that neither a NMA nor an unanchored PAIC could be performed, as in each case, the available evidence did not meet the current guidelines for performing objective comparative clinical effectiveness analyses.[7] The inclusion criteria of the PRIMA trial led to the enrollment of patients with a high risk of disease recurrence, which differed from the study populations of the comparator trials, among other sources of heterogeneity. Due to the identified heterogeneity between the trials available for the indirect comparisons, the comparative analyses were considered inappropriate for use in clinical decision making or reimbursement decisions.

Critical Appraisal:

All RCTs were excluded from a potential NMA or PAIC with the PRIMA trial due to the heterogeneity identified in the feasibility assessments. Although the published conference sources provided limited details in terms of methodology and the results of the feasibility assessment, a full report was included by the sponsor as part of the submission to CADTH. Overall, the CADTH Methods team agreed with the authors' conclusion that neither a NMA nor an unanchored PAIC would be feasible given the extent of clinical heterogeneity present among the clinical trials considered.

The feasibility assessment was based on a SLR that identified studies according to prespecified inclusion criteria. The literature search appeared comprehensive. The feasibility assessment identified several sources of heterogeneity that would preclude a NMA or a PAIC. The comparability of the trials in terms of study design, population characteristics, treatment groups, and outcome measures were assessed using guidelines from the Cochrane Handbook for Systematic Reviews of Interventions. While it was not clear how the authors identified the potential treatment effect modifiers and prognostic factors considered (other than those identified from the clinical expert validation), the CGP reviewed the factors that were considered, and agreed they were relevant.

The 12 eligible RCTs were deemed not sufficiently comparable for the purpose of conducting ITCs. The clinical heterogeneity observed across the trials, particularly related to the type of maintenance therapy (e.g., initiated alongside initial chemotherapy versus after chemotherapy), patient populations (e.g., risk of recurrence, imbalances in known treatment effect modifiers) and outcome assessment (e.g., method of assessment, availability of data limiting analysis to select outcomes) was considered by the CADTH Methods Team and the CGP to be a valid concern that would preclude a meaningful analysis and unbiased estimates of relative treatment effect.

Summary

In the absence of direct evidence, the sponsor submitted to CADTH a feasibility assessment for conducting an ITC between niraparib and other maintenance therapies for newly diagnosed advanced ovarian cancer. As the submitted feasibility report remains unpublished, a summary of the methods and results of the feasibility assessment were summarized based on published conference sources provided by the sponsor.

Based on the results of each feasibility assessment, the authors concluded that neither a NMA nor an unanchored PAIC could be performed, as in each case, the available evidence did not meet the current guidelines for performing objective comparative clinical effectiveness analyses. The inclusion criteria of the PRIMA trial led to the enrollment of patients with a high risk of disease recurrence, which differed from the study populations of the comparator trials, among other sources of heterogeneity. Due to the identified heterogeneity between the trials available for the indirect comparisons, the comparative analyses were considered inappropriate for use in clinical decision making or reimbursement decisions.

The CADTH Methods Team, in consultation with the CGP, reviewed the 12 eligible RCTs considered in the feasibility assessment and agreed with the authors' conclusion that the trials were not sufficiently comparable for the purpose of conducting an ITC (i.e., NMA or PAIC). The clinical heterogeneity observed across the trials, particularly related to the type of maintenance therapy (e.g., initiated alongside initial chemotherapy versus after chemotherapy), patient populations (e.g., risk of recurrence, imbalances in known treatment effect modifiers) and outcome assessment (e.g., method of assessment, availability of data limiting the analysis to

select outcomes) was considered by the CADTH Methods Team and CGP to be a valid concern that would preclude a meaningful analysis and unbiased estimates of relative treatment effect.

8 Comparison with Other Literature

The CADTH Methods Team and CGP did not identify other relevant literature as supporting information for this review.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Gynecology 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 niraparib as maintenance treatment for patients with newly diagnosed ovarian cancer who are in a complete or partial response to first-line platinum-based chemotherapy. 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.

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.

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Database(s): Cochrane Central Register of Controlled Trials (August 2020), Embase (1974 to 2020 September 28), Ovid MEDLINE All (1946 to September 28, 2020)

#	Searches	Results
1	(zejula* or niraparib* or MK4827 or MK-4827 or HMC2H89N35 or 75KE12AY9U or 195Q483UZD or L4JFC1PHCI or GTPL8275 or GSK-3985771 or GSK3985771 or JNJ-64091742 or JNJ64091742 or ZL-2306 or ZL2306).ti,ab,ot,kf,kw,hw,rn,nm.	1572
2	1 use cctr	124
3	1 use medall	239
4	limit 3 to english language	235
5	2 or 4	359
6	*niraparib/	347
7	(zejula* or niraparib* or MK4827 or MK-4827 or GTPL8275 or GSK-3985771 or GSK3985771 or JNJ-64091742 or JNJ64091742 or ZL-2306 or ZL2306).ti,ab,kw,dq.	967
8	6 or 7	986
9	8 use oemezd	645
10	limit 9 to english language	624
11	10 not (conference abstract or conference review).pt.	322
12	5 or 11	681
13	remove duplicates from 12	452
14	10 and (conference abstract or conference review).pt.	302
15	limit 14 to yr="2015 -Current"	264
16	13 or 15	716

2. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

3. Grey literature search via:

Clinical trials 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 Trials Register
https://www.clinicaltrialsregister.eu/ctr-search/search

Search: Zejula/niraparib, ovarian 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: Zejula/niraparib, ovarian cancer

Conference abstracts:

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

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

Search: Zejula/niraparib, ovarian cancer — last 5 years

Literature Search Methods

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).[4]

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 Zejula and niraparib.

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

The search is considered up to date as of January 4, 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).[82] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trials 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 5 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 through contacts with the CADTH CGP. As well, the manufacturer of the drug was contacted for additional information, as required by the CADTH 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 CADTH 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 1 member of the CADTH Methods Team with input provided by the CGP and other members of the CADTH Review Team. Additional limitations and sources of bias were identified by the CADTH Review Team.

Data Analysis

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

Writing of the Review Report

This report was written by the CADTH Methods Team, the CADTH CGP and CADTH:

- The CADTH 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 CGP 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 PAG, and by Registered Clinicians.

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