CADTH

CADTH PCODR INITIAL CLINICAL GUIDANCE REPORT

Clinical Report

NIRAPARIB (ZEJULA)

(GlaxoSmithKline Inc.)

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

Service Line:	CADTH pCODR Clinical Guidance Report
Version:	Final
Publication Date:	September 3, 2020
Report Length:	107 Pages

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
AML	acute myeloid leukemia
BRCA	breast cancer susceptibility gene
BRCAwt	BRCA wild type
CA-125	Cancer Antigen-125
CBC	complete blood cell count
CCO	Cancer Care Ontario
CFI	chemotherapy-free interval
CGP	Clinical Guidance Panel
CI	confidence interval
CrI	credible interval
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DAC	Drug Advisory Committee
DBL	database lock
DIC	deviance information criterion
ECOG PS	Eastern Cooperative Oncology Group performance status
ENGOT	European Network of Gynaecological Oncological Trial
EQ-5D-5L	European Quality of Life Scale, 5-Dimensions, 5-Level
FOSI	Functional Assessment of Cancer Therapy-Ovarian Symptom Index
gBRCAmut	germline BRCA mutation
GCIG	Gynecologic Cancer Intergroup
HR	hazard ratio
HRD	homologous recombination deficiency
HRQoL	health-related qualify of life
HUI	health utility index
IRC	independent review committee
ITC	indirect treatment comparison
ITT	intent-to-treat

KM	Kaplan-Meier
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimal important difference
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NSGO	Nordic Society of Gynecological Oncology
OCC	Ovarian Cancer Canada
ORR	objective response rate
OS	overall survival
OR	odds ratio
PAG	Provincial Advisory Group
PE	pharmacoeconomic
PARP	poly(ADP-ribose) polymerase
PD	progressive disease
pERC	pCODR Expert Review Committee
PFS	progression-free survival
PR	partial response
QoL	quality of life
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RR	relative risk
SAE	serious adverse event
sBRCAmut	somatic BRCA mutation
SD	standard deviation
TEAE	treatment-emergent adverse event
TFST	time-to-first subsequent therapy
TTST	time-to-second subsequent therapy
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) for ovarian cancer. 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 for patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete response (CR) or partial response (PR) to platinum-based chemotherapy.

The appropriate comparators for niraparib in this treatment setting are olaparib as monotherapy in patients with breast cancer susceptibility gene (BRCA)-mutated, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, which is funded in almost all provincial jurisdictions; and best-supportive care with active surveillance/observation in some patients. Currently, there are no publicly funded maintenance treatment options for patients without a BRCA mutation (BRCA wild type). The reimbursement request under review by CADTH is for niraparib as monotherapy for the maintenance treatment of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR. A notice of compliance (NOC) was issued by Health Canada for niraparib for this indication on June 27, 2019.[1] The reimbursement request is the same as the Health Canada NOC.

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 BRCA 1/2.[1] The recommended dosing of niraparib is 300 mg (3 x 100 mg capsules) taken orally once daily. In the phase III NOVA trial,[2] most patients in the niraparib group required dose modification due to treatment-emergent adverse events (TEAEs); however, these dose modifications did not affect treatment efficacy. Following the market authorization of niraparib in the United States and the European Union, the sponsor conducted exploratory analyses of the NOVA trial data to identify baseline characteristics that were associated with an increased risk of TEAEs.[3] These analyses 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.[4] Thus, a starting dose of 200 mg can be considered in patients with body weight < 77 kg and platelet count < 150,000/µL to decrease the incidence of TEAEs without loss of treatment efficacy.[3] These dosing considerations are consistent with the Health Canada product monograph, which outlines specific guidelines on dose adjustment to manage hematologic and non-hematologic adverse events (AEs).[1]

1.1 Key Results and Interpretation

1.1.1 Systematic Review Evidence

The CADTH systematic review included one randomized controlled trial (RCT), the NOVA trial (n=553).[2] A summary of the trial and its results is provided below.

NOVA

NOVA is an international, double-blind, placebo-controlled, phase III randomized trial that evaluated the efficacy and safety of niraparib compared to placebo as maintenance treatment in female adult patients with platinum-sensitive, recurrent ovarian, fallopian tube, or primary peritoneal cancer (henceforth referred to as ovarian cancer).[2] Patients randomized to niraparib received a 300 mg once daily oral dose in 28-day cycles until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up.[5] Patients randomized to placebo received a once daily oral dose marked as equivalent to niraparib and according to the same schedule.

To be eligible, patients had to have predominantly high-grade serous ovarian cancer, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and demonstrated sensitivity to platinum-based treatment.[5] Enrolled patients had to have received at least two prior platinum-based therapies.[2] For their penultimate (i.e. second to last) platinum-containing therapy before trial enrollment, patients were required to have demonstrated platinum-sensitive disease following this treatment, which was defined as a CR or PR and disease progression more than six months after completion of platinum therapy. For the last platinum-containing therapy received before randomization, patients were required to have received a minimum of four cycles of treatment, and following treatment, have an investigator-defined CR or PR with observable residual disease of less than 2 cm and Cancer Antigen-125 (CA-125) values either within the normal range or a decrease of more than 90% that was stable for at least seven days.

Eligible patients were randomized in a 2:1 ratio to receive either niraparib or placebo.[5] Randomization occurred separately in two cohorts based on the germline BRCA mutation (gBRCAmut) status of the patient: 203 patients comprised the gBRCAmut cohort (niraparib: n=138; placebo: n=65) and 350 patients comprised the non-germline BRCA mutation (non-gBRCAmut) cohort (niraparib: n=234; placebo: n=116). Randomization was stratified by the following factors: time-to-progression after the penultimate platinum therapy received before trial enrolment (six to <12 months and ≥12 months), use of bevacizumab in the penultimate or last platinum regimen received, and best response during last platinum treatment (CR or PR). Patients in the non-gBRCAmut cohort were also grouped based on the tumour status of homologous recombination deficiency (HRD) and somatic BRCA mutation (sBRCAmut).

The primary endpoint of the trial was progression-free survival (PFS), defined as the time from treatment randomization to the date of disease progression or death from any cause, whichever occurred first.[5 2] Disease progression was assessed by independent central radiological and clinical review (IRC) according to RECIST, version 1.1 and assessments were performed in a blinded fashion by IRC.[5] The secondary outcomes assessed included overall survival (OS), time-to-first subsequent therapy (TFST), time-to-second subsequent therapy (TSST), chemotherapy-free interval (CFI), progression-free survival on next line of therapy (PFS-2), and patient-reported outcomes (PRO).[2] The PROs included the Functional Assessment of Cancer Therapy-Ovarian Symptom Index (FOSI), the European Quality of Life Scale, 5-Dimensions, 5-Level (EQ-5D-5L), and the Chemotherapy Induced Peripheral Neuropathy (CIPN) questionnaire.[6]

Three primary efficacy populations were analyzed: gBRCAmut, HRD-positive non-gBRCAmut cohort, and the overall non-gBRCAmut cohort.[2] For the assessment of PFS in the non-gBRCAmut cohort, a hierarchical-testing procedure was used, which prespecified that efficacy analyses were first performed in patients with HRD-positive tumours, and if the results were statistically significant, a test of the overall non-gBRCAmut cohort was performed.[2] Therefore, for the non-gBRCAmut cohort, the HRD-positive subgroup was the primary efficacy population.[5] Additional exploratory analyses of PFS were also prespecified and performed in three subgroups of the non-gBRCAmut cohort: HRD-positive plus sBRCAmut, HRD-positive plus BRCA wild type (wt), and HRD-negative.

A total of 553 patients were randomized in the trial. In the gBRCAmut cohort, 138 patients were randomized to receive niraparib and 65 patients were randomized to receive placebo.[5] The mean age of patients was 57.0 years in the niraparib group and 58.0 years in the placebo group. In the non-gBRCAmut cohort, 234 patients were randomized to receive niraparib and 116 patients were randomized to receive placebo.[5] The median age of patients was 63.0 years in the niraparib group and 60.5 years in the placebo group. In both cohorts (range across treatment groups), the majority of patients were 'White' (84.6% to 89.1%), had an ECOG PS of 0 (65.9% to 73.8%), stage IIIC cancer (55.4% to 63.7%), and ovary as their primary tumour site (81.5% to 88.4%). The mean weight of trial patients ranged from 68.0 kg to 71.8 kg.[7] Almost all trial patients had more than three previous lines of chemotherapy and two or more prior platinum therapies; and a small proportion of patients had prior treatment with bevacizumab (23.9% to 26.2%). Most patients had greater than 12 months elapse between completion of their penultimate platinum therapy and disease progression (60%

to 62.1%). A similar proportion of patients in each treatment group had a CR or PR as the best response to most recent platinum therapy.[2]

Efficacy

The results for the primary and secondary efficacy outcomes from the NOVA trial are summarized in Table 1. As of the June 20, 2016 database lock (DBL), the median duration of follow-up in the full trial population was 16.9 months (gBRCAmut cohort: 16.4 months; non-gBRCAmut cohort: 17.5 months).[2] The median duration of study drug exposure was longer in the niraparib group compared to the placebo group at approximately nine cycles and six cycles, respectively.[7] Although the starting dose of niraparib was 300 mg once daily, the most commonly used dose of niraparib was 200 mg. The trial is still ongoing for patient follow-up.

As of the June 20, 2016 DBL, the NOVA trial met its primary endpoint by demonstrating a statistically significant longer duration of PFS in the niraparib group compared to the placebo group (*P*<0.001) in all three primary efficacy populations. In the gBRCAmut cohort, median PFS was 21.0 months in the niraparib group and 5.5 months in the placebo group, corresponding to an absolute PFS benefit of 15.5 months (hazard ratio [HR]= 0.27; 95% confidence interval [CI], 0.17 to 0.41; *P*<0.0001).[5] In the HRD-positive non-gBRCAmut cohort, median PFS was 12.9 months in the niraparib group and 3.8 months in the placebo group, corresponding to an absolute PFS benefit of 9.1 months (HR= 0.38; 95% CI, 0.24 to 0.59; *P*<0.0001). In the overall non-gBRCAmut cohort, median PFS was 9.3 months in the niraparib group and 3.9 months in the placebo group, corresponding to an absolute PFS benefit of 5.4 months (HR= 0.45; 95% CI, 0.34 to 0.61; *P*<0.0001). For all three efficacy populations, the estimated proportion of patients who were progression-free at 6, 12, 18 and 24 months was greater in the niraparib group compared to the placebo group.[8] The results of all prespecified subgroup analyses for PFS were consistent with the primary efficacy analysis results.

At the time of the June 20, 2016 DBL OS data were immature based on a total of 95 deaths (17% maturity) .[5] The median OS was not estimable for either treatment group in any of the three efficacy populations. In the gBRCAmut cohort, 24 patients had died that included 16 (12%) deaths in the niraparib group and eight (12%) deaths in the placebo group ((HR=0.91; 95% CI, 0.36 to 2.28). In the HRD-positive non-gBRCAmut cohort, 30 patients had died that included 23 deaths (22%) in the niraparib group and seven deaths (13%) in the placebo group (HR=1.39; 95% CI, 0.57 to 3.42).[7] In the overall non-gBRCAmut cohort, 71 patients had died that included 44 deaths (19%) in the niraparib group and 27 deaths (23%) in the placebo group (HR=0.74; 95% CI, 0.45 to 1.20).[5] The results of the secondary outcomes assessed (CFI, PFS-2, TFST, and TSST) were consistent with the primary efficacy analysis and all showed treatment effect estimates that favoured niraparib compared to placebo (Table 1).[5]

Patient-Reported Outcomes – FOSI, EQ-5D-5L, CIPN

To assess health-related qualify of life (HRQoL), the FOSI, EQ-5D-5L, and CIPN questionnaires were administered at the screening visit, throughout treatment (every eight weeks through cycle 14, then every twelve weeks thereafter[8]), at the time of study treatment discontinuation, and eight weeks after the last dose of niraparib or placebo.[2] If a patient discontinued, PRO data were collected at discontinuation and during a post-progression visit eight ± two weeks later.[8] In both treatment groups of each cohort, completion rates were greater than 75% at all assessment timepoints up to Cycle 6; completion rates beyond this treatment cycle were not reported except for post-progression FOSI assessments. At baseline, mean FOSI scores were similar between niraparib and placebo treatment groups in both the gBRCAmut and the non-gBRCAmut cohorts;[8] the most common symptoms reported by patients were lack of energy (79%, with 18% reporting severe symptoms), pain (44%), and nausea (22%). Scores for the individual FOSI subscales were similar between the treatment groups through the trial during both the maintenance (treatment) period and post-progression. In the niraparib group, all symptoms except for nausea either remained stable or improved over treatment. In the placebo group, approximately 20% of patients reported experiencing nausea. For all symptoms assessed there were no differences between the treatment groups at any timepoint that met the minimal important difference (MID) of two to three points.

At baseline, mean EQ-5D-5L health utility index (HUI) and EQ-5D-5L visual analog scale (VAS) scores were similar between niraparib and placebo treatment groups in both the gBRCAmut and the non-gBRCAmut cohorts.[8] Mean HUI and VAS scores were similar throughout the trial during the maintenance (treatment) period and post progression in each treatment group and by cohort. After adjusting for histology, region, age, prior treatment type, duration of previous treatment, and baseline EQ-5D-5L score, the adjusted mean HUI scores were also similar between the niraparib and placebo groups, and between group differences were less than the MID of 0.08 when averaged across pre-progression timepoints.

Neuropathy, measured by the degree of tingling or numbness in the feet and hands, was similar between treatment groups at baseline in both the gBRCAmut cohort (feet: 59% in the niraparib group versus 60% in the placebo group; hands: 80% versus 79%, respectively) and the non-gBRCAmut cohort (feet: 56% in the niraparib group versus 58% in the placebo group; hands: 76% versus 74%, respectively).[7] In the gBRCAmut cohort, the degree of neuropathy did not meaningfully change throughout the trial with no differences between the treatment groups that met the MID (two to three points) during the treatment (maintenance) period and post-progression for each outcome (i.e., hands and feet). In the non-gBRCAmut cohort, similar results were observed; however, at post-progression, a higher proportion of patients treated with niraparib had limited to no neuropathy in the feet compared to placebo (feet: 53% in the niraparib group versus 41% in the placebo group; hands: 62% versus 62%, respectively). It is unclear whether this difference met the MID threshold for the CIPN.

Harms

Overall, the incidence of all categories of TEAEs was higher in the niraparib group compared to the placebo group. No on-treatment deaths occurred in either treatment group; however, one patient in the niraparib group and two patients in the placebo group died from the myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) during follow-up (one death in each group was assessed as treatment-related by the investigator).

At least one TEAE occurred in all patients (100%) who received niraparib and in 95.5% of patients who received placebo;[2] and treatment-related TEAEs occurred in 97.5% and 70.9% of patients, respectively. The most common TEAEs of any grade that occurred in the niraparib group (versus the placebo group) were nausea (73.6% versus 35.2%), thrombocytopenia (61.3% versus 5.6%), fatigue (59.4% versus 41.3%), anemia (50.1% versus 6.7%), constipation (39.8% versus 20.1%), vomiting (34.3% versus 16.2%), and neutropenia (30.2% versus 6.1%). The incidence of grade ≥ 3 TEAEs was 74.1% in the niraparib group compared to 22.9% in the placebo group, of which most were hematological laboratory abnormities,[5] and included (niraparib versus placebo) thrombocytopenia (33.8% versus 0.6%), anemia (25.3% versus 0%), neutropenia (19.6% versus 1.7%), fatigue (8.2% versus 0.6%), and hypertension (8.2% versus 2.2%).

At least one dose interruption due to TEAEs occurred in 66.5% of patients in the niraparib group and 14.5% of patients in the placebo group; and at least one dose reduction due to TEAEs occurred in 68.9% and 5.0% of patients, respectively.[5] The majority of dose interruptions and dose reductions in the niraparib group were attributable to thrombocytopenia (30.8% and 30.5%, respectively) and anemia (19.6% and 17.7%, respectively).[3] The incidence of grade ≥ 3 TEAEs decreased following a reduction in the dose of niraparib to 200 mg, with the exception of anemia and hypertension, which decreased at a dose of 100 mg.[5] Most of the hematologic laboratory abnormalities occurred within the first three treatment cycles, after which the incidence of grade 3 or 4 thrombocytopenia, neutropenia, and fatigue was infrequent beyond the cycle following dose adjustments.[2]

Treatment discontinuations attributable to TEAEs were also higher in the niraparib group at 14.7% compared to 2.2% in the placebo group.[2] Fatigue accounted for the majority of non-hematologic TEAEs leading to treatment discontinuation in the niraparib group at 2.7% followed by nausea at 1.6%; and thrombocytopenia accounted for the majority of hematologic TEAEs leading to treatment discontinuation at 3.3%.[5]

The incidence of MDS/AML was similar in the niraparib group versus the placebo group (1.4% versus 1.1%).[5] Most patients who developed MDS/AML had a prior history of myelosuppression (eight of nine), and had received other DNA damaging agents and radiotherapy.

Limitations and Potential Sources of Bias

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

- Potential differences in treatment response between patients in the gBRCAmut and non-gBRCAmut cohort were accounted for in the trial by randomizing the two cohorts independently and analyzing outcomes using hierarchical hypothesis testing. However, there were many predefined subgroup analyses and multiple secondary efficacy outcomes assessed in the trial 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 additional subgroups and outcomes, the results of these analyses should be interpreted as exploratory in nature.

- According to the CGP, HRD testing is not routinely performed in Canadian clinical practice since the test has not been clinically validated. Therefore, there is uncertainty in the reliability and validity of the trial results based on HRD status.
- Patients were considered platinum-sensitive in the trial if they had a CR or PR to their last platinum-based chemotherapy and had observable residual disease of less than 2 cm, and had CA-125 values either within the normal range or a decrease of more than 90% that was stable for at least seven days. According to the CGP, these criteria are more stringent than what would be considered a clinical response in the Canadian standard of care setting. The CGP indicated PR and CR are defined using RECIST criteria, and changes in tumour size and CA-125 are not typically used. These differences in response criteria between the trial and clinical practice may have implications in terms of external generalizability of the trial results.
- At the time of the primary efficacy analysis, OS data for the full trial population were at approximately 17% maturity and showed no statistically significant differences between treatment groups in the gBRCAmut cohort (HR=0.91; 95% CI, 0.36 to 2.28), the HRD positive non-gBRCAmut cohort (HR=1.39; 95% CI, 0.57 to 3.42), and the overall non-gBRCAmut cohort (HR=0.74; 95% CI, 0.45 to 1.20). The median OS had not been reached in any treatment group of any cohort, making the magnitude of long-term OS benefit unknown. The sponsor indicated that an update to the analysis of OS will be performed when a data maturity of 60% is achieved.[9] Although patient crossover upon disease progression was not permitted in the trial, longer term survival data will be confounded by the use of post-trial treatments, which was high in the trial.

Table 1: Highlights of Key Outcomes in the NOVA trial

Outcomes	NOVA Trial					
	gBRCAmut Cohort (n=203)		Non-gBRCAmut Cohort (n=350)			
			HRD-positive (n=162)		Overall (n=350)	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=234)	Placebo (n=116)
Primary Outcome						
PFS						
Median (95% CI) in months[a]	21.0 (12.9 to NE)	5.5 (3.8 to 7.2)	12.9 (8.1 to 15.9)	3.8 (3.5 to 5.7)	9.3 (7.2 to 11.2)	3.9 (3.7 to 5.5)
HR (95% CI)[b]	0.27 (0.17 to 0.41)		0.38 (0.24 to 0.59)		0.45 (0.34 to 0.61)	
p-value[c]	<0.0001		<0.0001		<0.0001	
Survival distribution function (95% CI)[d]						
6-months	0.80 (0.72 to 0.86)	0.43 (0.30 to 0.55)	0.69 (0.58 to 0.77)	0.35 (0.23 to 0.48)	0.61 (0.54 to 0.68)	0.36 (0.26 to 0.45)
12-months	0.62 (0.53 to 0.70)	0.16 (0.07 to 0.28)	0.51 (0.40 to 0.61)	0.13 (0.05 to 0.25)	0.41 (0.33 to 0.48)	0.14 (0.08 to 0.22)
18-months	0.50 (0.40 to 0.59)	0.16 (0.07 to 0.28)	0.37 (0.26 to 0.48)	0.09 (0.02 to 0.22)	0.30 (0.23 to 0.38)	0.12 (0.06 to 0.21)
24-months	0.42 (0.30 to 0.55)	0.16 (0.07 to 0.28)	0.31 (0.20 to 0.43)	0.09 (0.02 to 0.22)	0.27 (0.19 to 0.35)	0.12 (0.06 to 0.21)
Key Secondary Outcomes						
OS						
Median (95% CI) in months[a]	NE (24.5 to NE)	NE (NE to NE)	NE (28.3 to NE)	NE (NE to NE)	NE (28.3 to NE)	NE (20.2 to NE)
HR (95% CI)[b]	0.91 (0.36 to 2.28)		1.39 (0.57 to 3.42)		0.74 (0.45 to 1.20)	
TFST						
Median (95% CI) (months)[a]	21.0 (17.5 to NE)	8.4 (6.6 to 10.6)	15.9 (12.4 to NE)	6.0 (4.7 to 9.8)	11.8 (9.7 to 13.1)	7.2 (5.7 to 8.5)
HR (95% CI)	0.31 (0.21 to 0.48)		0.36 (0.23 to 0.57)		0.55 (0.41 to 0.72)	
TSST						
Median (95% CI) in months[a]	25.8 (22.4 to NE)	20.5 (16.0 to NE)	NE (20.3 to NE)	20.8 (15.4 to NE)	21.1 (18.5 to NE)	20.3 (15.1 to NE)
HR (95% CI)[b]	0.48 (0.27 to 0.85)		0.66 (0.36 to 1.23)		0.74 (0.52 to 1.07)	
CFI						

Outcomes	NOVA Trial					
	gBRCAmut Cohort (n=203)		Non-gBRCAmut Cohort (n=350)			
			HRD-positive (n=162)		Overall (n=350)	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=234)	Placebo (n=116)
Median (95% CI) in months[a]	22.8 (17.9 to NE)	9.4 (7.9 to 10.6)	18.2 (14.2 to 24.3)	7.7 (6.3 to 10.6)	12.7 (11.0 to 14.7)	8.6 (6.9 to 10.0)
HR (95% CI)[b]	0.26 (0.17 to 0.41)		0.31 (0.19 to 0.49)		0.50 (0.37 to 0.67)	
PFS-2						
Median (95% CI) in months[a]	25.8 (20.3 to NE)	19.5 (13.3 to NE)	22.3 (18.6 to NE)	17.6 (12.9 to NE)	18.6 (16.2 to 21.7)	15.6 (13.2 to 20.9)
HR (95% CI)[b]	0.48 (0.27 to 0.85)		0.65 (0.37 to 1.12)		0.69 (0.49 to 0.96)	
Harms, n (%)	Niraparib (n=367)			Placebo (n=179)		
TEAE (any grade)	367 (100.0)			171 (95.5)		
TEAE grade ≥3	272 (74.1)			41 (22.9)		
TEAE leading to treatment interruption	244 (66.5)			26 (14.5)		
TEAE leading to dose reduction	253 (68.9)			9 (5.0)		
TEAE leading to treatment discontinuation	54 (14.7)			4 (2.2)		

BRCA = breast cancer susceptibility gene; CFI = chemotherapy-free interval; CI = confidence interval; gBRCAmut = germline BRCA mutation; HR = hazard ratio; NE = not estimable; NR = not reported; OS = overall survival; PFS = progression-free survival; PFS-2 = progression-free survival on next line of therapy; SE = standard error; SD = standard deviation; TEAE = treatment- emergent adverse event; TFST = time-to-first subsequent therapy; TSST = time-to-second subsequent therapy.

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

[b] Based on stratified log-rank test using randomization stratification factors.

[c] Niraparib versus placebo comparison based on stratified Cox Proportional Hazards Model using randomization stratification factor.

[d] Estimates from product-limit method. Confidence intervals constructed using log-log transformation.

*HR < 1.00 favour the niraparib group.

Data sources: Mirza et al. 2016,[2] Oza et al. 2018,[8] EPAR 2017,[5] Clinical Study Report[7]

1.2.2 Additional Evidence

Refer to Sections 3, 4, and 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 for the maintenance treatment, as monotherapy, of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy. Input from patients living with ovarian cancer and their caregivers were elicited through an anonymous online survey conducted from November 26, 2019 to January 15, 2020. A total of 56 people responded to the survey and included 51 patients with ovarian cancer and five caregivers, none of whom had received or cared for a patient who had experience with niraparib. From the patient's perspective, ovarian cancer impacts many aspects of life, namely sexual relationship, work life, well-being, and sleep. Caregivers reported that their work balance and sleep patterns were most negatively impacted. The risk of disease recurrence and having limited treatment options, particularly in BRCAwt patients, were concerns raised by respondents in the survey. Patients and caregivers felt that side effects of current chemotherapy treatments including fatigue, neuropathy, and hair loss have a very or extremely negative impact on their life. In terms of patients' values and expectations for new treatment, prolonging survival, lengthening time until recurrence, and improving QoL were identified as highly or extremely important. Respondents were also willing to tolerate many side effects (e.g., tiredness, taste changes, nausea, anemia/bruising, headaches, and bowel problems), if overall daily functioning and prognosis were improved; and were least willing to tolerate side effects such as bone marrow problems or blood cancer, respiratory problems, infections, and high blood pressure. Most respondents believed niraparib should be available as a treatment option in Canada for women who have ovarian cancer, and OCC highlighted the need for new treatment in this patient population.

PAG Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) and a federal drug plan participating in pCODR. PAG identified the following as factors that could affect the feasibility of implementing a funding recommendation.

Clinical factors:
- Place in therapy relative to olaparib
- Eligible patient population

Economic factors:
- Availability and funding of BRCA and HRD testing
- Clarity on treatment duration and criteria for discontinuation

Registered Clinician Input

One joint submission on behalf of six oncologists from the Cancer Care Ontario (CCO) Gynecologic Cancers Drug Advisory Committee (DAC) provided input on niraparib for the maintenance treatment of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Clinicians noted that there is a large unmet need in the non-BRCA mutated population. For BRCA-mutated patients, olaparib may be an option. Overall, the clinicians stated that although there are no head-to-head data comparing the two drugs, treatment efficacy appears similar between olaparib and niraparib, and olaparib may be slightly more tolerable. The clinicians also felt that olaparib has a more established safety profile, and that many patients will not be able to tolerate the 300 mg dose of niraparib due to toxicity. Nevertheless, the DAC noted that they would appreciate having a choice between PARP inhibitors and that studies are underway that may provide evidence to answer questions related to sequencing of treatment. As BRCA mutation status is already required diagnostic testing, the need for additional companion diagnostics (i.e., HRD) will depend on whether reimbursement is recommended for all groups of patients or limited to those with BRCA/HRD mutation status.

Summary of Supplemental Questions

The following supplemental questions were identified during development of the review protocol as relevant to the CADTH review of niraparib:

- Summary and critical appraisal of a sponsor-submitted indirect treatment comparison (ITC) and network meta-analysis (NMA),comparing niraparib with olaparib for the maintenance treatment of female adult patients with platinum-sensitive, recurrent ovarian cancer, and a gBRCAmut[10]

The CADTH Methods Team identified an ITC/NMA conducted by the sponsor of niraparib for their submission to the National Institute for Health and Care Excellence (NICE), which CADTH requested to review for this submission. The ITC/NMA was provided to CADTH as an unpublished report and compared olaparib to niraparib in patients with platinum-sensitive, recurrent ovarian cancer with a gBRCAmut. A systematic literature search identified three trials that met the eligibility criteria and were included in the ITC/NMA; the trials evaluated the following treatments, all compared to placebo: niraparib 300 mg daily, olaparib 300 mg twice daily, and olaparib 400 mg twice daily. Results of the ITC/NMA suggested that all active treatments were favoured over placebo for the efficacy outcome of PFS, however none of the active treatments were favoured over each other. Compared to patients treated with olaparib, patients treated with niraparib had a higher relative risk for grade 3/4 events of both neutropenia and thrombocytopenia. Results of the analyses for AEs suggested that both niraparib and olaparib had a higher risk for treatment discontinuations due to AEs compared to placebo, but not over each other. The key limitations of the ITC/NMA include the small size and structure of the evidence network, which had no closed loop (therefore it was not possible to check for consistency of results between direct and indirect comparisons), and potential sources of heterogeneity across the trials related to differences in patient and study characteristics. The results of the ITC/NMA should be interpreted with consideration of these limitations.

Refer to Section 7 for more information.

Comparison with Other Literature

Two ITCs were included as part of the submission to CADTH that informed the sponsor's submitted pharmacoeconomic (PE) model. Both ITCs were available as conference proceedings and their results remain unpublished in full in the peer-reviewed literature. These conference sources lacked important information on patient populations and methodology that is required to perform a thorough critical appraisal. As such, the available information from these reports was summarized along with any potential limitations that could be identified.

- Comparative efficacy and safety of olaparib 400 mg and niraparib 300 mg as maintenance treatment after response to chemotherapy in patients with platinum-sensitive relapsed non-gBRCAmut ovarian cancer [11]
- Comparative efficacy and safety of olaparib 300 mg tablets and niraparib 300 mg tablets as maintenance treatment after response to chemotherapy in patients with platinum-sensitive relapsed gBRCAmut ovarian cancer [12]

Overall, both ITCs demonstrated that for all efficacy outcomes analyzed (investigator-assessed PFS, IRC-assessed PFS, and TFST), no differences in treatment effect were shown between olaparib and niraparib. In both ITCs, for the analyses of safety outcomes, olaparib was favoured over niraparib, demonstrating lower odds of grade 3 or 4 AEs and AEs leading to dose interruption. Neither treatment was favoured over the other for the odds of AEs leading to treatment discontinuation or dose reduction.

Refer to Section 8 for more information.

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1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence from the NOVA trial; an assessment of its limitations and potential 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 NOVA trial of Niraparib as Maintenance Treatment for Recurrent Ovarian Cancer

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence From the NOVA trial[2,5]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>Prior treatment</td><td>Some patients in the NOVA trial had prior therapy with bevacizumab:

<table>
<tr><td rowspan="2">Prior Bevacizumab

n (%)</td><td colspan="2">gBRCAmut Cohort (n=203)</td><td colspan="2">Non-gBRCAmut Cohort (n=350)</td></tr>
<tr><td>Niraparib (n=138)</td><td>Placebo (n=65)</td><td>Niraparib (n=234)</td><td>Placebo (n=116)</td></tr>
<tr><td>Yes</td><td>33 (23.9)</td><td>17 (26.2)</td><td>62 (26.5)</td><td>30 (25.9)</td></tr>
<tr><td>No</td><td>105 (76.1)</td><td>48 (73.8)</td><td>172 (73.5)</td><td>86 (74.1)</td></tr>
</table>

The PFS benefit with niraparib (versus placebo) was observed in patients with and without prior therapy with bevacizumab.</td><td>Do the results of the trial apply to patients who have received prior treatment with bevacizumab combined with first-line chemotherapy or as maintenance?</td><td>Approximately one quarter of patients in the NOVA trial had prior therapy with bevacizumab; therefore, the CGP believes patients who have received bevacizumab in the first-line setting should be eligible for niraparib maintenance.</td></tr>
<tr><td>Intervention</td><td>Response criteria</td><td>The NOVA trial required patients to have received at least two platinum-based treatment therapies.

For the penultimate platinum-based chemotherapy before study enrollment, a patient must have had platinum-sensitive disease after this treatment, which was defined as having a CR or PR and disease progression more than six months after completion of the last round of platinum therapy.

For the last platinum-containing therapy, patients were required to have received a minimum of four cycles of treatment and, following treatment, have an investigator-defined CR or PR, with observable residual disease of <2 cm and CA-125 values either within the normal range, or a CA-125 decrease of more than 90% that was stable for at least seven days.</td><td>Are the criteria used in the trial to define response to chemotherapy used in Canadian practice?</td><td>The CGP believe that the criteria used in the NOVA trial to define response to the last platinum-containing chemotherapy regimen are more stringent than what would be considered a clinical response in a standard of care setting. If a patient has a CR or PR to their last platinum containing chemotherapy by RECIST criteria, the CGP would consider the patient eligible for niraparib.</td></tr>
</table>

BRCA = breast cancer susceptibility gene; CA-125 = cancer antigen 125; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; gBRCAmut = germline BRCA mutation; PARP = poly(adenosine diphosphate [ADP]–ribose) polymerase; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors. Data sources: Mirza et al. 2016,[2] EPAR 2017.[5]

1.2.4 Interpretation

Use of maintenance niraparib (a PARP Inhibitor) in recurrent ovarian, primary peritoneal, and/or fallopian tube cancers that are platinum-sensitive with demonstrated CR or PR to last platinum-based chemotherapy was evaluated in the NOVA trial.[2] NOVA is a phase III RCT that randomized two independent cohorts of eligible patients to niraparib or placebo according to the presence or absence of a germline BRCA mutation (gBRCAmut cohort and non-gBRCAmut cohort, respectively). The trial demonstrated a statistically significant longer duration of PFS, the primary endpoint of the trial, compared with placebo. At the time of the primary efficacy analysis, the median PFS was 21.0 months in the niraparib group versus 5.5 months in the placebo group (HR 0.27; 95% CI, 0.17 to 0.41; *P*<0.001) in the a gBRCAmut cohort, corresponding to an absolute improvement in median PFS of 15.5 months in the niraparib group.[2] For patients who had HRD-positive tumours in the non-gBRCAmut cohort, which was the primary efficacy analysis population of this cohort, the median PFS was 12.9 months in the niraparib group versus 3.8 months in the placebo group (HR 0.38; 95% CI, 0.24 to 0.59; *P*<0.001), which corresponds to an absolute improvement in median PFS of 9.1 months in the niraparib group. Considering all patients in the non gBRCAmut cohort, median PFS was 9.3 months in the niraparib group versus 3.9 months in the placebo group (HR 0.45; 95% CI, 0.34 to 0.61); *P*<0.0001), which corresponds to an absolute improvement in median PFS of 5.4 months. Prespecified subgroup analyses by demographic and clinical characteristics demonstrated that the treatment effect was consistent within subgroups, and multiple sensitivity analyses were performed in the trial that confirmed the robustness of the primary efficacy analysis results.[5]

Additional exploratory analyses of PFS were also prespecified in the trial protocol and performed in three groups of patients in the non-gBRCAmut cohort: HRD-positive plus sBRCAmut (n=47), HRD-positive plus BRCAwt (n=115), and HRD-negative (n=134).[2] These subgroup analyses were performed to further investigate the consistency of the PFS results and to explore whether treatment effect was driven by the presence of a somatic BRCA mutation. Although these analyses were exploratory in nature the results are notable. Among patients who were HRD-positive with a sBRCAmut, median PFS was 20.9 months in the niraparib group versus 11.0 months in the placebo group, corresponding to an absolute improvement in median PFS of 9.9 months (HR=0.27; 95% CI, 0.08 to 0.90).[7] Among patients who were HRD-positive with BRCAwt, the median PFS was 9.3 months in the niraparib group versus 3.7 months in the placebo group, corresponding to an absolute improvement in median PFS of 5.6 months (HR=0.38; 95% CI, 0.23 to 0.63).[7] Among patients who were HRD-negative, median PFS was 6.9 months in the niraparib group versus 3.8 months in the placebo group, corresponding to an improvement in median PFS of 3.1 months (HR=0.58; 95% CI, 0.36 to 0.92).[7]

The secondary efficacy endpoints assessed in the NOVA trial included OS, CFI, PFS-2, TFST, and TSST. At the time of the primary efficacy analysis the OS data were considered immature with a total of 95 patient deaths, which included 60 (16%) of all 372 patients randomized to niraparib and 35 (19%) of all patients randomized to placebo.[5] The median OS had not been reached in any treatment group of either cohort. In the gBRCAmut cohort, patients in the niraparib group had a significantly longer CFI, TFST, TTST, and PFS-2 compared to placebo. Similar results were observed in both the non-gBRCAmut cohort for CFI and TFST but not for TSST or PFS-2; however, data for PFS-2 and TTST were considered immature at the time of the primary efficacy analysis. The results of these secondary outcomes provide evidence of a consistent treatment benefit with niraparib.

In the NOVA trial, the starting dose of niraparib was 300 mg once daily; however, the most commonly used dose of niraparib was 200 mg. At the time of the primary analysis, 66.8% of trial patients had been exposed to ≥6 to <12 months of niraparib, and 44.4% had been exposed for ≥12 months.[5] The mean dose intensity was lower in the niraparib group compared to the placebo group.[5] At least one dose interruption had occurred in 66.5% of patients in the niraparib group compared to 14.5% patients in the placebo group; and at least one dose reduction attributable to AEs occurred in 68.9% of patients in the niraparib group versus 5.0% of patients in the placebo group.[5] Overall, rates of dose interruptions or dose reductions for any reason were much higher in the niraparib group (80% and 73% respectively), than in the placebo group (19% and 6% respectively).[5] Despite the higher frequency of dose interruptions and dose reductions, it is notable that the median duration of study treatment in the safety population was longer in niraparib group compared to the placebo group (11 cycles versus 6 cycles);[5] the longer treatment exposure was observed in each of the gBRCAmut and non-gBRCAmut cohorts. Most of the hematologic toxicity associated with niraparib occurred within the first three treatment cycles, after which the incidence of grade 3 or 4 thrombocytopenia, neutropenia, and fatigue was infrequent beyond the cycle following dose adjustments.[2]

The AE profile of niraparib is primarily comprised of hematologic toxicity, fatigue, and hypertension.[2] The most common AEs of any grade reported in the niraparib group (versus the placebo group) included nausea (73.6% versus 35.2%), thrombocytopenia (61.3%

versus 5.6%), fatigue (59.4% versus 41.3%), anemia (50.1% versus 6.7%), constipation (39.8% versus 20.1%), vomiting (34.3% versus 16.2%), and neutropenia (30.2% versus 6.1%). The most common grade 3 or 4 TEAEs reported in the niraparib group (versus the placebo group) were thrombocytopenia (33.8% versus 0.6%), anemia (25.3% versus 0%), neutropenia (19.6% versus 1.7%), fatigue (8.2% versus 0.6%), and hypertension (8.2% versus 2.2%). Hypertension is a unique side effect of niraparib that is not necessarily associated with every PARP inhibitor in the class (e.g. olaparib). Notably, there was a higher frequency of grade 3 or 4 TEAEs in the niraparib group at 74.1%, compared to 22.9% of patients in the placebo group. The relationship between TEAEs and the niraparib dose at the onset of AEs was explored in the trial, and it was noted that the incidence of commonly reported grade ≥3 events was highest at the 300 mg dose of niraparib compared to lower doses of 200 mg and 100 mg. In the niraparib group, 14.7% of patients discontinued treatment due to an AE of any grade compared to 2.2% in the placebo group. There were no on-treatment deaths that occurred in either treatment group, however, one patient in the niraparib group and two patients in the placebo group died from MDS or AML during trial follow-up, with one death in each treatment group assessed as treatment-related by the investigator. The incidence of MDS/AML in the trial was similar in the niraparib and the placebo groups (1.4% versus 1.1%, respectively). Most patients who developed MDS/AML in either group had a prior history of myelosuppression (eight out of nine patients) and had received other DNA damaging agents and radiotherapy.[5] These data indicate that many patients may have a better tolerance for the lower dose of niraparib than the indicated dose of 300 mg and still derive clinical benefit, and there is no excessive death or MDS/AML presumably caused by niraparib.

Patient-reported QoL outcomes were measured using the FOSI, EQ-5D-5L HUI and VAS, and CIPN questionnaires.[13] Baseline scores for symptoms (FOSI) and QoL (EQ-5D-5L HUI and VAS) were similar between the treatment groups in each cohort. Patient responses to both instruments were also similar between the treatment groups in both the gBRCAmut and non-gBRCAmut cohorts during the maintenance (treatment) period and post-progression. Analysis of FOSI scores showed that all symptoms, with the exception of nausea, either remained stable or improved over time in the niraparib and placebo groups. In the niraparib group, the proportion of patients reporting nausea increased at Cycle 2 but steadily declined at later timepoints and approached baseline levels, and the difference between the groups did not meet the MID. The analyses of time-to-symptom worsening also showed no statistically significant differences between niraparib and placebo for the overall FOSI symptom score. Mean EQ-5D-5L HUI scores and mean adjusted HUI scores (for differences in histology, region, age, prior treatment type, duration of previous treatment, and baseline score) were similar between the treatment groups in each cohort and mean differences between the groups did not meet the MID when averaged across pre-progression timepoints. Similar results were also observed for the EQ-5D-5L VAS. For both the FOSI and EQ-5D-5L, additional analyses showed that the hematological toxicity associated with niraparib (anemia, neutropenia, or thrombocytopenia) had no negative effect on QoL outcomes in either cohort. Neuropathy, assessed using the CIPN, was equivalent between treatment groups at baseline in both cohorts. In the gBRCAmut cohort, no significant differences were observed between treatment groups during the treatment (maintenance) period and at post-progression for each patient outcome (i.e., hands and feet). In the non-gBRCAmut cohort, similar results were observed throughout the treatment period, but at post-progression, a higher proportion of patients treated with niraparib had limited to no neuropathy in the feet compared to placebo. The PRO data from the NOVA trial showed ovarian cancer symptoms (which include pain, fatigue, nausea, vomiting, bloating, cramping, and worry) did not worsen in patients over the course of niraparib maintenance treatment, and QoL appeared maintained despite the overall higher incidence of toxicity in the niraparib group.

The patient advocacy group who contributed input for this submission (OCC) indicated that the disease burden of ovarian cancer and its impact on day-to-day life are substantial. In their survey, OCC identified that 65% of respondents (n=31 out of 48 patients and caregivers) would consider taking niraparib as new treatment. Additionally, of 47 respondents who answered the question, the following outcomes were prioritized as highly or extremely important for taking the drug: prolonging survival, lengthening time until recurrence, and improving QoL. Specifically, patients believed that the greatest benefit of niraparib treatment would be lengthening time before recurrence and thus prolonging life. There were no respondents who had experience with niraparib. Patient respondents highlighted that the potential for disease recurrence has a toll on the emotional, physical, and practical aspects of life for women with ovarian cancer and their families, which in turn affects QoL. Limitations of current therapy were mentioned, namely the high risk of developing platinum resistance, a lack of options for maintenance therapy in BRCA wild type disease, and extremely limited options for treatment of platinum-resistant disease. Since niraparib has the potential to prolong the use of platinum-based chemotherapy and the time between treatments, patients would have greater opportunity to focus on physical and emotional recovery. Also, as niraparib is administered orally, it was noted patients would be able to live their lives without having to plan around hospital appointments for treatment.

The clinicians who provided input for this submission also noted that there is a large unmet need in the non-BRCA mutated population since there currently is no targeted maintenance therapy available for these patients. For BRCA-mutated patients, olaparib is funded in almost all jurisdictions and may be a treatment option. Overall, the clinicians stated that although there are no head-to-head data comparing the two PARP inhibitors, efficacy appears similar between olaparib and niraparib but olaparib may be slightly more tolerable as many patients will not be able to tolerate the 300 mg dose of niraparib due to toxicity. Nevertheless, the clinicians noted that they would appreciate having a choice between PARP inhibitors.

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), PAG, and the sponsor all agreed with pERC's initial recommendation to conditionally reimburse niraparib (upon cost-effectiveness being addressed) and supported early conversion to a final recommendation, the registered clinician group (CCO Gynecology 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. The CGP has responded to the feedback below, and has also clarified, in response to PAG, the use of niraparib in the context of prior PARP inhibitor use and intolerance (refer to Table 3):

- *Concern with offering niraparib to non-gBRCAmut and HRD-negative patients* – the subgroup analysis of this patient group (n=134) was not part of the primary efficacy analysis of the NOVA trial, and therefore exploratory in nature, but results of this analysis showed an approximate three-month PFS benefit (HR=0.58; 95% CI, 0.36 to 0.92). The registered clinician group noted that this patient group will make up a large percentage of the patients who will be eligible for niraparib and they expressed concern with offering it to these patients considering the magnitude of PFS benefit that was observed, significant toxicities, and the potentially huge expense.
    - CGP response: As pointed out by the registered clinician group, the NOVA trial was not powered to detect differences in efficacy endpoints in the non-gBRCAmut and HRD-negative subgroup since it was an exploratory analysis. At the time of the primary efficacy analysis, the primary endpoint of the trial (PFS) was met in all three pre-specified efficacy populations (i.e., gBRCAmut, HRD-positive non-gBRCAmut cohort, and the overall non-gBRCAmut cohort) with a clinically meaningful improvement in PFS. Therefore, the CGP believe there is no statistical justification for excluding this group of patients from receiving niraparib since they comprised part of the overall non-gBRCAmut cohort. As well, there are no data from the NOVA trial on the efficacy of niraparib in exclusively HRD-negative patients with no BRCA mutations, as the non-gBRCAmut and HRD-negative subgroup included patients who had somatic BRCA mutations. A PFS improvement of three months is similar to other treatments in ovarian cancer where the clinical benefits observed were deemed to be clinically meaningful and thus regulatory approved for use in patients with recurrent ovarian cancer, given their limited treatment options and poor outcomes (i.e., Health Canada approval of olaparib based on Study 19 in patients with non-BRCA recurrent platinum-sensitive ovarian cancer;[14] and bevacizumab in recurrent ovarian cancer).[15] Therefore, the CGP disagree that a three-month PFS improvement is not clinically meaningful and consider this the opinion of the registered clinician group, and not necessarily one that is supported by patients or other precedents in this disease.
- *HRD testing is required to identify patients who will derive the most benefit from niraparib* – The registered clinician group disagreed with statements made by pERC and the CGP that HRD testing has not been clinically validated; they noted that a number of HRD tests are commercially available and the test could be developed in-house within Canadian centres. The registered clinician group believes the availability of a validated HRD test is essential for clinicians and patients to make informed decisions about the risks and benefits of niraparib maintenance treatment.
    - CGP response: The NOVA trial used the MyChoice® Myriad HRD test to determine patients' HRD status, which is a commercially available proprietary product that has demonstrated a high 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.[16] Although BRCA defect and HRD score are correlated, it is currently unclear which genomic changes in HRD are linked with response to PARP inhibitors. The HRD score has not been prospectively tested to clinically validate HRD testing in ovarian cancer patients considering specific genomic changes, and the NOVA trial does not

necessarily validate the scoring system used. For example, studies of PARP inhibitors in prostate cancer have shown that certain genes involved in HRD may be more predictive of PARP inhibitor response than others.[17,18] Currently, genetic testing for HRD is not commonly used in Canada as the test is not available across all centres and centres with local HRD tests have not been standardized. Therefore, the CGP disagree with the registered clinician group that HRD testing is required for patients to receive niraparib. Further studies are required to confirm that HRD score, and more specifically which genes in HRD, will reliably predict a response to PARP inhibitors in ovarian cancer.

Based on the feedback and responses summarized above, the CGP agreed that no changes should be made to pERC's initial recommendation with respect to the eligible patient population and HRD testing.

1.3 Conclusions

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

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

- For patients who were in the gBRCAmut cohort, the median PFS benefit with niraparib was 15.5 months; and for patients who had HRD-positive tumours in the non-gBRCAmut cohort, which was the primary efficacy analysis population of this cohort, the median PFS benefit with niraparib was 9.1 months. Considering all patients in the non gBRCAmut cohort, which included a proportion of patients with sBRCAmut, median PFS was improved by 5.4 months with niraparib.
- In relapsed ovarian cancer PFS is recognized as a clinically important and valid primary outcome, as the goals of maintenance treatment are to delay subsequent progression and chemotherapy. Although the OS data from NOVA trial are currently immature the long-term OS data will be difficult to interpret due to the confounding introduced by patients' use of subsequent anti-cancer therapy which included a different PARP inhibitor in some patients.
- The PFS benefit was observed in all trial patients who received niraparib maintenance. This included patients with gBRCAmut mutations and non-gBRCAmut (i.e., HRD-positive plus sBRCAmut, HRD-positive plus BRCAwt, and HRD-negative). While all patient subgroups examined showed improvements in PFS, the magnitude of PFS benefit was greatest in patients with gBRCAmut (HR=0.27; 95% CI, 0.17 to 0.41), HRD-positive plus sBRCAmut (HR=0.27; 95% CI, 0.08 to 0.90), and HRD-positive tumours (HR=0.38; 95% CI, 0.24 to 0.59).[2,5]
- The treatment benefit with niraparib was consistent among all secondary efficacy outcomes assessed, including CFI and TTST.
- Niraparib was felt to fulfil an unmet need for maintenance treatment in BRCAwt disease; a PFS benefit was observed in the subgroups of patients who were HRD-positive BRCAwt (HR=0.38; 95% CI, 0.23 to 0.63) and HRD-negative (HR=0.58; 95% CI, 0.36 to 0.92).[5] This group of patients do not currently have a funded option for maintenance treatment.
- The majority of trial patients in the NOVA trial had serous histology; however, the CGP felt that all histologies included in the NOVA trial - all serous and endometrioid histology type - should be considered for treatment with niraparib.
- HRD testing, while used in the NOVA trial, is not commonly used in Canadian practice and has not been clinically validated. The CGP agreed that HRD testing alone should not be used as the sole basis for treatment with niraparib.
- The CGP agreed that based on data from the NOVA trial, many patients will likely require dose interruption or reduction of niraparib for tolerability the dose adjustments and delays in the trial did not impact treatment exposure or the efficacy of niraparib treatment. The mean weight of trial patients ranged from 68.0 kg to 71.8 kg. The CGP agreed that a consideration to a lower starting dose of 200 mg once daily was reasonable and recommended especially for patients at high risk of adverse outcomes which included those who weigh <77 kg or have a low platelet count (<150,000/μL).[3] While bone marrow suppression is the most

notable safety concern with niraparib, based on the NOVA trial, the rate of MDS/AML was not higher than in the placebo group; and hematologic toxicity did not seem 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 NOVA 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	
Olaparib is funded in almost all jurisdictions as monotherapy maintenance treatment of platinum sensitive, relapsed, BRCA-mutated, high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. Some patients may receive best supportive care/observation. The comparator in the NOVA trial was placebo, PAG is seeking comparative data on niraparib compared to olaparib.	Currently, only indirect comparisons can be made between niraparib and olaparib, as no trial to date has directly compared these two drugs. In general, the CGP agrees that niraparib and olaparib provide a similar magnitude of clinical benefit based on PFS data in the BRCA mutated population (refer to Sections 7 and 8 for a summary and critical appraisal of the ITCs/NMA included in this submission), but have somewhat different side effect profiles that may affect clinician decision on which drug to choose, should a patient be equally eligible for both treatment options.
Eligible Patient Population	
PAG is seeking clarity on the definition of partial response to be used in clinical practice.	The CGP recommends that the definition of PR as described by RECIST version 1.1 be used in clinical practice.
PAG is seeking clarity on whether the following patient subgroups should be eligible for niraparib:	
• Diagnosis other than high grade serous histology.	• The trial results would not necessarily be generalizable to low grade cancer (i.e., low grade serous cancer). However, any other high-grade histology may still benefit from maintenance strategy (i.e. ARIEL-3 and SOLO-2 trials of olaparib included patients with high grade serous or endometrioid histology). Similar to olaparib, it may be reasonable to consider use in any high-grade histology with a BRCA mutation or at least in high grade endometrioid or serous histology in all comers.
• Known to have BRCA mutation that is other than germline (gBRCAmut) (i.e., somatic); patients without or unknown BRCA or HRD mutation	• Based on subgroup analyses from the NOVA trial, all patients in the NOVA trial derived benefit from treatment regardless of mutation status; however, the magnitude of treatment benefit depends on the specific mutation and HRD status.
• Has received less than two previous courses of platinum-containing therapy	• At least two courses of platinum containing therapy would be required if one assumes that the first course is for first-line therapy and the second course is for recurrence.
• Has received two previous courses of platinum containing chemotherapy and has disease that was considered platinum sensitive following the penultimate (next to last) platinum course (more than six month period between penultimate platinum regimen and progression of disease) but it is more than eight weeks since completion of the last	• For platinum-sensitive recurrent patients who are eligible for maintenance treatment with niraparib, the CGP agreed that niraparib should be offered as long as the treatment can be started within 12 weeks of the last chemotherapy treatment, since multiple factors such as logistics and chemotherapy side effects can prevent some eligible patients from starting niraparib within the eight weeks as mandated in the NOVA trial. If more than eight weeks has elapsed

PAG Implementation Questions	CGP Response
platinum regimen. If yes, what is the maximum timeframe since last platinum treatment?	from last chemotherapy treatment, consideration should be given to exclude disease progression before starting maintenance therapy as patients who have disease progression should not be treated with niraparib maintenance.
• ECOG > 1	• All trials evaluating a maintenance strategy have been conducted in patients with an ECOG PS of 0-1. A distinction should be made among patients with an ECOG PS >1; a patient's status may be due to lingering side effects from chemotherapy and non-modifiable factors (e.g. comorbidities). In clinical practice, patients with an ECOG PS of 0-1, as well as patients with an ECOG PS of 2 will likely improve in functional status in the short term and therefore may benefit from maintenance therapy with niraparib.
• Received prior treatment with a known PARP inhibitor	• Based on the trial criteria used in the NOVA trial, patients who have progressed on a prior PARP inhibitor would not be eligible for niraparib. ○ PAG requested clarification of whether retreatment with a PARP inhibitor (in the absence of disease progression) applies to patients who have received a PARP inhibitor in an earlier treatment setting (i.e., first-line). The CGP agreed that the line of therapy is not relevant and that if a patient has progressed on a PARP inhibitor, they would not be eligible to receive niraparib or another PARP inhibitor again.
• Symptomatic uncontrolled brain metastasis	• Maintenance therapy should not be offered to patients with symptomatic uncontrolled brain metastasis.
• Are allergic or unable to tolerate platinum-based chemotherapy and would therefore have received non-platinum therapy	• The CGP was in agreement that in patients who had non-platinum therapy due to an inability to complete platinum therapy (e.g. allergy) and had a response, it is reasonable to consider a PARP inhibitor after chemotherapy is finished provided that the patient has not had progression on the PARP inhibitor and otherwise met the criteria for maintenance with niraparib.
• If patients discontinue niraparib at their request without experiencing disease progression, and then experience disease progression, but are considered platinum sensitive and receive a third course of platinum chemotherapy and are in response (complete or partial).	• If patients tried a PARP inhibitor in the past but discontinued due to intolerance or other reasons without disease progression, it is reasonable to try a maintenance strategy after chemotherapy provided that patients have platinum sensitive disease and can tolerate the proposed PARP inhibitor.
• PAG is seeking to clarify whether patients who are currently receiving olaparib with BRCA mutation (whether germline or somatic) with intolerance could be considered for a treatment switch to niraparib. PAG would like to clarify that patients who had prior treatment with a PARP inhibitor are not eligible for niraparib (unless due to switching because of intolerance).	• As noted above, patients who previously discontinued a PARP-inhibitor due to intolerance/patient preference may consider maintenance therapy with niraparib provided it is thought that the patient will tolerate niraparib. Patients who have progressed on a prior PARP inhibitor would not be eligible for niraparib based on the NOVA trial eligibility criteria. ○ PAG requested clarification on whether a switch to niraparib in patients who discontinue olaparib due to intolerance/toxicity applies only to the relapsed setting (and not the first-line setting). The CGP agreed that if a patient discontinued a PARP inhibitor due to intolerance or for reasons other than disease progression, it is reasonable to offer niraparib as maintenance. For patients

PAG Implementation Questions	CGP Response
	who stopped treatment with a PARP inhibitor in an earlier line of treatment due to a treatment break or holiday, and then experience disease progression during the treatment break (i.e., not on treatment with a PARP inhibitor) the CGP agreed that it would be reasonable to treat with another PARP inhibitor since the patient did not progress while on a PARP inhibitor.
Implementation Factors	
The recommended dose of niraparib monotherapy is 300 mg (three 100 mg capsules) taken orally once daily. For those weighing <58 kg, a starting dose of 200 mg may be considered to reduce grade 3 or 4 AEs as per the proposed product monograph. PAG is seeking guidance on the recommended starting dose for patients with low body weight (e.g.<58kg)?	For patients with low body weight (defined in the Health Canada product monograph as < 58 kg), the CGP felt a starting dose of 200 mg once daily is reasonable based on additional analyses of the NOVA trial data that examined dosing and safety outcomes by baseline weight (< 77 kg versus ≥ 77 kg) that showed the starting dose of 200 mg reduced the incidence of grade 3/4 AEs and other safety outcomes without compromising efficacy.
PAG is seeking confirmation that niraparib treatment should be continued until disease progression or unacceptable toxicity.	The CGP confirms that niraparib should be continued until disease progression or unacceptable toxicity.
PAG is seeking to confirm that the minimum number of cycles required of second or subsequent line of platinum-based therapy prior to starting maintenance therapy with niraparib is four as per the NOVA trial.	The CGP agreed that at least four cycles of platinum-containing chemotherapy should be given before starting niraparib maintenance therapy.
Sequencing and Priority of Treatment	

PAG Implementation Questions	CGP Response
Olaparib recently received an initial positive recommendation for reimbursement for maintenance treatment of adult patients with newly diagnosed, advanced, BRCA-mutated (germline or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in response (complete or partial) to first-line platinum-based chemotherapy as per SOLO1 trial. PAG is seeking clarity for place in therapy for niraparib:	
• For patients who may receive olaparib after first line platinum-based treatment, should they receive another PARP inhibitor upon progression (i.e., niraparib)? Would the use of niraparib be time sensitive, i.e. duration of use more than or less than two years? If yes, what is the reasonable time frame from time of completion of maintenance to progression that would make patients qualify for retreatment?	• There is currently no evidence to suggest that retreatment with a PARP inhibitor after prior progression on a PARP inhibitor is beneficial. This is an area of ongoing research and until trials are completed,[19,20] retreatment with a PARP inhibitor in these patients is not recommended.
• Would sequencing between olaparib and niraparib be permitted as maintenance progression options? If yes, which would be the preferred therapy? What patient or disease factors will lead to a preference of niraparib over olaparib?	• The CGP noted that a switch between these two agents that are within the same line of therapy would not be considered part of standard practice for maintenance treatment as olaparib and niraparib have a similar mechanism of action and currently, there is no evidence to inform the sequencing of these agents. If a choice needs to be made between olaparib and niraparib maintenance, factors to consider are presence of BRCA mutation, side effect profile and potential tolerability, schedule consideration (twice daily versus once daily), patient preference, and cost. Niraparib may be preferred over olaparib in patients who are BRCA wild type, given that the evidence for use of niraparib in this group of patients comes from a phase III trial, as opposed to a phase II trial for olaparib in BRCAwt.[14]
Companion Diagnostic Testing	
PAG is seeking guidance as to whether one or both of BRCA and/or HRD testing is/are required to identify eligible patients for niraparib. PAG is seeking guidance on whether eligibility for niraparib should be extended to all patients regardless of BRCA status (i.e. gBRCAmut and non-gBRCAmut) or to specific HRD subgroups? If BRCA testing is required, would both germline and somatic testing be recommended? Is testing for somatic BRCA testing required for those with a negative gBRCAmut? If BRCA status was determined earlier in the diagnosis and treatment, is BRCA (both germline and somatic) testing required to be repeated to determine eligibility for niraparib?	All patients should have at least germline BRCA testing at baseline regardless of treatment consideration, as it has important implications as a predictive marker and hereditary cancer gene in the family. Regardless of BRCA or HRD, all patients should be offered an opportunity for niraparib maintenance therapy based on the evidence from the NOVA trial. BRCA or HRD testing should be done as needed, but their results should not be required to receive niraparib.

BRCA = breast cancer susceptibility gene; CGP = Clinical Guidance Panel; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; gBRCAmut = germline BRCA mutation; HRD = homologous recombination deficiency; PAG = Provincial Advisory Group; PARP = poly(adenosine diphosphate [ADP]–ribose) polymerase; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

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.[21] 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 stage of disease (III/IV). 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 four 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. Most patients with recurrent ovarian cancer therefore 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; therefore, there is a significant unmet need for additional treatment options for patients with recurrent ovarian cancer.

It is now well recognized that 15-20% 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.[22-24] BRCA1 and BRCA2 genes are human tumour suppressor genes and a key component in homologous recombination, a repair pathway of double-stranded DNA breaks.[25-27] HR deficiency (HRD) such as pathogenic BRCA mutations causes cells to repair via less precise and more error-prone repair pathways such as non-homologous end-joining ; inhibition of PARP can confer synthetic lethality in cells with HRD.[28] It is estimated that approximately 50% of high grade serous ovarian carcinomas (the most common but lethal ovarian cancer) have aberrations in HR repair pathways.[29] Recently, PARP inhibitors have emerged as an effective therapeutic strategy in ovarian cancer, particularly for those patients with germline or somatic pathogenic BRCA mutations. Multiple phase II and III studies have previously demonstrated a significantly prolonged PFS in patients with recurrent platinum-sensitive ovarian cancer and presence of germline or somatic BRCA mutations, as well as in patients with or without HRD.[30-34]

2.2 Accepted Clinical Practice

Ovarian cancer recurrence is considered incurable and therefore the goals of therapy are to delay the time to subsequent progression, improve QoL and extend survival as much as possible. Once disease recurrence has developed, patients can expect to receive multiple lines of different chemotherapy during the course of their disease. Platinum sensitive disease is commonly defined as disease that has recurred ≥ six months from the completion of first-line platinum-based therapy. Standard of care treatment for recurrent platinum-sensitive ovarian cancer involves platinum-based systemic therapy (most often carboplatin based).[35] In such patients, retreatment with a platinum-based combination (typically six to nine cycles) can result in response rates of >50%, with higher rates observed with longer time to first relapse.[36] The current standard of care following a response in the recurrent setting is to watch and wait, and then to retreat with cytotoxic agents at the time of next recurrence/progression. Patients are monitored for clinical progression, at which point another platinum-based chemotherapy or single agent chemotherapy with or without bevacizumab may be offered, based on sensitivity to platinum, toxicity profile, functional status of the patient and availability of therapy options. Overall, prognosis is guarded, with increased resistance to chemotherapy with repeated exposure. The exception to this approach is in patients with a BRCA mutation (somatic/germline), for whom olaparib is approved as maintenance treatment and recommended for reimbursement,[37] and bevacizumab with platinum-based chemotherapy upon recurrence has variable uptake across jurisdictions. Repeat cytoreductive surgery may be considered for a limited number of patients who meet appropriate criteria.[38,39] With the introduction of olaparib maintenance therapy, patients with BRCAmut platinum-sensitive recurrent ovarian cancer may receive olaparib maintenance therapy after a response to platinum-containing chemotherapy.

Guidelines from the National Comprehensive Cancer Network,[40] the Society of Gynecologic Oncology [41] and the European Society of Medical Oncology[35] are some of the widely accepted international guidelines for the management of epithelial ovarian cancer, including use in Canada; however, treatment practices across the provinces may vary depending on provincial guidelines.

3 Summary of Patient Advocacy Group Input

Ovarian Cancer Canada provided input on niraparib, for the maintenance treatment, as monotherapy, of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy, and their input is summarized below.

Input from patients living with ovarian cancer and their caregivers were elicited through an anonymous online survey conducted from November 26, 2019 to January 15, 2020. Eligible respondents were patients with ovarian cancer and caregivers of a patient with ovarian cancer, who had been treated with platinum-based chemotherapy, and had at least one recurrence that occurred six months or longer after the end of chemotherapy. A total of 56 people responded to the survey: 51 were patients with ovarian cancer and 5 were caregivers. None had received or cared for a patient who had received niraparib. Two responses were received from France and the remainder from Canada (54), though none were from Alberta, Saskatchewan, Newfoundland, Prince Edward Island, Northwest Territories, Yukon, or Nunavut. Age of respondents ranged from 33 to 69 years, with the majority above 50 years of age. Of note, the number of respondents may differ between questions, as some may have chosen to skip questions.

Of the total group (N=56), respondents included those living with or caring for an individual with epithelial ovarian cancer (n=39, 70%), followed by fallopian tube cancer (n=8, 14%), primary peritoneal cancer (n=4, 7%), and ovarian cancer of unknown type (n=5, 9%). Most patients (n=33 of 55 respondents who answered the question; 60%) received their diagnosis more recently between 2016-2018. The majority of 52 respondents (n=42, 81%) reported being diagnosed at stage III. Of 55 patient and caregiver respondents, approximately half (n=28, 51%) had experienced one recurrence, while 33% (n=18), 12% (n=7), and 4% (n=2) had experienced two, three, and more than three occurrences, respectively.

From the patient's perspective, ovarian cancer impacts many aspects of life, namely sexual relationship, work life, well-being, and sleep. Caregivers reported that their work balance and sleep patterns were most negatively impacted. Despite identifying numerous different medications that were used for treatment of their recurrence, many patients stated they were indifferent or did not believe that their disease was managed with currently available treatment. The risk of disease recurrence and having limited treatment options, particularly in BRCA wild type patients, were concerns raised by respondents in the survey. Patients and caregivers felt that side effects of current treatment such as fatigue, neuropathy, and hair loss have a very or extremely negative impact on their life. In terms of patients' values and expectations for new treatment, prolonging survival, lengthening time until recurrence, and improving quality of life were identified as highly or extremely important. Respondents were also willing to tolerate many side effects (e.g., tiredness, taste changes, nausea, anemia/bruising, headaches, and bowel problems), if overall daily functioning and prognosis were improved. Of note, respondents were least willing to tolerate side effects such as bone marrow problems or blood cancer, respiratory problems, infections, and high blood pressure. Most respondents believed niraparib should be available as a treatment option in Canada for women who have ovarian cancer, and OCC highlighted the need for new treatment in this population.

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 with Ovarian Cancer

OCC reported that many aspects of life are significantly affected by ovarian cancer. Respondents (n=51) reported four main areas of life which were most negatively impacted by ovarian cancer: sexual relationship (62%), work life (60%), level of well being (58%) and sleep pattern (47%). These areas were ranked as 4 on a scale of 1 (no effect) to 5 (extremely negative). When asked to describe how their life has been affected by the diagnosis, patients provided the following responses:

"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."

3.1.2 Patients' Experiences with Current Therapy for Ovarian Cancer

In addition to carboplatin, cisplatin, and paclitaxel, respondents had identified six other agents that were used to treat their recurrent disease: bevacizumab, docetaxel, doxorubicin, gemcitabine, nanoparticle albumin-bound-paclitaxel (nab-paclitaxel), rucaparib (commercially unavailable in Canada), and different combinations. Over half of the 46 patient respondents of this question (n=27, 59%) neither agreed nor disagreed that the treatment was managing their ovarian cancer, whereas 24% (n=11) strongly agreed and 17% (n=8) strongly disagreed. The following comments were also provided, including one which highlights part of the psychological challenges perceived about the overall treatment experience:

"The first recurrence (15 mos.) was treated with carbo & taxel & I was platinum sensitive so had very good response. The second recurrence (12 mos.) was treated with carbo only & the response has been mild."

"Short term control...first recurrence was 6 months, second one was 8 months."

"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."

"Mentally: Once treatments are over, you don't know how to handle knowing that you no longer have something helping to get rid of the disease."

Side effects of treatment were also addressed in the survey. Respondents were asked to rate, on a scale of 1 (no effect) to 5 (extremely negative effect), the impact current treatment has on aspects of their life. From their experience, 51 respondents (including both patients and caregivers) ranked the following side effects as having an impact of 4 (very negative) or 5 (extremely negative): fatigue (n=33, 65%), neuropathy (n=21, 41%), hair loss (n=20, 39%), anemia (n=17, 33%), aching joints (n=16, 32%).

The OCC noted that some of the 51 respondents reported issues with availability (n=11, 22%), travel (n=7, 14%), or finances (n=7, 14%) as significant or extremely significant barriers to accessing treatment. The following responses were also provided, reflecting the impact these barriers have on patients:

"I did ask about some other drugs but my Dr said he had to contact the Ministry of Health and have not heard anything back and that was almost 3 months ago. I was referred to a different oncologist and sometimes I feel I am alone and they have given up on me."

"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."

3.1.3 Impact of Ovarian Cancer and Current Therapy on Caregivers

Five caregivers responded to the survey; they included family members (e.g., spouse/partner, mother) and had been providing care for generally one to three hours each day. Two out of the five who responded had been providing care for more than four years, whereas the rest had been providing care for one to three years. Work life and sleep patterns were identified as the issues that were most negatively impacted, as demonstrated by the following responses:

"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 Niraparib or New Therapies

In their survey, OCC identified that 65% of respondents (n=31 out of 48 patients and caregivers) would consider taking niraparib as new treatment. Additionally, of 47 respondents who answered the question, the following outcomes were prioritized as highly or extremely important for taking the drug: prolonging survival, lengthening time until recurrence, and improving quality of life. Specifically, patients believed that the greatest benefit of niraparib treatment would be lengthening time before recurrence and thus prolonging life, with the following quotes provided:

"I have a lot of hope that it could prolong my survival."

"Live a far more normal life, whilst not being forced to be confined to my home for fear of an infection. Extending time I have before relapse, and prolonging my time off chemotherapy. This is very important for me."

OCC also highlighted the need for a new drug that improves chance of survival and the low threshold of improvement women had for considering new treatment. This was demonstrated by the high number of respondents, 25 of the 42 (60%) who answered the question, stating that they are willing to take niraparib if there was no or mild or moderate improvement in their ovarian cancer. With this, OCC reflected on the desperate needs of these women, and particularly those who are BRCA wild type due to limited options in this population. Furthermore, a significant number of respondents were willing to tolerate the potential side effects of niraparib, such as tiredness, taste changes, nausea, anemia/bruising, headaches, or bowel problems, if overall daily functioning and prognosis were improved. Of these six reported potential side effects, tiredness (n=33) and taste changes (n=31) were rated as most tolerable. On the other hand, patients were least willing to tolerate side effects such as bone marrow problems or blood cancer, respiratory problems, infections, and high blood pressure. The following responses provide insight to a patient's willingness to tolerate niraparib's side effects:

"If it can prolong my life I feel it is a good trade off."

"Going through most of these now due to chemo & taking meds to help with these side effects already."

"I just want more time to live, and these side effects can be managed effectively with medications whilst giving me a good quality of life."

Overall, when inquiring about risks, OCC reported that 39% (n=15) of 38 patient respondents identified side effects to be a risk of niraparib, whereas 26% (n=10) were unsure of potential risks. Furthermore, 4 patients (11%) specifically identified blood cancer/bone marrow issues. Of the 42 who responded to the question, most (n=31, 74%) considered the benefits of niraparib to outweigh the risks, whereas 26% (n=11) were not certain. A few quotes capturing patient expectations are as follows:

"Would have more time with my family."

"I was diagnosed 3c so I want to do whatever I can to live as long as I can."

"Continue to have quality of life being with my family."

3.2.2 Patient Experiences to Date with Niraparib

The patient input did not include patient experience with niraparib.

3.3 Companion Diagnostic Testing

The patient input did not include comments on companion diagnostic testing with niraparib.

3.4 Additional Information

Of the 44 patients and caregivers who responded to the question, 43 (98%) believed that niraparib should be available as a treatment option for ovarian cancer in Canada. OCC emphasized the overwhelming number of respondents who believe that an effective drug that can improve quality of life should be available, and that the cost should be covered regardless of BRCA mutation status. Specific patient responses include the following:

“Any drug that can extend life of a cancer patient, especially with ovarian cancer where options are limited must be considered.”

"Lynparza is already approved and is free for those with BRCA. But another med like Zejula might benefit people without mutation.”

“More treatment options are desperately needed. Canada needs to follow suit with other developed nations and offer Zejula immediately.”

OCC also summarized information from the Target Ovarian Cancer (U.K.) patient submission to the Scottish Medicines Consortium consultation. Similar to the input compiled from OCC’s survey, the U.K. group notes that the potential for disease recurrence has a toll on the emotional, physical, and practical aspects of life for women with ovarian cancer and their families, which in turn affects quality of life. Furthermore, limitations of current therapy are mentioned, namely the high risk of developing platinum resistance and extremely limited options for treatment of platinum-resistant disease. Since niraparib has potential to prolong use of platinum-based chemotherapy and time between treatments, patients would have greater opportunity to focus on physical and emotional recovery. Also, as niraparib is administered orally, these women will be able to live their lives without having to plan around hospital appointments for treatment.

Overall, OCC believes that since niraparib is not dependent on BRCA mutation status, the majority of women with ovarian cancer will benefit from being able to access this treatment.

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 nine provinces (Ministries of Health and/or cancer agencies) and a federal drug plan participating in pCODR. PAG identified the following as factors that could affect the feasibility of implementing a funding recommendation.

Clinical factors:

- Place in therapy relative to olaparib
- Eligible patient population

Economic factors:

- Availability and funding of BRCA and HRD testing
- Clarity on treatment duration and criteria for discontinuation

Please see below for more details.

4.1 Currently Funded Treatments

Olaparib is funded in almost all jurisdictions as monotherapy maintenance treatment of platinum sensitive, relapsed, BRCA-mutated, high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. Some patients may receive best supportive care/observation.

The comparator in the ENGOT-OV16/NOVA trial was placebo. PAG is seeking comparative data on niraparib compared to olaparib.

4.2 Eligible Patient Population

PAG is seeking clarity on the definition of partial response to be used in clinical practice.

PAG is seeking clarity whether the following patient subgroups should be eligible for niraparib:

- has a diagnosis other than high grade serous histology,
- known to have BRCA mutation that is other than germline (i.e. somatic),
- patients without or unknown BRCA mutation or HRD status,
- has received less than two previous courses of platinum-containing therapy,
- has received two previous courses of platinum containing chemotherapy and has disease that was considered platinum sensitive following the penultimate (next to last) platinum course (more than six month period between penultimate platinum regimen and progression of disease) but it is more than eight weeks since completion of the last platinum regimen. If yes, what is the maximum timeframe since last platinum treatment?
- ECOG >1
- Received prior treatment with a known PARP inhibitor
- Symptomatic uncontrolled brain metastasis
- Are allergic or unable to tolerate platinum-based chemotherapy and would therefore have received non-platinum therapy

- If patients discontinue niraparib at their request without experiencing disease progression, and then experience disease progression, but are considered platinum sensitive and receive a third course of platinum chemotherapy and are in response (complete or partial)

PAG is seeking to clarify whether patients who are currently receiving olaparib with a BRCA mutation (whether germline or somatic) with intolerance could be considered for a treatment switch to niraparib. PAG would like to clarify that patients who had prior treatment with a PARP inhibitor are not eligible for niraparib (unless due to switching because of intolerance).

There is a potential for indication creep for niraparib use in the first-line setting in combination with chemotherapy, and after first line treatment in BRCA negative disease.

PAG noted the following groups would be out of scope of this review: patients who did not have complete or partial response to platinum based therapy, chemotherapy refractory after platinum or non platinum chemotherapy in both gBRCAmut and non-gBRCAmut, those who previously received a PARP inhibitor and have progressed and are then treated with niraparib, use of PARP inhibitors after first line treatment with platinum chemotherapy instead of waiting until first relapse.

There is a time limited need for patients that are currently on maintenance treatment with olaparib (if sequencing is permitted), those patients on observation, those that are BRCA negative, patients who completed 2 lines of therapy and had a complete or partial response but may exceed the eight-week window of completion (if eligibility is confirmed).

4.3 Implementation Factors

The recommended dose of niraparib monotherapy is 300 mg (three 100 mg capsules) taken orally once daily. For those weighing <58kg, a starting dose of 200mg may be considered to reduce grade 3 or 4 AEs as per the Health Canada product monograph. PAG is seeking guidance on the recommended starting dose for patients with low body weight (e.g.<58kg)?

The availability of 100mg oral capsules is an enabler to implementation and with dose reduction in increments of 100mg, should reduce the potential for drug wastage. The 3 x 100mg capsules may be a burden for some patients to take.

PAG is seeking confirmation that niraparib treatment should be continued until disease progression or unacceptable toxicity.

PAG is seeking to confirm that the minimum number of cycles required of second or subsequent line of platinum-based therapy prior to starting maintenance therapy with niraparib is four as per the ENGOT-OV16/NOVA trial.

PAG noted that patients should have a confirmatory CA-125 after completing platinum chemotherapy and prior to starting niraparib to ensure they are not experiencing biochemical progression. More frequent CA-125 monitoring may be required while patients are on niraparib compared to observation, but frequency of CA-125 monitoring is likely dependent on individual physician practice or provincial guidelines for follow up. PAG also noted additional resources would be required with niraparib such as increased blood work and monitoring by nursing.

PAG noted that niraparib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home, and no chemotherapy chair time would be required. PAG identified the oral route of administration is an enabler to implementation. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

Olaparib recently received an initial positive recommendation for reimbursement for maintenance treatment of adult patients with newly diagnosed, advanced, BRCA-mutated (germline or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in response (complete or partial) to first-line platinum-based chemotherapy as per SOLO1 trial.

PAG is seeking clarity for place in therapy for niraparib:

- For patients who may receive olaparib after 1st line platinum-based treatment, should they receive another PARP inhibitor upon progression (i.e., niraparib)? Would the use of niraparib be time sensitive, i.e. duration of use more than or less than 2 years? If yes, what is the reasonable time frame from time of completion of maintenance to progression that would make patients qualify for retreatment?
- Would sequencing between olaparib and niraparib be permitted as maintenance progression options? If yes, which would be the preferred therapy? What patient or disease factors will lead to a preference of niraparib over olaparib?

4.5 Companion Diagnostic Testing

PAG is seeking guidance as to whether one or both of BRCA and/or HRD testing is/are required to identify eligible patients for niraparib. PAG is seeking guidance on whether eligibility for niraparib should be extended to all patients regardless of BRCA status (i.e. gBRCAmut and non-gBRCAmut) or to specific HRD subgroups? If BRCA testing is required, would both germline and somatic testing be recommended? Is testing for somatic BRCA testing required for those with a negative gBRCAmut? If BRCA status was determined earlier in the diagnosis and treatment, is BRCA (both germline and somatic) testing required to be repeated to determine eligibility for niraparib?

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

One joint submission on behalf of six oncologists from the CCO Gynecologic Cancers DAC provided input on the review of niraparib for the maintenance treatment, as monotherapy, of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Clinicians noted that there is a large unmet need in the non-BRCA mutated population. For BRCA-mutated patients, olaparib may be an option. Overall, the clinicians stated that although there are no head-to-head data comparing the two, efficacy appears similar between olaparib and niraparib; olaparib may be slightly more tolerable. They also felt that olaparib has a more established safety profile, and that many patients will not be able to tolerate the 300 mg dose of niraparib due to toxicity. Nevertheless, the DAC noted that they would appreciate having a choice between PARP inhibitors. At this time, studies are underway that would provide evidence in the future to answer many outstanding questions, such as sequencing of treatment. As stated by the clinicians, BRCA mutation status is already required, and further need for additional companion diagnostic testing (i.e., HRD) will depend on whether reimbursement is recommended for all groups or limited to the BRCA/HRD mutation status.

Please see below for details from the clinician input(s).

5.1 Current Treatment(s) for Ovarian Cancer

Olaparib is funded in almost all jurisdictions as monotherapy maintenance treatment of platinum sensitive, relapsed, BRCA-mutated, high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. As such, the clinicians state that olaparib may be an option for patients with BRCA-mutated status. For non-BRCA-mutated cancers, there is no targeted maintenance therapy available. Currently, there are no other options beyond what is listed in the funding algorithm; the clinicians indicated that most patients would be placed on observation.

5.2 Eligible Patient Population

Clinicians felt that the inclusion and exclusion criteria from the ENGOT-OV16/NOVA trial seems reasonable and are applicable to clinical practice.

5.2.1 For patients who discontinue niraparib at their request without experiencing disease progression, and then experience disease progression, but are considered platinum sensitive and receive a third course of platinum chemotherapy and are in response, is there evidence whether they could be considered eligible for niraparib again?

This is an evolving area and the clinicians expressed that currently there is no evidence that can answer this question; there are ongoing trials examining PARP sequencing. The DAC felt that if a patient stops niraparib due to toxicity, it would be reasonable to start the patient on an alternative PARP inhibitor, especially if they have a BRCA mutation.

5.3 Relevance to Clinical Practice

The clinicians providing input have experience with treating patients using niraparib. Notably, the clinicians expressed that there is a large unmet need in the non-BRCA mutated population. They also stated that although there are no head-to-head comparisons, efficacy is similar between olaparib and niraparib. Additionally, they felt that the safety profile is more established for olaparib. The oncologists commented that the 300 mg dose of niraparib can be quite toxic and not many patients will be able to tolerate it; dose reduction to 200 mg adds a layer of complexity. They also noted that the benefit of niraparib in the non-gBRCAmut population may be overstated in the pivotal trial due to the inclusion of somatic BRCA patients in this cohort.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

According to the CCO clinicians, niraparib would follow chemotherapy treatment.

5.4.1 Is there evidence to support clinical situations where niraparib is preferred to olaparib (e.g., for BRCA mutated patients)?

Although there is no head-to-head comparison data, the oncologists stated that overall, olaparib may be slightly better than niraparib from a toxicity perspective. They further felt that clinicians in Canada are more experienced with olaparib (in the BRCA mutated population) and would be comfortable managing most adverse events. Nonetheless, the DAC noted that it would be nice to have a choice between PARP inhibitors.

5.4.2 Is there evidence to support sequencing of olaparib and niraparib?

The clinicians noted that currently there is no evidence in this regard. The DAC felt that switching would be reasonable if the patient did not progress on the initial PARP inhibitor and is switching for toxicity reasons.

5.4.3 Is there evidence to inform whether patients who are currently receiving olaparib (BRCA mutated) with intolerance could be considered for a treatment switch to niraparib?

The clinicians commented that there is also currently no evidence for this scenario, but that it would make sense to keep the patient on a PARP inhibitor.

5.4.4 Is there evidence to confirm that if patients receive olaparib after 1st line treatment (BRCA mutated patients only) for two years, would treatment of platinum-based chemotherapy followed by another PARP inhibitor be recommended?

Similar to above, the clinicians stated that at this time there is no data to inform this decision, but trials are underway. Therefore, the DAC does not currently recommend this practice, but recognizes the evidence is evolving.

5.5 Companion Diagnostic Testing

Input from clinicians highlighted the lack of a common definition for HRD, as well as the significant heterozygosity in the cut-offs and tests used in the trials (there are no HRD tests that are conclusive). They do note that if niraparib is funded for the entire cohort, no additional companion diagnostics are needed (i.e., BRCA is done already).

5.5.1 Is BRCA mutation and/or HRD status required to determine eligibility of niraparib?

According to the CCO clinicians, BRCA mutation status is already required. HRD status is variable and the requirement will depend on whether reimbursement is recommended for all groups or limited to BRCA/HRD mutation status.

5.6 Implementation Questions

5.6.1 Is there evidence to support the recommended starting dose of niraparib for patients with low body weight (e.g., <58 kg)?

In response to this question, the clinicians referred to the Health Canada product monograph. They also noted that in the PRIMA protocol, all the patients started at a fixed dose of 300 mg once daily. The trial was amended on November 27, 2017, to incorporate an individualized starting dose of 200 mg once daily for patients with a baseline body weight of less than 77 kg, a platelet count of less than 150,000 per cubic millimeter, or both.

5.6.2 Is there evidence for non-BRCA mutated patients that are currently on observation, what is the appropriate time frame to initiate treatment with niraparib?

The clinicians indicated a time frame of eight weeks to initiate treatment with niraparib, provided that the patient has not progressed.

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 for the maintenance treatment of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

Supplemental questions and comparison with other literature most relevant to the CADTH review and to the PAG were identified while developing the review protocol and are outlined in sections 7 and 8:

- Section 7: Summary and critical appraisal of a sponsor-submitted ITC/NMA comparing niraparib with olaparib for the maintenance treatment of female adult patients with platinum-sensitive, recurrent ovarian cancer, and a gBRCAmut [10]
- Section 8: Summary of two sponsor-submitted ITCs available in conference form:
  - Comparative efficacy and safety of olaparib 400 mg and niraparib 300 mg as maintenance treatment after response to chemotherapy in patients with platinum-sensitive relapsed non-g BRCA-mut ovarian cancer[11]
  - Comparative efficacy and safety of olaparib 300 mg tablets and niraparib 300 mg tablets as maintenance treatment after response to chemotherapy in patients with platinum-sensitive relapsed gBRCAmut ovarian cancer[12]

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. The 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 recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy
	
	Subgroups of interest:
	• Germline BRCA mutation
	• Non-germline BRCA mutation
	  ○ HRD negative
	  ○ HRD positive with somatic BRCA mutation
	  ○ HRD positive with wild-type BRCA mutation
		Niraparib	Olaparib (for gBRCAmut), best supportive care, observation, placebo	• **PFS**
				• **OS**
				• CFI
				• PFS-2
				• TFST
				• TSST
				• **HRQoL**
				• AEs of special interest include: MDS/AML, myelosuppression, hypertension, and nausea

AE = adverse event; AML = acute myeloid leukemia; BRCA = breast cancer susceptibility gene; CFI = chemotherapy-free interval; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; HRD = homologous recombination deficiency; HRQoL – health-related quality of life; MDS = myelodysplastic syndrome;
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; TSST = time-to-second subsequent therapy.

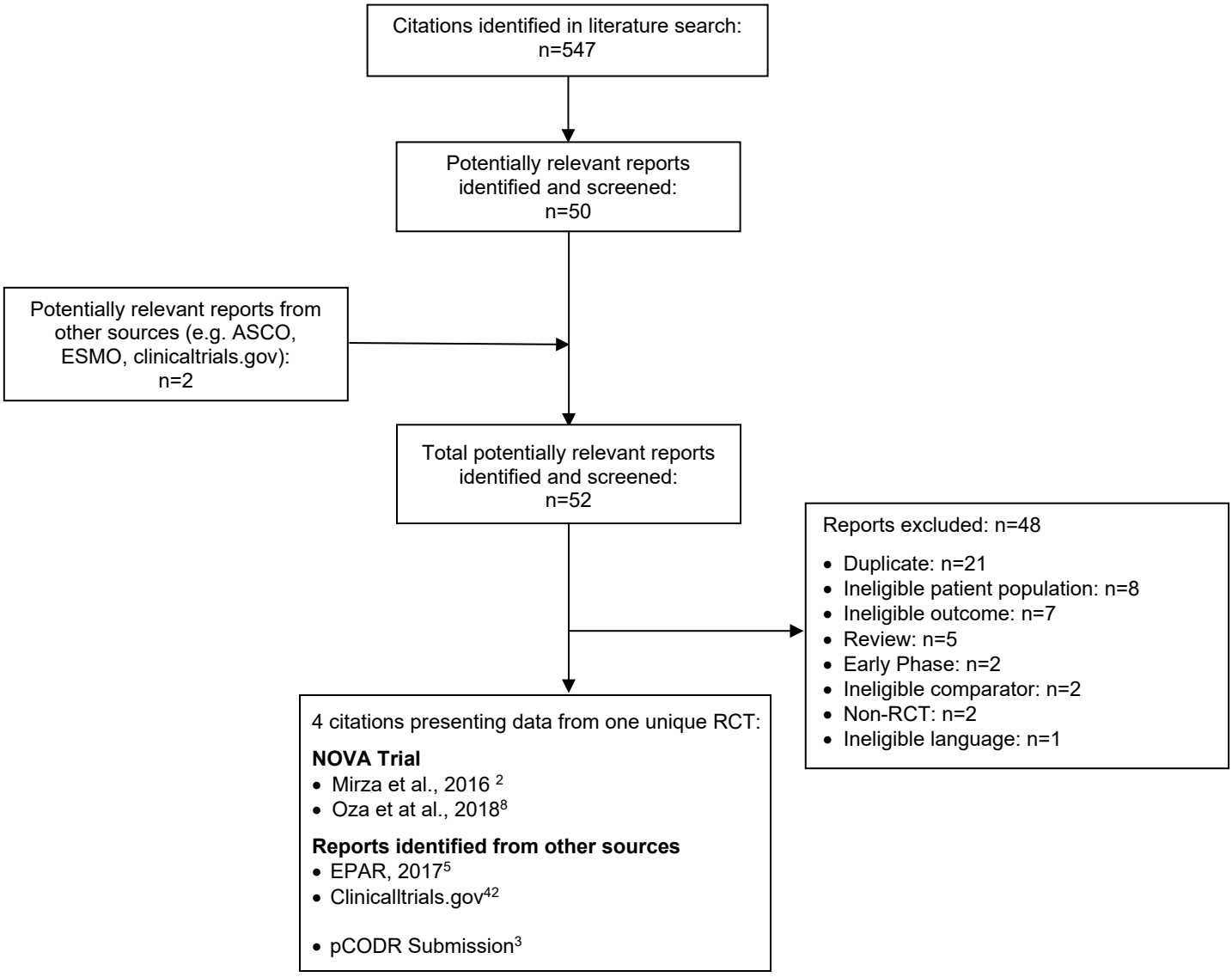
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

6.3 Results

6.3.1 Literature Search Results

Of the 52 potentially relevant reports identified, four reports representing one unique phase III RCT (NOVA) were included in the pCODR systematic review[2,5,8,42] and 48 reports were excluded. Reports were excluded because they contained duplicate data,[13,43-59] included ineligible patient populations,[4,60-66] assessed ineligible study outcomes, [67-73], reported data from an early phase trial,[74,75] reported data for an ineligible comparator,[76,77] were not an RCT, [78,79] were a review,[80-84] or were not reported in English.[85]

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to the NOVA trial were also obtained through requests to the sponsor by CADTH. [3,6,7,9,86,87]

6.3.2 Summary of Included Studies

One RCT, NOVA, met the selection criteria of the systematic review. Key characteristics of the NOVA 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 Criteria	Intervention and Comparator	Trial Outcomes

ENGOT-OV16/NOVA
NCT01847274
 	
Characteristics:
Phase III, double-blind, randomized (2:1), placebo-controlled
• n randomized = 553 (niraparib: n = 372; placebo: n = 181)
  ○ Two cohorts: gBRCAmut (n=203), non-gBRCA (n=350)
 	
• n treated = 546 (niraparib: n = 367; placebo: n = 179)
  ○ Two cohorts: gBRCAmut (n=201), non-gBRCA (n=345)
 	
Setting:
107 sites in 15 countries (Austria, Belgium, Canada, Denmark, France, Germany, Hungary, Israel, Italy, Norway, Poland, Spain, Sweden, United Kingdom, and United States)
 	
Patient Enrolment Dates:
August 26, 2013 to June 1, 2015[9]
 	
Data cut-off:
May 30, 2016
 	
Database lock:
June 20, 2016
 	
Status:
Ongoing for patient follow-up
 	
Funding
Tesaro/GlaxoSmithKline Inc.
	Key Inclusion Criteria:
	• Female patients ≥ 18 years of age
	• Histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with predominantly high-grade serous histologic features.
	• For the penultimate platinum-based chemotherapy received before study enrollment, a patient must have had platinum-sensitive disease after this treatment, which was defined as having a complete or partial response and disease progression more than 6 months after completion of the last round of platinum therapy
	• For the last platinum-containing therapy received before randomization, patients were required to have received a minimum of 4 cycles of treatment and, following treatment, have an investigator-defined complete or partial response to their last platinum regimen with observable residual disease of <2 cm and CA-125 values either within the normal range, or a CA-125 decrease of more than 90% that was stable for at least 7 days.
	• ECOG PS 0-1
	• Adequate hematologic, renal, and liver function
	• Availability of formalin-fixed, paraffin-embedded archival tumour from the primary or recurrent cancer[7]
	
	Key Exclusion Criteria:
	• Known hypersensitivity to the components of niraparib
	• Invasive cancer other than ovarian cancer ≤2 years prior to randomization (except basal or squamous cell carcinoma of the skin that has been definitely treated)[42]
	• Symptomatic uncontrolled brain metastasis
	• Pregnant or breast feeding
	• Immunocompromised patients
		Intervention:
		Niraparib (300 mg) once daily in 28-day cycles until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up
		
		Comparator:
		Placebo administered once daily continuously in 28-day cycles until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up
			Primary:
			• PFS
			
			Secondary:
			• TFST[b]
			• CFI[b]
			• PFS2[b]
			• OS[b]
			• TSST[b]
			• Change from baseline in FOSI[b]
			• Change from baseline in EQ-5D-5L[b]
			
			Exploratory:
			• ORR for the next anti-cancer therapy following study treatment[7]
			• Duration of objective response for the next anti-cancer therapy following study treatment[7]
			• Rate of conversion from PR to CR during study treatment[7]
			• Assessment of the primary and secondary efficacy outcomes in various mutational subgroups within the non-gBRCAmut cohort[5]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Known active hepatic disease • Prior treatment with a known PARP inhibitor • Baseline QT prolongation > 470 milliseconds [5]		

BRCA = breast cancer susceptibility gene; CA-125 = cancer antigen 125; CFI = chemotherapy-free interval; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; EQ-5D-5L: European Quality of Life scale, 5-Dimensions; FOSI = Functional Assessment of Cancer Therapy - Ovarian Symptom Index; gBRCAmut = germline BRCA mutation; ORR = objective response rate; OS = overall survival; PARP = poly(adenosine diphosphate [ADP]–ribose) polymerase; PFS = progression-free survival; PFS-2 = progression-free survival on next line of therapy; PR = partial response; TFST = time-to-first subsequent therapy; TSST = time-to-second subsequent therapy.

[a] Evaluated in each of the gBRCA, non-gBRCA and non-gBRCA HRD+ cohorts; [b] Evaluated in each of the gBRCA and non-gBRCA cohorts.

Data sources: Mirza et al. 2016,[2] EPAR 2017,[5] Clinical Study Protocol,[6] GlaxoSmithKline Inc. Checkpoint Responses 2020[9]

a) Trial

NOVA is an 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 platinum-sensitive, recurrent ovarian, fallopian tube, or primary peritoneal cancer (henceforth referred to as ovarian cancer).[2] The trial was conducted in 107 sites in 15 countries, including nine sites in Canada from which [redacted] patients were randomized[3] (refer to Table 5 for a list of participating countries). (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the CADTH Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Trial Design

Screening, Eligibility Criteria, and Randomization

The NOVA study design is depicted in Figure 2[5] and key eligibility criteria are outlined in Table 5. In brief, eligible patients had relapsed and predominantly high-grade serous ovarian cancer, demonstrated sensitivity to platinum-based treatment, and an ECOG performance status of 0 or 1. Enrolled patients had to have received at least two prior platinum-based therapies.[2] For their penultimate (i.e. second to last) platinum-containing therapy before trial enrollment, patients were required to have demonstrated platinum-sensitive disease following this treatment. Platinum-sensitive disease was defined as a CR or PR and disease progression more than six months after completion of platinum therapy. For the last platinum-containing therapy received before randomization, patients were required to have received a minimum of four cycles of treatment, and following treatment, have an investigator-defined CR or PR with observable residual disease of less than 2 cm and CA-125 values either within the normal range, or a CA-125 decrease of more than 90% that was stable for at least seven days. Patients were randomized no later than eight weeks after completing their last dose of platinum-based therapy.

Biomarker testing was performed for all patients to determine both their BRCA status and the status of their individual tumours for HRD.[2] Prior to a protocol amendment (Amendment 4, which is further described below) that required tumour tissue samples be tested for HRD, HRD testing was not mandatory. All testing for HRD was completed prior to DBL and was not performed again at the time of disease progression. The definitions for biomarker test results used in the trial for BRCA and HRD are summarized in Table 6.

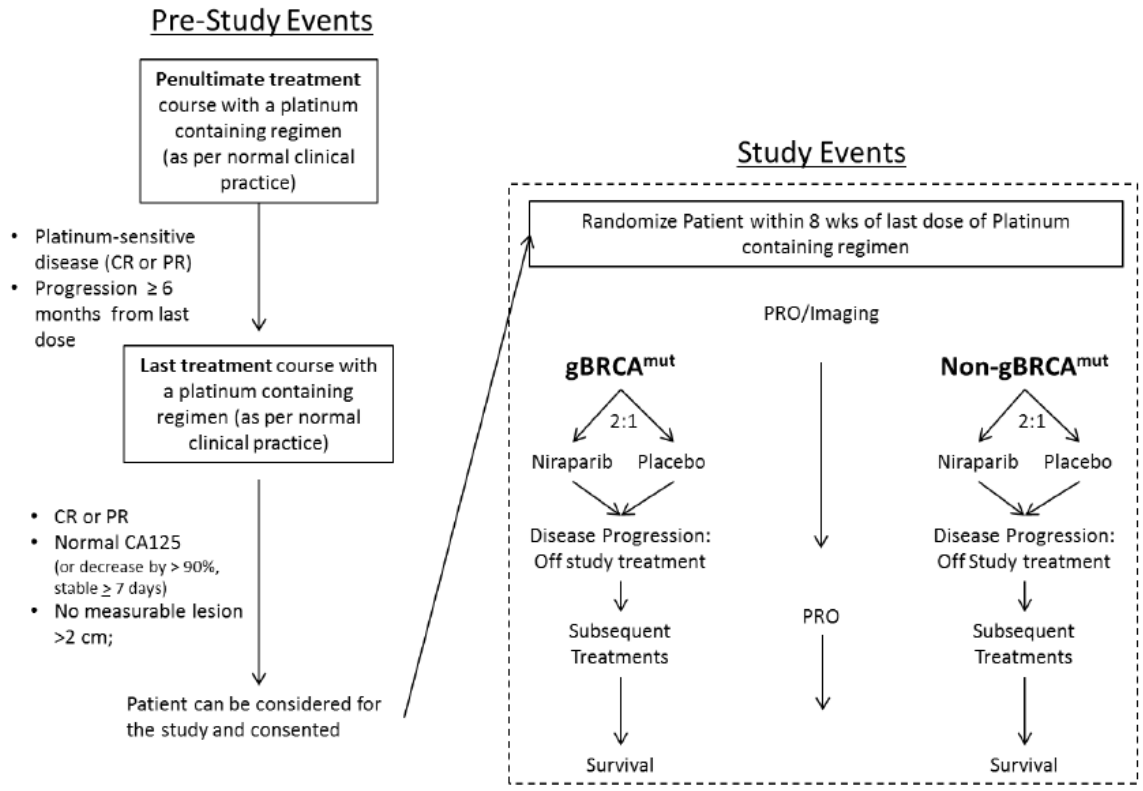
The trial was double-blind, and therefore, patients and investigators were blinded to treatment assignment.[8] The sponsor was also blinded to the treatment assignment and to the HRD status of patients' tumours until unblinding, as were the statisticians involved in data analyses. The treatment allocation sequence was created by an independent statistician and patients were randomized in a 2:1 ratio to receive niraparib or placebo via an interactive web response system.[5,8] Randomization was carried out using permuted blocks and occurred separately for the following two cohorts of patients: [2,5]

- gBRCAmut cohort
- non-gBRCAmut cohort – this cohort comprised of patients who had either HRD-positive tumours with a sBRCAmut (n=47), HRD-positive tumours with BRCAwt (n=115), and HRD-negative tumours irrespective of sBRCAmut status (n=134)

Randomization was stratified by the following factors:

- Time-to-progression after the penultimate platinum therapy received before trial enrolment (six to < 12 months and ≥12 months)
- Use of bevacizumab in the penultimate or last platinum regimen received
- Best response during last platinum treatment (CR or PR)

Figure 2: NOVA Study Design Flow Chart



Data source: EPAR 2017[5]

Table 6: Terminology of Biomarker Test Results used in the NOVA trial

Terminology	Definition and details
Germline BRCA mutation (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)	Dysregulation in the homologous recombination DNA repair pathway (due to genetic mutations or alterations) leading to cellular genomic instability and an inability to efficiently repair damaged DNA. HRD-positive cells are more susceptible to the effects of DNA damaging agents such as platinum agents or PARP inhibitors.
HRD-positive	HRD-positive status was determined by the myChoice® HRD test. Any tumour that scored ≥42 or had a deleterious or suspected deleterious BRCA 1/2 mutation was considered HRD positive via this test. Within the non-gBRCAmut cohort, tumours with somatic BRCA mutations were identified by this test. These tumors have a defective homologous recombination repair pathway.
HRD-negative	HRD-negative status was determined by the myChoice® HRD test. Any tumour that scored <42 and did not possess a deleterious or suspected deleterious BRCA 1/2 mutation was considered HRD negative via this test. These tumours have a functional homologous recombination repair pathway.

BRCA = breast cancer susceptibility gene; gBRCAmut = germline BRCA mutation; HRD = homologous recombination deficiency.

Data source: Mirza et al. 2016[2]

Study Endpoints and Statistical Analyses

Efficacy Outcomes

All efficacy outcomes were analyzed in the intent-to-treat (ITT) population, defined as all patients who underwent randomization in each of the two cohorts (gBRCAmut and non-gBRCAmut).[2] Definitions of the efficacy outcomes assessed in the NOVA trial are summarized in Table 7.

The primary endpoint of the trial was PFS assessed by IRC, defined as the time from treatment randomization to the date of disease progression or death from any cause, whichever occurred first.[5] Progressive disease (PD) was defined as meeting at least one of the following criteria:

1) tumour progression according to RECIST version 1.1 assessed by computed tomography (CT) or magnetic resonance imaging (MRI)
2) identification of new lesions or determination that existing lesions qualified as PD (using additional diagnostic tests such as, histology/cytology, ultrasound techniques, endoscopy, and positron emission tomography) and CA-125 progression according to Gynecologic Cancer Intergroup (GCIG) criteria
3) definitive clinical signs and symptoms of PD unrelated to non-malignant or iatrogenic causes 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: OS, TFST, TSST, CFI, PFS-2, and PROs (FOSI, EQ-5D-5L, CIPN).[2] Additionally, the following exploratory secondary efficacy outcomes were also analysed (only the first outcome listed below is included in this report):[6]

- assessment of the primary and secondary efficacy outcomes in various mutational subgroups within the non-gBRCAmut cohort
- objective response rate (ORR) for the next anti-cancer therapy following study treatment
- duration of objective response for the next anti-cancer therapy following study treatment (defined as time measurement criteria for PR or CR are met in the next anti-cancer therapy until recurrent or progressive disease)
- rate of conversion from PR to CR during study treatment

Table 7: Definitions of Primary and Secondary Efficacy Endpoints Assessed in the NOVA trial

Primary efficacy endpoint	
Progression-free survival (PFS)	The primary efficacy endpoint PFS, defined as the time from the date of treatment randomization to the date of first documentation of progression or death by any cause, was assessed by IRC per RECIST v.1.1 criteria. The independent oncologist in addition reviewed relevant clinical data, including anatomic site(s) of prior radiotherapy, on-study cytology and/or histology results, on-study interventions (surgery, radiotherapy, etc), additional diagnostic test results, CA-125 values and clinical signs and symptoms of disease progression.
Secondary efficacy endpoints	
Time to first subsequent treatment (TFST)	Date of randomization in the current study to the start date of the first subsequent anti-cancer therapy after maintenance treatment
Chemotherapy-free interval (CFI)	The time from the last platinum therapy dose until initiation of the next anti-cancer therapy (excluding maintenance therapy)
Progression-free survival 2 (PFS2)	Date of randomization in the current study to the earlier date of assessment of progression on the next anti-cancer therapy following study treatment or death by any cause. If progression on next anti-cancer therapy was not determined, but the patient received a second subsequent anti-cancer therapy the date of the next line of therapy was used as a surrogate for PD.
Time to second subsequent treatment (TSST)	Date of randomization in the current study to the start date of the second subsequent anti-cancer therapy after maintenance treatment
Overall survival (OS)	Time from study randomization to the date of death by any cause
Patient-reported outcome (PRO)	• FOSI (PRO): Validated, 8-item measure of symptom response to treatment for ovarian cancer • EQ-5D-5L (PRO): Validated general preference-based health related QOL instrument in oncology, as well as other conditions, and is intended to compliment other QOL instruments • Neuropathy Questionnaire: As of the prior 7 days, patients provided a response on a scale of 0 (not at all) to 4 (very much), to "My feet feel numb or have prickling/ tingling feelings," "My hands feel numb or have prickling/tingling feelings"

Data source: EPAR 2017[5]

Time-to-event outcomes were analyzed using Kaplan-Meier (KM) methods and a two-sided log-rank test (stratified by randomization factors).[2] Hazard ratios and two-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 one-sided 0.025 significance level.

Three efficacy populations were analyzed: gBRCAmut, HRD-positive non-gBRCAmut cohort, and the overall non-gBRCAmut cohort.[2] For the assessment of PFS in the non-gBRCAmut cohort, a hierarchical-testing procedure was used, which pre-specified that efficacy analyses were first performed in patients with HRD-positive tumours, and if the results were statistically significant, a test of the overall non-gBRCAmut cohort was performed.[2] Therefore, for the non-gBRCAmut cohort, the HRD-positive subgroup was the primary efficacy population.[5] Primary efficacy analyses were planned for when at least 98 patients in the gBRCAmut cohort and at least 98 patients in the HRD-positive non-gBRCAmut cohort had a PFS event. The primary efficacy analyses were based on a June 20, 2016 DBL.

To assess the consistency of the treatment effect, analyses of PFS (and OS, although these have not been reported) were prespecified and performed in the following patient subgroups based on demographic and clinical characteristics: age, race, geographic region, time-to-progression after the penultimate platinum therapy before study enrollment, use of bevacizumab in conjunction with the penultimate or last platinum regimen, best response during the last platinum regimen (CR and PR), concomitant chemotherapy with platinum in the last and penultimate regimens, and the number of prior platinum regimens (two and >2).[6] Cox proportional hazards models were used to estimate the HR (95% CI) for each subgroup and statistical tests for interaction were performed where treatment by subgroup interactions were deemed statistically significant at a 10% significance level ($p<0.10$).

Additional exploratory analyses of PFS were also prespecified and performed in three subgroups of the non-gBRCAmut cohort: HRD-positive plus sBRCAmut, HRD-positive plus BRCAwt, and HRD-negative.[2] These analyses were performed to further investigate the consistency of the PFS results and no formal hypothesis testing was carried out for these analyses.

Safety Outcomes

Safety outcomes were analyzed in the safety population, defined as all patients who had received at least one dose of either niraparib or placebo.[5] Patients were analyzed according to the study drug consumed. Safety data were summarized using descriptive statistics.

Patient Reported Outcomes - FOSI, EQ-5D-5L, and CIPN

To assess HRQoL, the FOSI, EQ-5D-5L, and CIPN questionnaires were administered at the screening visit, throughout treatment (every eight weeks through cycle 14, then every twelve weeks thereafter[8]), at the time of study treatment discontinuation, and eight weeks after the last dose of niraparib or placebo.[2] If a patient discontinued, PRO data were collected at discontinuation and during a post-progression visit eight ± two weeks later.[8] The questionnaires are further described below.

The FOSI is a validated eight-item questionnaire that assesses the symptoms of ovarian cancer and is based on a subset of eight questions from the Functional Assessment of Cancer Therapy - Ovarian questionnaire related to pain, fatigue, nausea, vomiting, bloating, cramping, worry, and QoL.[8] Patients report their symptoms over seven days on a Likert scale (score range: 0=not at all to 4=very much). Individual symptoms are categorized as symptomatic (response ≥1) or as severely symptomatic (response of 3 or 4). An overall FOSI score is obtained by multiplying the sum of the eight individual item scores and dividing the result by the number of responses, where the overall FOSI score can range from 0 (severely symptomatic) to 32 (asymptomatic). A difference in mean scores between treatment groups of two to three points[88] was considered the MID.[86]

The EQ-5D-5L HUI is a general preference-based HRQoL scale consisting of five dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), with five levels of response in each dimension (level 1=no problems to level 5=extreme problems).[8] The EQ-5D-5L HUI scores were determined from health states using the US value set. 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). For the EQ-5D-5L HUI, scores for all post-baseline visits before disease progression were averaged. The averaged scores were then adjusted using a mixed model with the following prespecified covariates: histology, region, previous treatment, age, duration on previous treatment, and baseline EQ-5D-5L score. Least squares mean estimates and the standard errors of the adjusted HUI scores were presented by treatment group. A difference in mean scores between treatment groups of 0.08 was considered the MID for the EQ-5D-5L HUI; the MID for the VAS was not specified.

To assess neuropathy, the CIPN questionnaire was administered at each assessment time point.[7] The CIPN measures the degree of tingling and numbness in the feet and hands with severity scores ranging from 0 (not at all) to 4 (very much). A difference in mean scores between treatment groups of two to three points was considered the MID.[6]

Patient-reported outcomes were evaluated in the ITT population.[8] For continuous variables, changes from baseline in PRO scores (overall scores, sub scores, and individual items) were analyzed descriptively by treatment group. The FOSI, EQ-5D-5L HUI and VAS scores were analyzed using a mixed-effects growth-curve model that adjusted for fixed (time, baseline demographic values, and the three stratification factors) and random (patient) covariates in order to assess the association between treatment assignment and PRO score. The time-to-symptom worsening on the overall FOSI score was analyzed using time-to-event methodology. Individual items from the neuropathy questionnaire were analyzed using the Pearson chi-square test for association between treatment and ordinal response.[6]

To assess the effect of hematological AEs on HRQoL, EQ-5D-5L HUI and FOSI scores were adjusted based on mixed models that included the following covariates: histology, region, previous treatment, age, duration on previous treatment, and baseline FOSI or EQ-5D-5L score.[8] Separate models were developed to assess the contribution of each type of AE and separate disutility estimates were developed for AEs of grade 3 and 4. The effect of each AE on individual FOSI and EQ-5D-5L HUI scores were presented using least squares mean estimates of the AE as a fixed-effect relative to a reference point. The reference point was determined using the least squares mean score estimates of patients who did not present with the AE during the stable treatment period.

Study Assessments

To assess for disease progression, CT or MRI was performed at baseline, every eight weeks through cycle 14 and every 12 weeks thereafter until treatment discontinuation.[2] Disease progression was assessed by IRC according to RECIST, version 1.1. Assessments were performed in a blinded fashion by IRC.[5]

CA-125 testing was conducted at screening and at day one of each treatment cycle.[2] Progression of CA-125 was assessed as per the GCIG criteria. Physical examinations, vital sign measurements, and clinical laboratory tests were conducted on days one and 15 of the first treatment cycle, and on day one of each following cycle. Additionally, complete blood cell count (CBCs) were conducted on days eight and 21 of the first cycle. Tumour samples were collected and HRD testing was performed prior to DBL.

Assessment of survival status and use of subsequent anti-cancer therapies was performed every 90 ± 7 days after the study treatment discontinuation visit.[2] New malignancy information was collected during this assessment, and the following information was collected form source documentation: next anticancer therapy, start date of subsequent therapies, dose limiting toxicities, best response (i.e., CR, PR, stable disease, and partial disease), and date of progression.

Safety data, AEs and serious adverse events (SAEs), were collected from study enrolment (time of signing the consent form) and through treatment.[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 Common Terminology Criteria for Adverse Events (CTCAE) version 4.02.

Sample Size

The target enrollment for the NOVA trial was 490 patients. The required sample size was calculated to provide a power of more than 90% to determine statistical significance at a one-sided alpha level of 0.025.[2] The cohorts were treated like independent studies where each cohort was allocated a 1-sided alpha of 0.025.[5] The targeted enrollment was 180 patients in the gBRCAmut cohort and 310 patients in the non-gBRCAmut cohort. The target sample size was based on the assumption of a median duration of PFS of 9.6 months in the niraparib group and 4.8 months in the placebo group, which corresponded to a HR of 0.50 in each of the two primary efficacy cohorts. It was assumed that 40% of patients in the non-gBRCAmut cohort would have an HRD-positive tumour.

Interim Analysis

An interim analysis was planned for the gBRCAmut cohort after approximately 85 PD events; however, this analysis was removed in protocol amendment six following the change in power of the gBRCAmut cohort as the timing of accruing this number of events would approximately coincide with the planned analysis of data (for more details refer to Table 8).[5]

Sensitivity Analyses

Several sensitivity analyses were pre-planned for the primary outcome of PFS in the ITT population:[5]

- unstratified log-rank test and Cox proportional hazards regression modeling using treatment only as a covariate
- investigator assessment of PFS (using stratified log-rank and associated Cox proportional hazards regression model)
- IRC analysis using only radiological assessment (RECIST version 1.1) of progression
- IRC analysis treating the following as events rather than being censored: subsequent anti-cancer treatment, discontinuation due to any reason, or missed tumour assessments
- utility of scheduled assessment date (for PD) if the actual assessment was conducted after the scheduled date and showed PD (only performed for progression events, not for censored observations)
- analysis whereby subsequent anti-cancer treatment was considered a PD event, and the event date was set at the date of initiation of the first subsequent anti-cancer treatment

Additionally, a sensitivity analysis was conducted of the per-protocol population, defined as all patients randomized who did not have a major protocol deviation that may have impacted the interpretation of the efficacy results.[5]

Protocol Amendments

A total of six global trial protocol amendments occurred, which have been summarized in Table 8.[5]

Table 8: Summary of Protocol Amendments in the NOVA trial

Amendment Number (Date)	Substantial amendment summary
Amendment 1 (May 3, 2013)	• Clinical criteria were added to the means (RECIST, blinded central review) by which disease progression was confirmed • QTc analyses were added to indicate that a formal analysis of ECG variables would be conducted that a separate population PK analysis plan would be written to describe the relationship between ECG and PK variables • Assessment of PROs were to continue after a patient discontinued treatment, regardless of disease progression status
Amendment 2 and 3 (April 9, 2014)	• The Integrated BRACAnalysis was specified as the diagnostic test to determine germline BRCA mutation status (no longer allowing local BRCA tests) • DNA from the sample submitted for Integrated BRACAnalysis testing was permitted to be stored for potential further biomarker testing
Amendment 4 (December 4, 2014)	• Text was added to the protocol to indicate patients would be tested centrally to assess their HRD status and the timing of testing was specified • A hierarchical testing procedure was added that specified patients with HRD-positive tumours in the non-gBRCAmut cohort would be evaluated first for PFS, followed by the full cohort of non-gBRCAmut patients • Statistical analysis methods were updated to indicate that the superiority of niraparib over placebo for PFS could be evaluated in the gBRCAmut cohort using a 1-sided alpha equal to 0.025 • Concordance of a candidate companion HRD diagnostic test was compared with the HRD diagnostic test used in the study. Baseline samples for HRD analysis were to be stored to possibly bridge the study's HRD diagnostic test to a candidate companion test
Amendment 5 (September 11, 2015)	• Guidance was added to the protocol on the monitoring of patients for new events of MDS/AML and the follow-up of patients with suspected MDS/AML
Amendment 6 (March 9, 2016)	• The required sample size of the gBRCAmut cohort was changed (from >95% to 90% power) in order to ensure that the gBRCAmut cohort would not be overpowered to detect small difference in PFS; and changes were made to provide the evidence needed to determine whether there may be a differential response in patients with gBRCAmut versus HRD positive tumours, somatic BRCA mutation versus HRD positive tumours, wild type BRCA tumours. The sample size changed to approximately 100 PFS events in the gBRCAmut cohort. • TSFT and TSST were added as secondary outcomes of • The planned interim analysis for the gBRCAmut cohort (after approximately 85 PFS events) was removed as the timing of these events would approximately coincide with the planned analysis of data

AML = acute myeloid leukemia; BRCA = breast cancer susceptibility gene; ECG = electrocardiogram; gBRCAmut = germline BRCA mutation; HRD = homologous recombination deficiency; MDS = myelodysplastic syndrome; OS = overall survival; PFS = progression-free survival; QTc = corrected QT interval; TFST = time-to-first subsequent therapy; TSST = time-to-second subsequent therapy.

Data source: EPAR 2017[5]

Funding

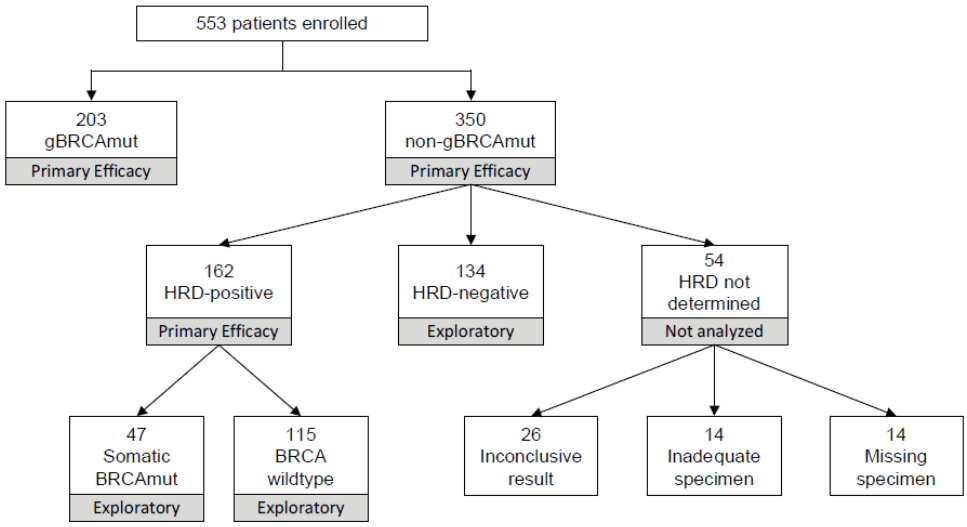
The trial was funded by Tesaro/GlaxoSmithKline Inc. and was conducted in collaboration with the European Network of Gynaecological Oncological Trial (ENGOT) Groups and academic research groups in the United States and Canada.[42] One of the trial authors was directly employed by the sponsor and two authors reported financial support from the sponsor or from a collaborator in the form of grants to the author's institution, lecture fees, consulting fees and fees for serving on an advisory board.[2] The Nordic Society of Gynecological Oncology (NSGO) was the principal group that led the NOVA trial but the sponsor oversaw all trial conduct. A clinical research organization, Veristat, developed the statistical design of the trial and preformed final data analyses. All analyses were independently reviewed and approved by a statistician from NSGO.

b) Populations

Biomarker populations

The biomarker populations in the trial are summarized in Figure 3.[2] A total of 553 patients were enrolled in the trial, with 203 patients in the gBRCAmut cohort and 350 patients in the non-gBRCAmut cohort. In the non-gBRCAmut cohort, 162 patients had HRD-positive tumours (47 with sBRCAmut and 115 with BRCAwt), 134 had HRD-negative tumours, and the HRD status of the tumours was not determined for 54 patients (26 with inconclusive results, 14 with inadequate specimens, and 14 with missing specimens).

Figure 3: Biomarker Populations in the NOVA trial



Source: From The New England Journal of Medicine, Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer, Vol. no. 375, Issue No. 22, Supplement, Page No. 18. Copyright ©2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. [2]

Demographic Characteristics

The baseline demographic and clinical characteristics of the NOVA trial population are summarized in Table 9.[2] In the gBRCAmut cohort, 138 patients were randomized to receive niraparib and 65 patients were randomized to receive placebo.[5] The median age was 57.0 years in the niraparib group and 58.0 years in the placebo group. The majority of patients were 'White' (niraparib group: 89.1%; placebo group: 84.6%) and had an ECOG PS of 0 (niraparib group: 65.9%; placebo group: 73.8%). The mean weight of patients in the niraparib and placebo groups was 66.7 kg and 69.0 kg, respectively.[7]

In the non-gBRCAmut cohort, 234 patients were randomized to receive niraparib and 116 patients were randomized to receive placebo.[5] The median age was 63.0 years in the niraparib group and 60.5 years in the placebo group. The majority of patients were

'White' (niraparib group: 85.9%; placebo group: 87.1%) and had an ECOG PS of 0 (niraparib group: 68.4%; placebo group: 67.2%). The mean weight of patients in the niraparib and placebo groups was 69.6 kg and 68.0 kg, respectively.[7]

Disease Characteristics

Disease characteristics of the NOVA trial population by biomarker cohort are summarized in Table 9.[5]

In the gBRCAmut cohort, there were small imbalances between the groups for the primary tumour site; the majority of patients (niraparib group versus the placebo group) had ovary as their primary tumour site (88.4% versus 81.5%) versus other locations that included primary peritoneal (5.1% versus 9.2%) and fallopian tube (6.5% versus 9.2%).[5] There were also some imbalances between groups for the germline BRCA variant; most patients in each group had a BRCA1 mutation (61.6% versus 66.2%), compared to BRCA2 (37.0% versus 27.7%) and BRCA 1/2 rearrangements (6.5% versus 6.2%). Histological subtypes were relatively balanced between the treatment groups with the following subtypes represented in the trial: serous (88.6% versus 90.8%), endometrioid (6.1% versus 4.6%), mucinous (0% versus 0%), and 'other' (9.8% versus 4.6%). Most patients in each treatment group had stage IIIC cancer (58.7% versus 55.4%) and less than three metastatic sites (64.5% versus 61.5%). The mean time since diagnosis was 4.37 years in the niraparib group and 4.07 years in the placebo group. In the niraparib group, 60.9% of patients had ≥ 12 months to progression after the penultimate platinum therapy, compared to 60.0% in the placebo group. Similar proportions of patients in each treatment group had a CR (51.4% versus 50.8%) or PR (48.6% versus 49.2%) as the best response to most recent platinum therapy.

In the non-gBRCAmut cohort, baseline disease characteristics were generally well balanced between the treatment groups and similar to the gBRCAmut cohort.[5] The primary tumour sites (niraparib group versus the placebo group) were ovarian (82.1% versus 82.8%), primary peritoneal (10.3% versus 6.9%) and fallopian tube (7.7% versus 9.5%); and histological subtypes were serous (96.4% versus 99.1%), endometrioid (0.4% versus 0.9%), mucinous (0% versus 0%), and 'other' (4.9% versus 2.7%). Most patients in each treatment group had stage IIIC cancer (63.7% versus 56.9%) and less than three metastatic sites (67.1% versus 68.1%). The mean time since diagnosis was 3.33 years in the niraparib group and 3.59 years in the placebo group. In the niraparib group, 61.5% of patients had ≥ 12 months to progression after the penultimate platinum therapy, compared to 62.1% in the placebo group. Similar proportions of patients in each treatment group had a CR (50.0% versus 51.7%) or PR (50.0% versus 48.3%) as the best response to most recent platinum therapy.

Patients' prior history of myelosuppression (including thrombocytopenia, anemia, leukopenia, and neutropenia) was relatively balanced between the cohorts and treatment groups.[7] The prior history of myelosuppression among trial patients is summarized in Table 10.

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

Characteristic	gBRCAmut Cohort (N=203)		Non-gBRCAmut cohort (n=350)	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Age, median (range) years	57 (36-83)	58 (38-73)	63 (33-84)	61 (34-82)
Age – n (%) years 18-64 65-74 ≥ 65 ≥ 75	 110 (79.7) 24 (17.4) 28 (20.3) 4 (2.9)	 49 (75.4) 16 (24.6) 16 (24.6) 0	 130 (55.6) 85 (36.3) 104 (44.4) 19 (8.1)	 69 (59.5) 39 (33.6) 47 (40.5) 8 (6.9)
Race – n (%) White Black/Asian/Other/Unknown	 123 (89.1) 15 (10.9)	 55 (84.6) 10 (15.4)	 201 (85.9) 33 (14.1)	 101 (87.1) 15 (12.9)
Ethnicity – n (%) Non-Hispanic Hispanic/Other/Unknown	 121 (87.7) 17 (12.3)	 57 (87.7) 8 (12.3)	 202 (86.3) 32 (13.7)	 99 (85.3) 17 (14.7)
Region – n (%) Unites States, Canada Europe, Israel	 53 (38.4) 85 (61.6)	 28 (43.1) 37 (56.9)	 96 (41.0) 138 (59.0)	 44 (37.9) 72 (62.1)
ECOG PS – n (%) 0 1	 91 (65.9) 47 (34.1)	 48 (73.8) 17 (26.2)	 160 (68.4) 74 (31.6)	 78 (67.2) 38 (32.8)
Weight – kg Mean (SD) Median Min, Max	 69.9 (17.6) 66.7 36.2, 131.4	 71.8 (16.7) 69.0 45.6, 133.2	 69.6 (15.5) 66.1 43.9, 125.7	 68.0 (12.2) 66.5 48.0, 99.5
Primary tumour site – n (%) Ovarian Primary peritoneal Fallopian tube	 122 (88.4) 7 (5.1) 9 (6.5)	 53 (81.5) 6 (9.2) 6 (9.2)	 192 (82.1) 24 (10.3) 18 (7.7)	 96 (82.8) 8 (6.9) 11 (9.5
Histological subtype – n (%) Serous Endometroid Mucinous Other	 117 (88.6) 8 (6.1) 0 13 (9.8)	 59 (90.8) 3 (4.6) 0 3 (4.6)	 215 (96.4) 1 (0.4) 0 11 (4.9)	 110 (99.1) 1 (0.9) 0 3 (2.7)
Number of metastatic sites – n (%) < 3 ≥ 3	 89 (64.5) 49 (35.5)	 40 (61.5) 25 (38.5)	 157 (67.1) 77 (32.9)	 79 (68.1) 36 (31.0)
Cancer stage – n (%) I-II III-IIIB IIIC IV	 23 (16.7) 14 (10.1) 81 (58.7) 20 (14.5)	 10 (15.4) 10 (15.4) 36 (55.4) 9 (13.8)	 22 (9.4) 24 (10.3) 149 (63.7) 38 (16.2)	 5 (4.3) 20 (17.2) 66 (56.9) 24 (20.7)
Time to progression after penultimate platinum therapy — n (%) 6 to < 12 months ≥ 12 months	 54 (39.1) 84 (60.9)	 26 (40.0) 39 (60.0)	 90 (38.5) 144 (61.5)	 44 (37.9) 72 (62.1)

Characteristic	gBRCAmut Cohort (N=203)		Non-gBRCAmut cohort (n=350)	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Best response to most recent platinum therapy — n (%) CR PR	71 (51.4) 67 (48.6)	33 (50.8) 32 (49.2)	117 (50.0) 117 (50.0)	60 (51.7) 56 (48.3)
Prior bevacizumab use — n (%) Yes No	33 (23.9) 105 (76.1)	17 (26.2) 48 (73.8)	62 (26.5) 172 (73.5)	30 (25.9) 86 (74.1)
gBRCA mutations — n (%) BRCA1 mutation BRCA2 mutation BRCA1 and/or BRCA2 rearrangement	85 (61.6) 51 (37.0) 9 (6.5)	43 (66.2) 18 (27.7) 4 (6.2)	- - -	- - -
Prior lines of chemotherapy — n (%) 1 2 3 4 ≥ 5 Unknown	1 (0.7) 70 (50.7) 40 (29.0) 13 (9.4) 14 (10.1) 0	0 30 (46.2) 20 (30.8) 10 (15.4) 5 (7.7) 0	0 155 (66.2) 55 (23.5) 11 (4.7) 13 (5.6) 0	0 77 (66.4) 17 (14.7) 12 (10.3) 9 (7.8) 1 (0.9)
Prior platinum therapies — n (%) < 2 2 > 2 Unknown	1 (0.7) 79 (57.2) 58 (42.0) 0	0 37 (56.9) 28 (43.1) 0	0 174 (74.4) 60 (25.6) 0	0 87 (75.0) 28 (24.1) 1 (0.9)
Duration since diagnosis – years Mean (SD) Median Min, Max	4.37 (2.56) 3.66 0.3, 13.6	4.07 (3.0) 3.02 1.8, 19.5	3.33 (2.21) 2.69 0.1, 19.2	3.59 (2.0) 2.99 0.1, 9.3

BRCA = breast cancer susceptibility gene; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; gBRCAmut = germline BRCA mutation; ITT = intention-to-treat; PR = partial response; SD = standard deviation.

Data sources: Mirza et al. 2016,[2] EPAR 2017,[5] Clinical Study Report[7]

Table 10: Patients' Prior History of Myelosuppression (ITT population)

Prior History of Myelosuppression Grade	gBRCAmut Cohort (N=203)		Non-gBRCAmut Cohort (N=350)	
	Niraparib (N=138) n (%)	Placebo (N=65) n (%)	Niraparib (N=234) n (%)	Placebo (N=116) n (%)
Any prior history of myelosuppression	111 (80.4)	52 (80.0)	191 (81.6)	91 (78.4)
Thrombocytopenia	71 (51.4)	32 (49.2)	104 (44.4)	48 (41.4)
Grade 1	38 (27.5)	15 (23.1)	51 (21.8)	32 (27.6)
Grade 2	17 (12.3)	9 (13.8)	22 (9.4)	6 (5.2)
Grade 3	10 (7.2)	6 (9.2)	13 (5.6)	5 (4.3)
Grade 4	6 (4.3)	2 (3.1)	18 (7.7)	5 (4.3)
Anemia	93 (67.4)	43 (66.2)	145 (62.0)	72 (62.1)
Grade 1	28 (20.3)	15 (23.1)	51 (21.8)	28 (24.1)
Grade 2	49 (35.5)	22 (33.8)	73 (31.2)	36 (31.0)
Grade 3	15 (10.9)	6 (9.2)	20 (8.5)	7 (6.0)
Grade 4	1 (0.7)	0	1 (0.4)	1 (0.9)
Leukopenia	64 (46.4)	38 (58.5)	124 (53.0)	56 (48.3)
Grade 1	14 (10.1)	11 (16.9)	26 (11.1)	18 (15.5)
Grade 2	35 (25.4)	15 (23.1)	60 (25.6)	27 (23.3)
Grade 3	14 (10.1)	11 (16.9)	32 (13.7)	10 (8.6)
Grade 4	1 (0.7)	1 (1.5)	6 (2.6)	1 (0.9)
Neutropenia	73 (52.9)	37 (56.9)	135 (57.7)	65 (56.0)
Grade 1	13 (9.4)	3 (4.6)	18 (7.7)	10 (8.6)
Grade 2	23 (16.7)	8 (12.3)	38 (16.2)	22 (19.0)
Grade 3	29 (21.0)	19 (29.2)	50 (21.4)	28 (24.1)
Grade 4	8 (5.8)	7 (10.8)	29 (12.4)	5 (4.3)

Abbreviations: BRCA=breast cancer susceptibility gene; gBRCAmut=germline BRCA mutation; ITT=intent-to-treat; non-gBRCAmut=without a germline BRCA mutation

Data source: Clinical Study Report[7]

Previous Therapies

The prior treatments of trial patients included chemotherapy and platinum therapy.[5] It was reported that most patients received carboplatin or cisplatin in combination with another chemotherapy for their last line of platinum-based therapy, and treatment with a platinum therapy alone was rare.[7]

In the gBRCAmut cohort (niraparib versus placebo), most patients had received two or ≥3 previous lines of chemotherapy (50.7% and 46.2% versus 48.6% and 53.8%, respectively).[5] The number of previous lines of platinum therapy was balanced between treatment groups; in the niraparib group, 57.2% of patients had received two lines of platinum therapy and 42.0% of patients had received greater than two lines, compared to 56.9% and 43.1% of patients in the placebo group, respectively (Table 9). One patient in the niraparib group had received one previous line of platinum therapy. The median duration from completion of final platinum therapy to randomization was 42.0 days in the niraparib group versus 39.0 days in the placebo group.[7]

Similarly, in the non-gBRCAmut cohort (niraparib versus placebo), most patients had received two or ≥3 previous lines of chemotherapy (66.2% versus 66.4%, and 33.8% versus 32.8%, respectively).[5] The number of previous lines of platinum therapy was balanced between both groups; in the niraparib group, 74.4% of patients had received two lines of platinum therapy and 25.6% of patients had received greater than two lines, versus 75.0% and 24.1% of patients in the placebo group, respectively (Table 9). The median duration from completion of final platinum therapy to randomization was 43.5 days in the niraparib group versus 42.0 days in the placebo group.[7]

Overall, previous surgical and radiotherapy treatments for ovarian cancer were similar between the treatment groups and by cohort (Table 11).[7] In the gBRCAmut cohort, 85.5% of patients in the niraparib group had received ≥ 2 surgeries/procedures related to the study indication, versus 83.1% in the placebo group. Additionally, 15.9% had received radiotherapy prior to enrollment in the niraparib group versus 10.8% in the placebo group. In the non-gBRCAmut cohort, 82.5% of patients in the niraparib group had received ≥ 2 surgeries/procedures related to the study indication, versus 85.3% in the placebo group; and 5.1% had received radiotherapy prior to enrollment in the niraparib group versus 4.3% in the placebo group.

Table 11: Patients' Prior Non-systemic Treatment (ITT Population)

Cancer Treatment n (%)	gBRCAmut Cohort (N=203)		Non-gBRCAmut Cohort (n=350)			
			HRD-positive (n=162)		Overall (n=350)	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=234)	Placebo (n=116)
Any surgeries/procedures related to the study indication:						
Yes	138 (100)	65 (100)	106 (100.0)	55 (98.2)	234 (100.0)	114 (98.3)
No	0 (0)	0 (0)	0 (0)	1 (1.8)	0 (0)	2 (1.7)
Number of surgeries related to study indication:						
Missing	0 (0)	0 (0)	0 (0)	1 (1.8)	0 (0)	2 (1.7)
1	9 (6.5)	3 (4.6)	6 (5.7)	4 (7.1)	15 (6.4)	8 (6.9)
2	11 (8.0)	8 (12.3)	12 (11.3)	2 (3.6)	26 (11.1)	7 (6.0)
≥ 3	118 (85.5)	54 (83.1)	88 (83.0)	49 (87.5)	193 (82.5)	99 (85.3)
Any radiotherapy prior to enrollment:						
Yes	22 (15.9)	7 (10.8)	8 (7.5)	3 (5.4)	12 (5.1)	5 (4.3)
No	116 (84.1)	58 (89.2)	98 (92.5)	53 (94.6)	222 (94.9)	111 (95.7)

BRCA = breast cancer susceptibility gene; gBRCAmut = germline BRCA mutation; HRD = homologous recombination deficiency.

Data source: Clinical Study Report[7]

c) Interventions

Treatment

Patients in each cohort were randomized 2:1 to receive either niraparib or placebo.[2] Patients randomized to niraparib received a 300 mg once daily oral dose (3 x 100 mg capsules) in 28-day cycles until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up.[5] The dose was chosen based on results from a phase I dose-escalation study.[89] Patients randomized to placebo received a once daily oral dose marked as equivalent to niraparib, also in 28-day cycles until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up. Crossover to niraparib was not allowed after disease progression for patients randomized to placebo.[2] No other anti-cancer therapies were permitted during study treatment. Patients could receive corticosteroids as long as the corticosteroids were initiated at least four weeks prior to enrollment.[6]

Treatment/Dose Interruptions and Dose Reductions

Dose interruptions and/or reductions could have been implemented at any time for any grade toxicity that was considered intolerable by the patients.[2] For major surgery, dose interruptions were permitted for up to 28 days.

The guidelines used in the trial to manage dose reductions for non-hematological toxicities are summarized in Table 12.[2] Briefly, treatment interruptions were required for any non-hematological National Cancer Institute-CTCAE (version 4.02) grade 3 or 4 AE that the investigator considered to be related to treatment. If the toxicity was resolved to baseline or ≤ grade 1 within 28 days, treatment could be restarted at a reduced dose of 200 mg once daily (first dose reduction). If the toxicity recurred at a similar or worse grade, a second dose interruption was allowed if the toxicity resolved within 28 days, 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 if similar or worse grade toxicity recurred after two dose reductions, the patient was required to permanently discontinue treatment. No more than two dose reductions were permitted.

Table 12: Dose Reduction Guidelines for Non-Hematological Toxicity used in the NOVA trial

Event[1]	Dose[2]
Initial dose	300 mg QD
1st dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	200 mg QD
2nd dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	100 mg QD
Continued NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE ≥ 28 days	Discontinue study medication

Abbreviations: AE=adverse event; NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; QD=once daily; SAE=serious adverse event.
1. Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient; 2. Dose not to be decreased below 100 mg QD.

Source: From The New England Journal of Medicine, Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer, Vol. no. 375, Issue No. 22, Supplement, Page No. 14. Copyright ©2016 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 13.[2] If dose modifications were required to manage hematological toxicity, weekly blood draws for CBC were required for four weeks after the AE had resolved to prespecified levels. If a patient did not return to prespecified levels within four weeks of the dose interruption, or if the patient had already had two dose reductions, 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 13: Dose Modification and Reduction Guidelines for Hematologic Toxicity used in the NOVA trial

Finding	Modification
Platelet count 75,000-99,999/μL (grade 1)	Study drugs must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at same dose or reduced dose based on clinical judgment.
Second occurrence of platelet count 75,000-99,999/μL (grade 1)	Study drugs must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Platelet count <75,000/μL (grade 2 or higher)	Study drugs must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Neutrophil <1,000/μL (grade 3 or higher)	Study drugs must be interrupted until neutrophil counts ≥1,500/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Hemoglobin <8 g/dL (grade 3 or higher)	Study drugs must be interrupted until hemoglobin is ≥9 g/dL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.

Abbreviations: CBC=complete blood cell count.

Source: From The New England Journal of Medicine, Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer, Vol. no. 375, Issue No. 22, Supplement, Page No. 15. Copyright ©2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. [2]

Drug Exposure

Patient exposure to study drug was reported in the safety population (defined as all patients who had received at least one dose of either niraparib or placebo), which included a total of 546 patients comprised of 367 patients in the niraparib group and 179 patients in the placebo group.[5] The most commonly used dose of niraparib was 200 mg. At the time of DBL, 245 patients (66.8%) had been exposed to ≥ six months to <12 months of niraparib, and 163 patients (44.4%) had been exposed for ≥12 months. Treatment exposure data from the NOVA trial are summarized in Table 14.

In the safety population,[7] the mean duration of study drug exposure was longer in the niraparib group versus the placebo group (niraparib: 299.9 days - equivalent to 11.0 28-day cycles; placebo: 212.5 days - equivalent to 7.9 cycles).[5] The median duration of study drug exposure was longer in the niraparib group compared to the placebo group (niraparib: 250 days – equivalent to approximately nine cycles; placebo: 163 days – equivalent to approximately six cycles), which equates to a difference in median duration exposure of approximately three months between the study treatment groups. The mean dose intensity (sum of the daily doses actually consumed divided by total duration) was 194.98 mg/day in the niraparib group compared to 289.54 mg/day in the placebo group; and the mean relative dose intensity was 64.99% in the niraparib group, and 96.51% in the placebo group.

In the gBRCAmut cohort, the median number of treatment cycles was higher in the niraparib group (14 cycles) compared to the placebo group (seven cycles), and more patients continued treatment for more than 12 months in the niraparib group (54.4%) than in the placebo group (16.9%).[5] In the overall non-gBRCAmut cohort, the median number of treatment cycles was also higher in the niraparib group (eight cycles) versus the placebo group (five cycles), and more patients continued treatment for more than 12 months in the niraparib group (34.2%) compared to the placebo group (21.1%).

Table 14: Study Drug Exposure in the NOVA trial (Safety Population)

Exposure Parameter	Niraparib (N=367) n (%)	Placebo (N=179) n (%)
Number of Cycles Started, n	367	179
Mean (StD)	11.0 (7.66)	7.9 (5.93)
Median	9.0	6.0
Min, Max	1.0, 30.0	1.0, 34.0
Overall Treatment Exposure (days)[a], n	367	179
Mean (StD)	299.9 (210.89)	212.5 (163.79)
Median	250.0	163.0
Min, Max	1.0, 815.0	12.0, 926.0
Dose Intensity (mg/day)[b], n	364	178
Mean (StD)	194.98 (69.355)	289.54 (25.656)
Median	195.12	297.73
Min, Max	45.10, 360.00	141.05, 340.35
Relative Dose Intensity (%)[c], n	364	178
Mean (StD)	64.99 (23.118)	96.51 (8.552)
Median	65.04	99.24
Min, Max	15.03, 120.00	47.02, 113.45
Overall Dose Interruptions, n (%)	295 (80.4)	34 (19.0)
Overall Dose Reductions, n (%)	266 (72.5)	11 (6.1)

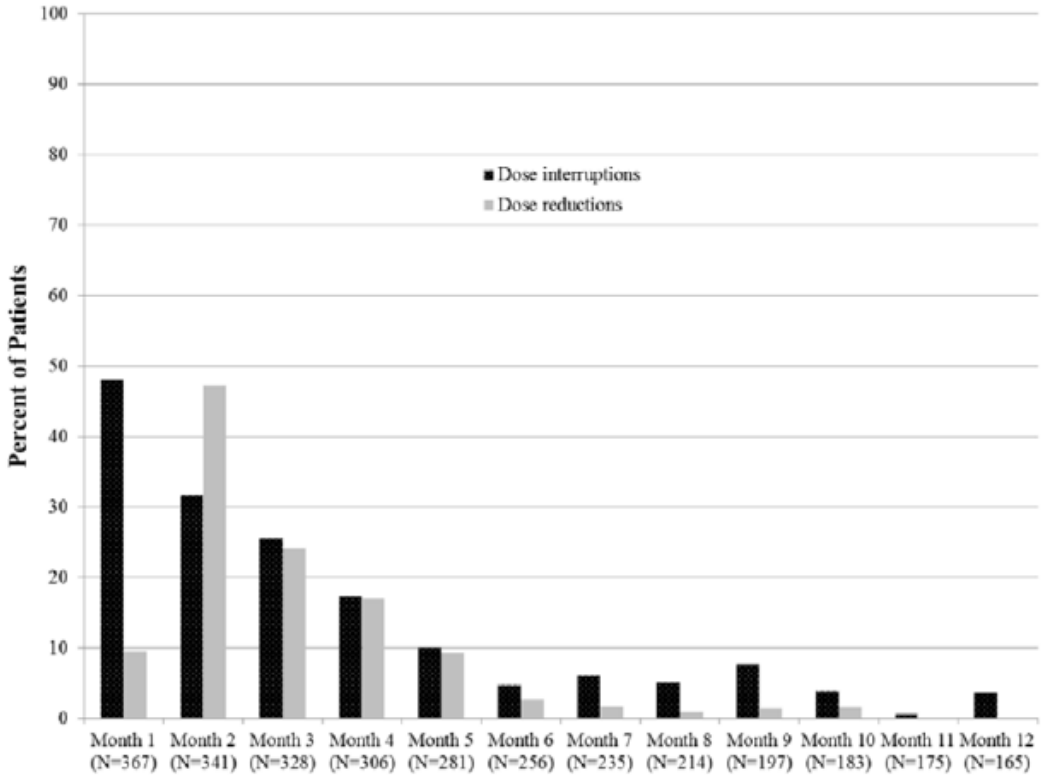
Abbreviations: SAF=safety; StD=standard deviation
[a] Overall treatment exposure is calculated as last dose date minus first dose date plus one.
[b] Dose intensity is calculated as sum of the daily doses actually consumed divided by total duration.
[c] Relative dose intensity is calculated as dose intensity (mg/day) divided by intended dose intensity (mg/day) multiplied by 100, where intended dose is 300 mg.

Data source: Clinical Study Report[7]

Overall, rates of dose interruption or dose reduction for any reason were higher in the niraparib group (80% and 73%, respectively) compared to the placebo group (19% and 6%, respectively). Details of the dose interruptions and reductions over time in the NOVA trial are shown in Figure 4. Most dose reductions occurred early during treatment with the majority of patients reaching their individual adjusted dose level by month four of treatment.[3] At month 12, of the 163 patients still on niraparib treatment, only 23% (n=37) remained on a daily dose of 300 mg with the remaining patients at either the 200 mg (39.9%; n=65) or 100 mg (37.4%; n=61) dose.[3]

As previously noted in Section 1 of this report, baseline body weight and platelet count have been identified as factors that increase the risk of TEAEs that then necessitate dose interruption and dose reduction.[3] In the NOVA trial, the median daily dose of niraparib taken during the first two months of the trial (when most dose interruptions and reductions occurred) was 207.1 mg in the 277 patients who had a baseline body weight < 77 kg or a baseline platelet count <150,000/μL; compared to a median dose of 294.6 mg in the 85 patients who had a baseline weight ≥ 77 kg or a baseline platelet count of ≥ 150,000/μL.[3]

Figure 4: Niraparib Dose Interruptions and Reductions Over Time in the NOVA trial (Safety Population)



Data Source: EPAR 2017[5]

Compliance to study drug in the safety population is summarized in Table 15. Treatment compliance was evaluated for individual patients based on pill counts and was defined as a patient taking between 80% and 120% of their assigned dose.[6] In the gBRCAmut cohort, the median compliance to treatment was 91.1% in the niraparib group and 99.8% in the placebo group. In the non-gBRCAmut cohort, median compliance to treatment was 89.5% in the niraparib group and 99.1% in the placebo group. The compliance rates observed in the niraparib group of both cohorts (78.7% and 77.5% in gBRCAmut and non-gBRCAmut patients, respectively) were lower compared to placebo and reflect the dose interruptions required in patients treated with niraparib.[7]

Table 15: Summary of Study Drug Compliance in the NOVA trial (Safety Population)

Compliance	gBRCAmut Cohort (N=203)		Non-gBRCAmut Cohort (N=345)	
	Niraparib (N=136)	Placebo (N=65)	Niraparib (N=231)	Placebo (N=114)
Overall, n	135	65	229	113
Mean (StD)	87.0 (14.39)	98.4 (6.07)	87.2 (13.84)	98.1 (3.60)
Median	91.1	99.8	89.5	99.1
Min, Max	19, 107	59, 113	27, 120	81, 109
Compliance rate, n (%)				
Compliant	107 (78.7)	64 (98.5)	179 (77.5)	113 (99.1)
<80% compliant	28 (20.6)	1 (1.5)	50 (21.6)	0
>120% compliant	0	0	0	0

Abbreviations: BRCA=breast cancer susceptibility gene; gBRCAmut=germline BRCA mutation; non-gBRCAmut=without a germline BRCA mutation; StD=standard deviation

Data Source: Clinical Study Report[7]

d) Patient Disposition

The disposition of patients through the NOVA trial are summarized in Table 16. In the gBRCAmut cohort, two patients were randomized but did not receive treatment; one withdrew consent and the other was randomized in error due to a failed screening.[9] In the non-gBRCAmut cohort, five patients were randomized but did not receive treatment for the following reasons: ineligible due to failing to meet the criteria of no measurable lesion >2 cm at time of study entry (n=1), lost to follow up before treatment began (n=1), randomized but not dosed due to low blood counts (n=1), and screen failure and randomized in error (n=2).[9]

As of the June 20, 2016 DBL, a larger proportion of patients in the placebo group of both cohorts had discontinued study treatment compared to the niraparib group (gBRCAmut: 93.8% versus 64.5%; non-gBRCAmut: 87.9% versus 79.1%).[2] The primary reason for treatment discontinuation in both groups was disease progression. A higher proportion of patients treated with niraparib discontinued treatment due to AEs compared to patients treated with placebo. The proportions of patients discontinuing treatment for other reasons were similar between the treatment groups and by cohort, except for a greater proportion of patients discontinuing due to subject request in the placebo group of the gBRCAmut cohort. No patients in the trial were lost to follow-up. A higher proportion of patients remained on treatment in the niraparib group compared to the placebo group for both the gBRCAmut and the non-gBRCAmut cohorts (34.1% versus 6.15%, and 19.7% versus 10.3%, respectively). All patients randomized were included the analyses of efficacy outcomes according to ITT.

Table 16: Patient Disposition and Analysis Populations in the NOVA trial

Patient Disposition, n (%)	gBRCAmut Cohort		Non-gBRCAmut Cohort	
	Niraparib	Placebo	Niraparib	Placebo
Patients randomized	138 (100.0)	65 (100.0)	234 (100.0)	116 (100.0)
Received treatment	136 (98.6)	65 (100.0)	231 (98.7)	114 (98.3)
Discontinued study treatment	89 (64.5)	61 (93.8)	185 (79.1)	102 (87.9)
Adverse Events	17 (12.3)	1 (1.5)	33 (14.1)	2 (1.7)
Disease Progression	63 (45.7)	49 (75.4)	129 (55.1)	98 (84.5)
Risk to Subject	0	2 (3.1)	2 (<1)	0
Severe Non-compliance	0	0	2 (0.85)	0
Subject Request	8 (5.8)	8 (12.3)	11 (4.7)	1 (<1)
Pregnancy	0	0	0	0
Loss to follow-up	0	0	0	0
Other	1 (0.72)	1 (1.5)	8 (3.4)	1 (<1)
Ongoing treatment	47 (34.1)	4 (6.2)	46 (19.7)	12 (10.3)

Data analysis sets, n (%)	gBRCAmut Cohort		non-gBRCAmut Cohort			
			HRD-positive Cohort		Overall	
	Niraparib	Placebo	Niraparib	Placebo	Niraparib	Placebo
ITT population	138 (100.0)	65 (100.0)	106 (100.0)	56 (10.00)	234 (100.0)	116 (100.0)
Safety Population	136 (98.6)	65 (100.0)	106 (100.0)	56 (100.0)	231 (98.7)	114 (98.3)
Per Protocol Population	125 (90.6)	64 (98.5)	101 (95.3)	50 (89.3)	217 (92.7)	106 (91.4)

BRCA = breast cancer susceptibility gene; gBRCAmut = germline BRCA mutation; HRD = homologous recombination deficiency; ITT = intention-to-treat.

Data sources: Mirza et al. 2016,[2] EPAR 2017[5]

Protocol Deviations

Overall, 7% (n=36) of trial patients had a major protocol deviation and 7.6% (n=42) had minor protocol violations.[5] Most protocol deviations were related to failure to meet eligibility requirements. In the gBRCAmut cohort, there were more patients with at least one major protocol deviation in the niraparib group compared to the placebo group (niraparib: 8% [n=11]; placebo: 1.5% [n=1]). In the non-gBRCAmut cohort, major protocol deviations occurred with similar frequency in the treatment groups (niraparib: 6.8% [n=16]; placebo: 6.9% [n=8]). The low incidence of protocol deviations is unlikely to have impacted the results of efficacy analyses; the per-protocol analysis that was performed as a sensitivity analysis showed results consistent with the primary efficacy analysis. The major protocol deviations that occurred in the trial are summarized in Table 17.

Table 17: Summary of Major Protocol Deviations in the NOVA trial

Deviation	gBRCAmut Cohort (N=203)		Non-gBRCAmut Cohort (N=350)	
	Niraparib (N=138) n (%)	Placebo (N=65) n (%)	Niraparib (N=234) n (%)	Placebo (N=116) n (%)
Patients with at least 1 major protocol deviation	11 (8.0)	1 (1.5)	16 (6.8)	8 (6.9)
Failed to meet eligibility criteria	9 (6.5)	0	15 (6.4)	5 (4.3)
Inclusion 5a or 5b[a]	6 (4.3)	0	11 (4.7)	4 (3.4)
Inclusion 9a[b]	2 (1.4)	0	3 (1.3)	1 (0.9)
Exclusion 7[c]	1 (0.7)	0	0	0
Exclusion 9[d]	0	0	1 (0.4)	0
Dispensed incorrect study medication kit	1 (0.7)	0	0	2 (1.7)
Non-compliant (<80%) with study drug	1 (0.7)	0	1 (0.4)	1 (0.9)
Misallocated to cohort[e]	0	1 (1.5)	0	0

Abbreviations: ANC=absolute neutrophil count; BRCA=breast cancer susceptibility gene; gBRCAmut=germline BRCA mutation; ITT=intent-to-treat; non-gBRCAmut=without a germline BRCA mutation

[a] Inclusion criteria 5a: platinum-sensitive disease or 5b: no measurable lesion >2 cm at study entry not met (see Section 9.7.1.4 for any windows applied to the evaluation).

[b] Inclusion criterion 9a: ANC ≥1500/μL not met

[c] Exclusion criterion 7: other malignancy met

[d] Exclusion criterion 9: blood transfusion within 4 weeks met

[e] Randomized to gBRCAmut cohort; central analysis not mutation positive.

Data source: EPAR 2017[5]

e) Critical Appraisal: Limitations and Potential Sources of Bias

Overall, the NOVA trial was well conducted. It is the first phase III trial to demonstrate a statistically significant and clinically meaningful PFS benefit in patients with platinum-sensitive, recurrent ovarian cancer regardless of BRCA mutation 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 between the treatment groups had the potential to unmask patients assigned to the niraparib group. The extent to which spontaneous unblinding of patients and investigators occurred in the trial is unknown, but the possible influence of this on PROs should be considered.
- Potential differences in treatment response between patients in the gBRCAmut and non-gBRCAmut cohort were accounted for in the trial by randomizing the two cohorts independently and analyzing outcomes using hierarchical hypothesis testing. However, there were many predefined subgroup analyses and multiple secondary efficacy outcomes assessed in the trial 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 additional subgroups and outcomes, the results of these analyses should be interpreted as exploratory in nature.

- 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 on HRD status.
- Patients were considered platinum-sensitive in the trial if they had a CR or PR to their last platinum-based chemotherapy and had observable residual disease of less than 2 cm, 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 seven days. According to the CGP, these 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 response criteria between the trial and clinical practice may have implications in terms of external generalizability of the trial results.
- At the time of the primary efficacy analysis, the data on OS for the full trial population were at approximately 17% maturity and showed no statistically significant differences between treatment groups in the gBRCAmut cohort (HR=0.91; 95% CI, 0.36 to 2.28), the HRD positive non-gBRCAmut cohort (HR=1.39; 95% CI, 0.57 to 3.42), and the overall non-gBRCAmut cohort (HR=0.74; 95% CI, 0.45 to 1.20). The median OS had not been reached in any treatment group of any cohort, making the magnitude of long-term OS benefit unknown. The sponsor indicated that an update to the analysis of OS will be performed when a data maturity of 60% is achieved.[9] Although patient crossover upon disease progression was not permitted in the trial, longer term survival data will be confounded by the use of post-trial treatments, which was high in the trial.
- 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.

6.3.3 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The results for the primary and secondary efficacy outcomes of the NOVA trial are summarized in Table 18. As of the June 20, 2016 DBL, the median duration of follow-up in the ITT population was 16.9 months (gBRCAmut cohort: 16.4 months; non-gBRCAmut cohort: 17.5 months).[2]

Table 18: Summary of Efficacy Outcomes in the NOVA trial (ITT population)

Efficacy Outcome	gBRCAmut Cohort (n=203)		Non-gBRCAmut Cohort (n=350)			
			HRD-positive (n=162)		Overall (n=350)	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=234)	Placebo (n=116)
PFS						
Median (95% CI) in months[a]	21.0 (12.9 to NE)	5.5 (3.8 to 7.2)	12.9 (8.1 to 15.9)	3.8 (3.5 to 5.7)	9.3 (7.2 to 11.2)	3.9 (3.7 to 5.5)
Censored observations, n (%)	79 (57.2)	21 (32.3)	50 (47.2)	11 (19.6)	109 (46.6)	28 (24.1)
Event rate, n (%)	59 (42.8)	44 (67.7)	56 (52.8)	45 (80.4)	125 (53.4)	88 (75.9)
p-value[b]	<0.0001		<0.0001		<0.0001	
HR (95% CI)[c]	0.27 (0.17 to 0.41)		0.38 (0.24 to 0.59)		0.45 (0.34 to 0.61)	
Survival distribution function (95% CI)[d]						
6-months	0.80 (0.72 to 0.86)	0.43 (0.30 to 0.55)	0.69 (0.58 to 0.77)	0.35 (0.23 to 0.48)	0.61 (0.54 to 0.68)	0.36 (0.26 to 0.45)
12-months	0.62 (0.53 to 0.70)	0.16 (0.07 to 0.28)	0.51 (0.40 to 0.61)	0.13 (0.05 to 0.25)	0.41 (0.33 to 0.48)	0.14 (0.08 to 0.22)
18-months	0.50 (0.40 to 0.59)	0.16 (0.07 to 0.28)	0.37 (0.26 to 0.48)	0.09 (0.02 to 0.22)	0.30 (0.23 to 0.38)	0.12 (0.06 to 0.21)
24-months	0.42 (0.30 to 0.55)	0.16 (0.07 to 0.28)	0.31 (0.20 to 0.43)	0.09 (0.02 to 0.22)	0.27 (0.19 to 0.35)	0.12 (0.06 to 0.21)
OS						
Median (95% CI) in months[a]	NE (24.5 to NE)	NE (NE to NE)	NE (28.3 to NE)	NE (NE to NE)	NE (28.3 to NE)	NE (20.2 to NE)
Censored observations, n (%)	122 (88.4)	57 (87.7)	83 (78.3)	49 (87.5)	190 (81.2)	89 (76.7)
Event rate, n (%)	16 (11.6)	8 (12.3)	23 (21.7)	7 (12.5)	44 (18.8)	27 (23.3)
HR (95% CI)[c]	0.91 (0.36 to 2.28)		1.39 (0.57 to 3.42)		0.74 (0.45 to 1.20)	
CFI						
Median (95% CI) in months[a]	22.8 (17.9 to NE)	9.4 (7.9 to 10.6)	18.2 (14.2 to 24.3)	7.7 (6.3 to 10.6)	12.7 (11.0 to 14.7)	8.6 (6.9 to 10.0)
Censored observations, n (%)	84 (60.9)	23 (35.4)	58 (54.7)	15 (26.8)	104 (44.4)	35 (30.2)
Event rate, n (%)	54 (39.1)	42 (64.6)	48 (45.3)	41 (73.2)	130 (55.6)	81 (69.8)
HR (95% CI)[c]	0.26 (0.17 to 0.41)		0.31 (0.19 to 0.49)		0.50 (0.37 to 0.67)	
PFS-2						

Efficacy Outcome	gBRCAmut Cohort (n=203)		Non-gBRCAmut Cohort (n=350)			
			HRD-positive (n=162)		Overall (n=350)	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=234)	Placebo (n=116)
Median (95% CI) in months[a]	25.8 (20.3 to NE)	19.5 (13.3 to NE)	22.3 (18.6 to NE)	17.6 (12.9 to NE)	18.6 (16.2 to 21.7)	15.6 (13.2 to 20.9)
Censored observations, n (%)	99 (71.7)	40 (61.5)	68 (64.2)	33 (58.9)	132 (56.4)	60 (51.7)
Event rate, n (%)	39 (28.3)	25 (38.5)	38 (35.8)	23 (41.1)	102 (43.6)	56 (48.3)
HR (95% CI)[c]	0.48 (0.28 to 0.82)		0.65 (0.37 to 1.12)		0.69 (0.49 to 0.96)	
TFST						
Median (95% CI) in months[a]	21.0 (17.5 to NE)	8.4 (6.6 to 10.6)	15.9 (12.4 to NE)	6.0 (4.7 to 9.8)	11.8 (9.7 to 13.1)	7.2 (5.7 to 8.5)
Censored observations, n (%)	80 (58.0)	22 (33.8)	53 (50.0)	13 (23.2)	96 (41.0)	29 (25.0)
Event rate, n (%)	58 (42.0)	43 (66.2)	53 (50.0)	43 (76.8)	138 (59.0)	87 (75.0)
HR (95% CI)[c]	0.31 (0.21 to 0.48)		0.36 (0.23 to 0.57)		0.55 (0.41 to 0.72)	
TSST						
Median (95% CI) in months[a]	25.8 (22.4 to NE)	20.5 (16.0 to NE)	NE (20.3 to NE)	20.8 (15.4 to NE)	21.1 (18.5 to NE)	20.3 (15.1 to NE)
Censored observations, n (%)	105 (76.1)	42 (64.6)	75 (70.8)	37 (66.1)	149 (63.7)	67 (57.8)
Event rate, n (%)	33 (23.9)	23 (35.4)	31 (29.2)	19 (33.9)	85 (36.3)	49 (42.2)
HR (95% CI)[c]	0.48 (0.27 to 0.85)		0.66 (0.36 to 1.23)		0.74 (0.52 to 1.07)	

BRCA = breast cancer susceptibility gene; CFI = chemotherapy-free interval; CI = confidence interval; gBRCAmut = germline BRCA mutation; HR = hazard ratio; NE = not estimable; NR = not reported; OS = overall survival; PFS = progression-free survival; PFS-2 = progression-free survival on next line of therapy; SE = standard error; SD = standard deviation; TFST = time-to-first subsequent therapy; TSST = time-to-second subsequent therapy.

[a] Estimates from product-limit (Kaplan-Meier) method. Confidence intervals are from Brookmeyer and Crowley method with log-log transformation.
[b] Based on stratified log-rank test using randomization stratification factors.
[c] Niraparib versus placebo comparison based on stratified Cox Proportional Hazards Model using randomization stratification factor.
[d] Estimates from product-limit method. Confidence intervals constructed using log-log transformation.

Data sources: EPAR 2017[5], Clinical Study Report[7]

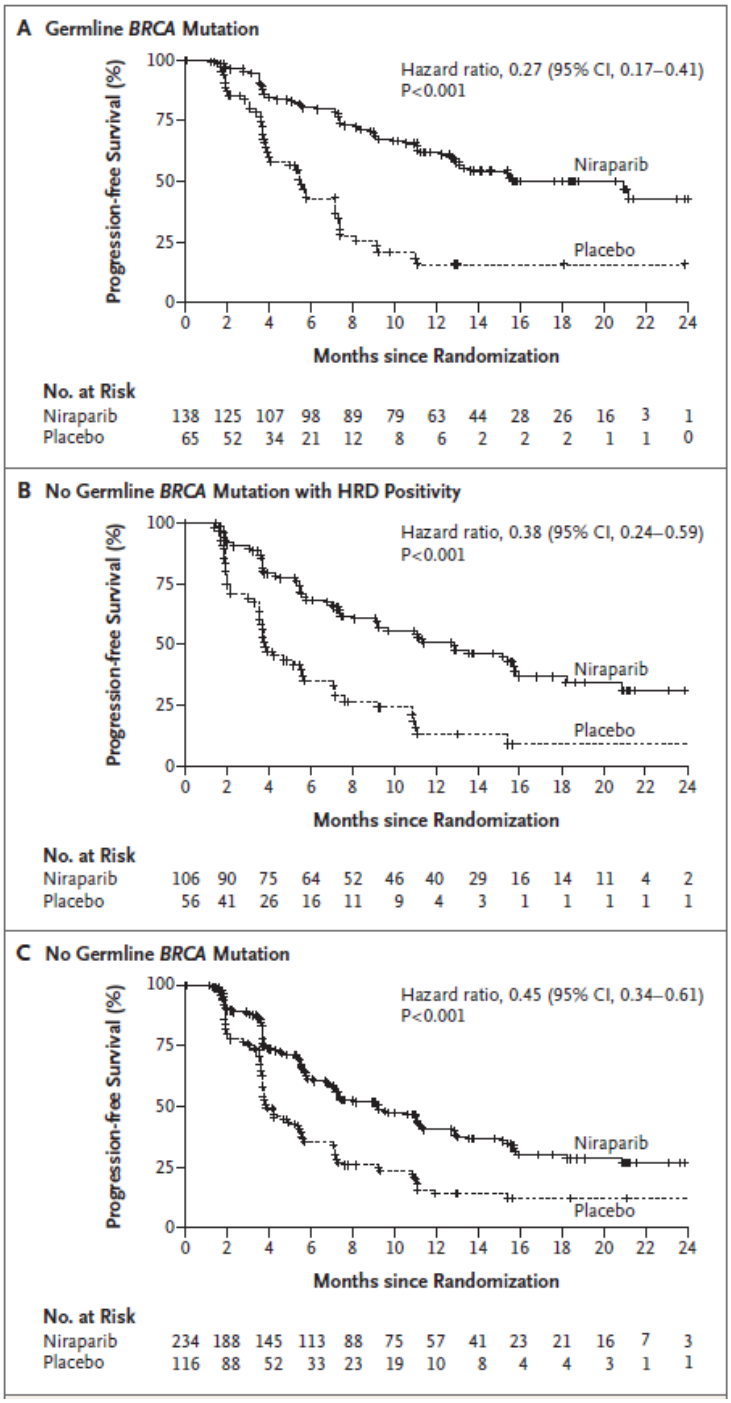
Primary Outcome: Progression-free Survival

At the time of DBL, a total of 316 PD events had occurred; there were 103 events in the gBRCAmut cohort and 213 events in the non-gBRCAmut cohort (101 of the 213 events were in the HRD-positive subgroup).[2] The PFS KM curves for the three primary efficacy patient populations are displayed in Figure 5. The NOVA trial met its primary endpoint, demonstrating a statistically significant longer duration of PFS in the niraparib group compared to the placebo group in all three primary efficacy populations.

In the gBRCAmut cohort, median PFS was 21.0 months in the niraparib group and 5.5 months in the placebo group, corresponding to an absolute median PFS benefit of 15.5 months in the niraparib group (HR: 0.27; 95% CI: 0.17 to 0.41; p <0.0001).[5] The estimated PFS at 6, 12, 18 and 24 months was greater in the niraparib group versus the placebo group at each time point (Table 18).[8]

In the HRD-positive non-gBRCAmut cohort, median PFS was 12.9 months in the niraparib group and 3.8 months in the placebo group, corresponding to an absolute median PFS benefit of 9.1 months (HR: 0.38; 95% CI: 0.24 to 0.59; p <0.0001).[5] In the overall non-gBRCAmut cohort, median PFS was 9.3 months in the niraparib group and 3.9 months in the placebo group, corresponding to an absolute median PFS benefit of 5.4 months (HR: 0.45; 95% CI, 0.34 to 0.61; p <0.0001).[5] For both patient populations (HRD-positive, non-gBRCAmut cohort and overall non-gBRCAmut cohort), estimates of PFS at 6, 12, 18 and 24 months were greater in the niraparib group versus the placebo group at each time point (Table 18).[8]

Figure 5: Kaplan–Meier Estimates of PFS in the NOVA trial



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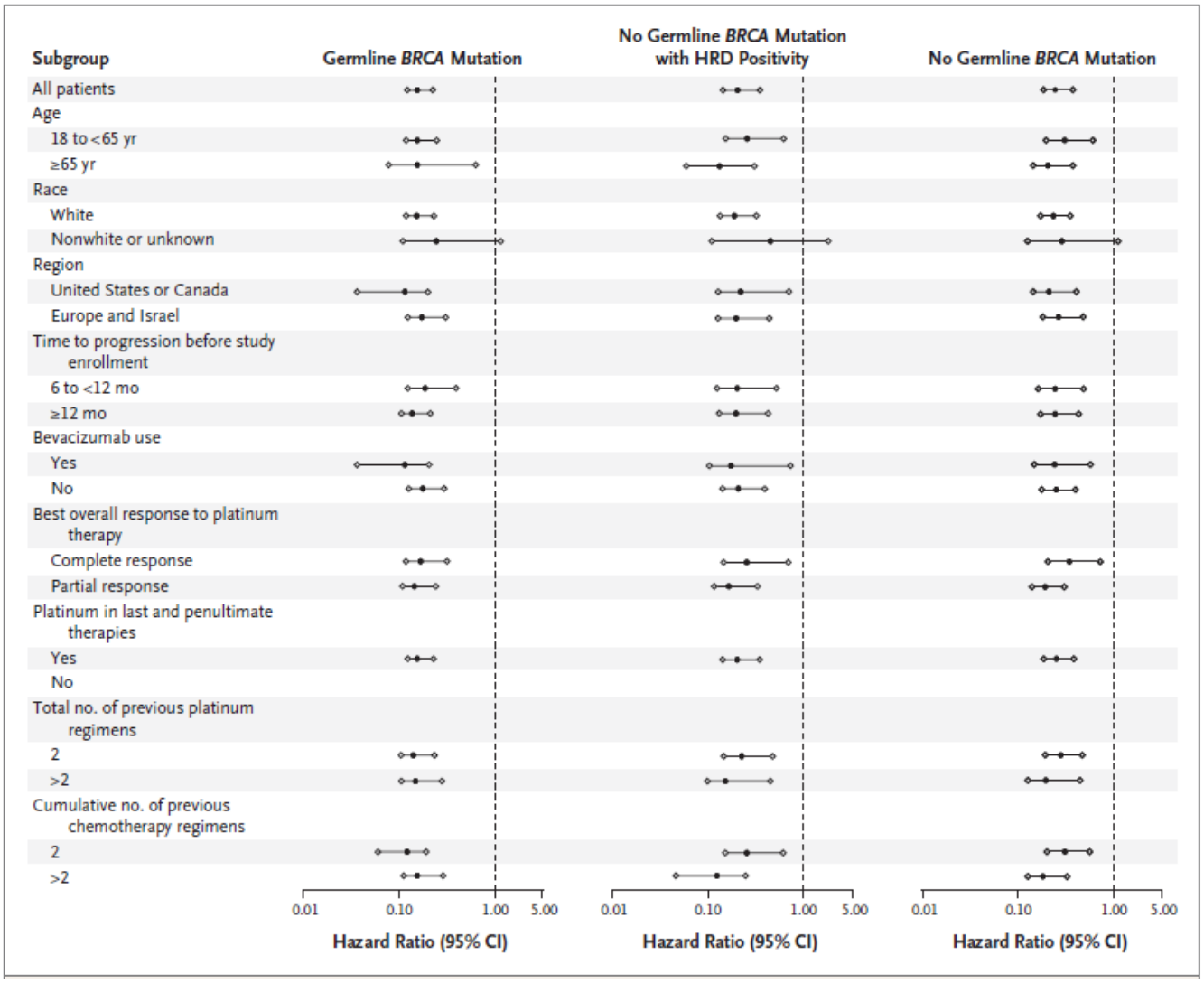
Progression-free Survival in Prespecified Subgroups

The results of prespecified subgroup analyses, based on baseline demographic and clinical characteristics, are presented in Figure 6 for the gBRCAmut cohort, the HRD-positive non-gBRCAmut cohort, and the overall non-gBRCAmut cohort.[2] The results of these analyses demonstrate that the treatment effect of niraparib was consistent within subgroups, showing a longer duration of PFS in the niraparib group compared to the placebo group except for the subgroup of 'nonwhite or unknown' race. In this subgroup, the treatment effect estimate 95% CI included the null value of 1 for all three patient populations (gBRCAmut cohort, HRD-positive non-gBRCAmut cohort, and overall non-gBRCAmut cohort), suggesting no difference in PFS between the treatment groups. None of the treatment by subgroup interaction tests were statistically significant ($p<0.10$).[7] Although prespecified, these subgroup analyses were not powered to detect statistically significant differences between treatment groups and the 'nonwhite or unknown' race subgroup may have been limited by small sample size.

Figure 6: Results of Prespecified Subgroup Analyses of PFS in the NOVA trial



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PFS was also evaluated in the following subgroups of the non-gBRCAmut cohort as exploratory analyses (Table 19): HRD-positive with sBRCAmut (niraparib: n=35; placebo: n=12), HRD-positive with BRCAwt (niraparib: n=71; placebo: n=44), and HRD-negative (niraparib: n=92; placebo: n=42).[5] These analyses were performed to explore whether treatment effect was driven by activity in patients with sBRCAmut. The results of these analyses were consistent with the primary efficacy analysis, showing a longer PFS in the niraparib group compared to the placebo group. Although prespecified, these subgroups analyses were not powered to detect statistically significant differences between treatment groups and were limited by small sample sizes in some subgroups.

Table 19: Prespecified Exploratory Analyses of PFS in the non-gBRCA cohort of the NOVA trial

PFS	Niraparib	Placebo
HRD-positive with sBRCAmut		
n	35	12
Median (95% CI) in months[a]	20.9 (9.7 to NE)	11.0 (2.0 to NE)
HR (95% CI)[b]	0.27 (0.08 to 0.90)	
HRD-positive with BRCAwt		
n	71	44
Median (95% CI) in months[a]	9.3 (5.8 to 15.4)	3.7 (3.3 to 5.6)
HR (95% CI)[b]	0.38 (0.23 to 0.63)	
HRD-negative		
n	92	42
Median (95% CI) in months[a]	6.9 (5.6 to 9.6)	3.8 (3.7 to 5.6)
HR (95% CI)[b]	0.58 (0.36 to 0.92)	

BRCA = breast cancer susceptibility gene; BRCAwt = BRCA-wild type; CI = confidence interval; gBRCAmut = germline BRCA mutation; HRD = homologous recombination deficiency; NE = not estimable; PFS = progression-free survival; sBRCAmut = somatic BRCA mutation.

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

[b] Niraparib versus placebo comparison based on stratified Cox Proportional Hazards Model using randomization stratification factor.

Data source: EPAR 2017[5]

Sensitivity Analyses

There were five sensitivity analyses performed to assess the robustness of the PFS results; these analyses considered different factors that included PFS by investigator assessment, PFS by IRC that was based on radiological assessment only, and analyzing receipt of subsequent anti-cancer treatment and treatment discontinuations as PD events in the analysis (refer to Section 6.3.2 for a more detailed description of these analyses). The results of these analyses in each of the three efficacy populations (gBRCAmut cohort, HRD-positive non-gBRCAmut cohort, and overall non-gBRCAmut cohort) were consistent with the primary efficacy analysis results, whereby there was a longer PFS in the niraparib group compared to the placebo group.[5]

Secondary Efficacy Outcomes

Overall Survival

At the time of the June 20, 2016 DBL the OS data were immature based on a total of 95 deaths (17% maturity) with data censored for over 75% of patients in both treatment groups.[5] The median OS was not estimable for either treatment group in the ITT population (HR=0.74; 95% CI, 0.45 to 1.20) nor in either treatment group of any of the three primary efficacy populations (Table 18). In the gBRCAmut cohort, 24 patients had died that included 16 deaths (12%) in the niraparib group and eight deaths (12%) in the placebo group for an HR (95% CI) of 0.91 (0.36 to 2.28). In the HRD-positive non-gBRCAmut cohort, 30 patients had died that included 23 deaths (22%) in the niraparib group and seven deaths (13%) in the placebo group for an HR (95% CI) of 1.39 (0.57 to 3.42).[7] In the overall non-gBRCAmut cohort, 71 patients had died that included 44 deaths (19%) in the niraparib group and 27 deaths (23%), in the placebo group for a HR (95% CI) of 0.74 (0.45 to 1.20).[5]

Other Secondary Outcomes

The detailed results for all of the secondary efficacy outcomes assessed in the trial (CFI, PFS-2, TFST, and TSST) are summarized in Table 18. Overall, the results for these outcomes were consistent with the primary efficacy analysis of PFS and showed treatment effect estimates that favoured niraparib compared to placebo.[5] The data for PFS-2 and TSST were considered immature at the time of DBL.

Patient Reported Outcomes – FOSI, EQ-5D-5L, CIPN

Patient completion rates for the FOSI and EQ-5D-5L questionnaires are shown in Table 20. Overall, scores for the FOSI and the EQ-5D-5L HUI questionnaires were similar between the niraparib and the placebo groups in both the gBRCAmut and the non-gBRCAmut cohorts at baseline, throughout the maintenance (treatment) period, and post-progression.[5] In both treatment groups of each cohort, completion rates were greater than 75% at all assessment timepoints up to Cycle 6; completion rates beyond this treatment cycle were not reported except for post-progression FOSI assessments. The results for the FOSI and EQ-5D-5L are displayed in Figure 7 by cohort, and details of these analyses are further described below.

Table 20: FOSI and EQ-5D-5L Questionnaire Completion Rates by Visit

Completed Questionnaires, n (%)	gBRCAmut		non-gBRCAmut	
	Niraparib	Placebo	Niraparib	Placebo
FOSI				
Baseline	134/138 (97.1)	62/65 (95.4)	228/234 (97.4)	113/116 (97.4)
Cycle 2	117/132 (88.6)	57/64 (89.1)	186/212 (87.7)	99/113 (87.6)
Cycle 4	113/120 (94.2)	45/54 (83.3)	155/181 (85.6)	79/95 (83.2)
Cycle 6	98/104 (94.2)	36/41 (87.8)	128/144 (88.9)	50/56 (89.3)
Post-progression	51/68 (75.0)	37/46 (80.4)	122/156 (77.6)	78/98 (79.6)
EQ-5D-5L				
Baseline	135/138 (97.8)	64/65 (98.5)	231/234 (98.7)	113/116 (97.4)
Cycle 2	118/132 (89.4)	60/64 (93.8)	189/212 (89.2)	99/113 (87.6)
Cycle 4	115/120 (95.8)	45/54 (83.3)	157/181 (86.7)	81/95 (85.3)
Cycle 6	99/104 (95.2)	36/41 (87.8)	129/144 (89.6)	51/56 (91.1)
Post-progression	NR	NR	NR	NR

BRCA = breast cancer susceptibility gene; EQ-5D-5L = European QOL 5-dimension 5-level questionnaire; FOSI= Functional Assessment of Cancer Therapy-Ovarian symptom index; gBRCAmut = germline BRCA mutation; NR = not reported.

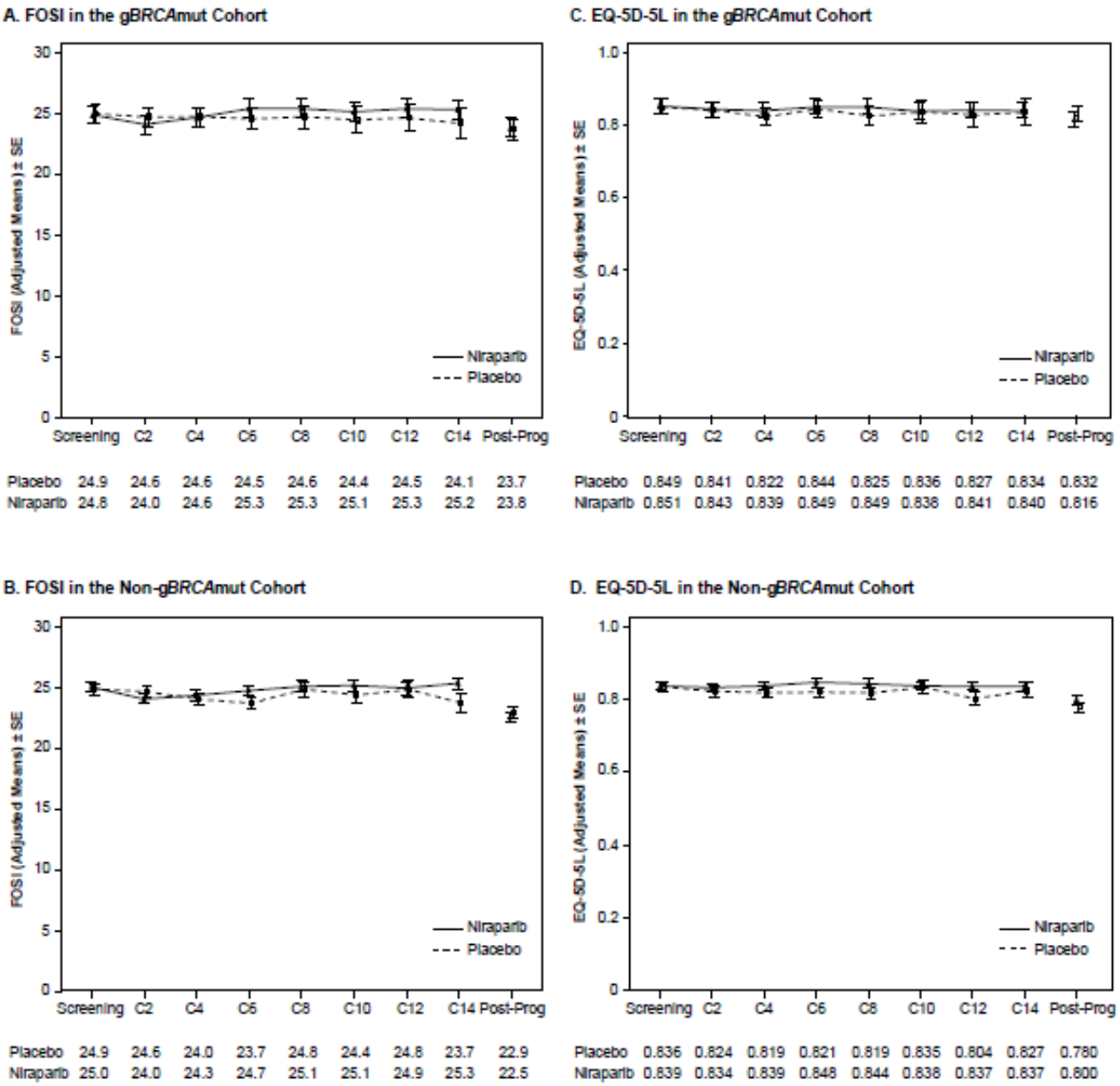
Data sources: Mirza et al. 2016,[2] Oza et al. 2018[8]

FOSI

At baseline, mean (SD) FOSI scores were similar between the niraparib and placebo treatment groups in both the gBRCAmut (niraparib: 25.1 [4.18]; placebo: 25.6 [3.84]) and the non-gBRCAmut cohorts (niraparib: 25.4 [3.92]; placebo: 25.0 [4.07]);[8] the most common symptoms reported by patients were lack of energy (79%, with 18% reporting severe symptoms), pain (44%), and nausea (22%). No differences in baseline symptoms were noted between patients who had a CR compared to a PR to their last platinum therapy.

Results for the individual FOSI subscales over time are shown in Figure 8.[8] Adjusted mean subscale scores were similar between the treatment groups throughout the trial during the maintenance (treatment) period and at post progression. At any timepoint there were no differences between the groups that met the MID (change in score of two to three points).[86] In the niraparib group, all symptoms except for nausea either remained stable or improved over treatment. Nausea increased at Cycle 2 but then decreased at later evaluation timepoints to near baseline levels. In the placebo group, approximately 20% of patients reported experiencing nausea. The KM curve for FOSI time-to-symptom worsening showed no difference between niraparib and placebo for the overall FOSI score.[7]

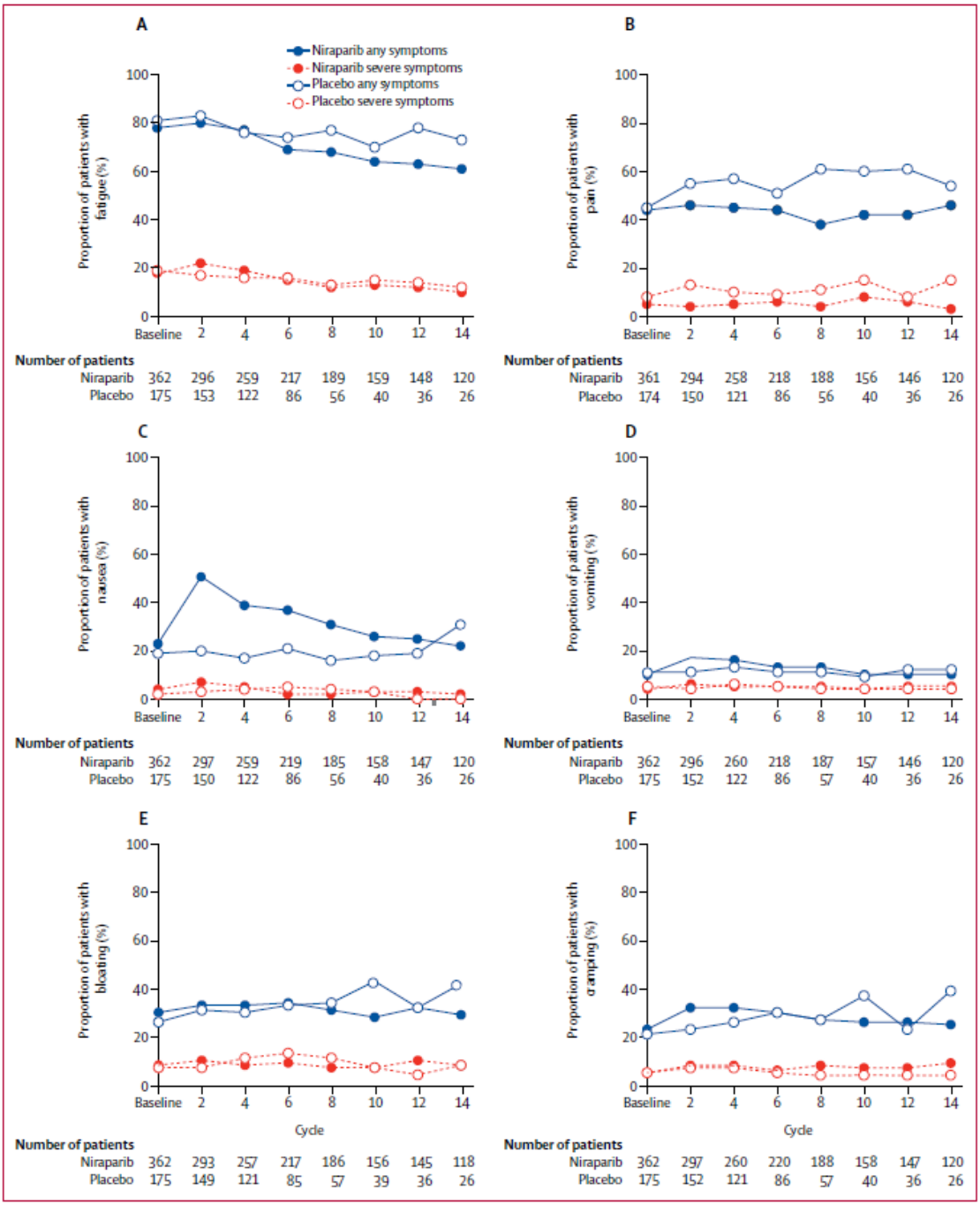
Figure 7: Adjusted FOSI Scores by Study Visit in the (A) gBRCAmut Cohort and (B) non-gBRCAmut Cohort; and EQ-5D-5L Scores in the (C) gBRCAmut Cohort and (D) non-gBRCAmut Cohort



Values displayed are adjusted means; a higher score indicates fewer symptoms. C denotes cycle, and post-prog denotes post progression.

Source: From The New England Journal of Medicine, Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer, Vol. no. 375, Issue No. 22, Supplement, Page No. 24. Copyright ©2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Figure 8: Individual FOSI Scores over time by Treatment Group in the NOVA trial



Symptoms include fatigue (A), pain (B), nausea (C), vomiting (D), bloating (E), and cramping (F)

Source: Reprinted from The Lancet Oncology, vol. 19 no. 8, Oza AM, Matulonis UA, Malander S, et al. Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOTOV16/NOVA): results from a double-blind, phase 3, randomised controlled trial, page no. 1122, Copyright (2018), with permission from Elsevier.[8]

EQ-5D-5L HUI

Mean EQ-5D-5L HUI scores were similar between the niraparib and placebo treatment groups in both the gBRCAmut (niraparib: 0.85; placebo: 0.85) and the non-gBRCAmut cohorts (niraparib: 0.84; placebo: 0.82)[8] at baseline, throughout the trial during the maintenance (treatment) period, and at post progression. After adjusting for histology, region, age, prior treatment type, duration of previous treatment, and baseline EQ-5D-5L score, the adjusted least squares mean HUI scores were also similar between the niraparib and placebo groups; any between group differences were less than the MID (0.08) when averaged across pre-progression timepoints (Table 21).

Table 21: Cross-sectional Adjusted EQ-5D-5L HUI Scores in the NOVA trial (US value set)

	Niraparib group	Placebo group
Germline BRCA mutation		
Patients, n	138	65
Baseline		
N	134	64
Mean	0·850 (0·0105)	0·847 (0·0163)
Adjusted least squares*	0·838 (0·0324)	0·834 (0·0365)
Preprogression†		
N	129	59
Mean	0·838 (0·0097)	0·834 (0·0173)
Adjusted least squares	0·812 (0·0257)	0·803 (0·0292)
Postprogression‡		
N	60	46
Mean	0·801 (0·0210)	0·794 (0·0178)
Adjusted least squares	0·851 (0·0541)	0·842 (0·0551)
No germline BRCA mutation		
Patients, n	234	116
Baseline		
N	227	112
Mean	0·837 (0·0078)	0·824 (0·0128)
Adjusted least squares*	0·870 (0·0215)	0·851 (0·0236)
Preprogression†		
N	208	97
Mean	0·833 (0·0077)	0·815 (0·0122)
Adjusted least squares	0·845 (0·0160)	0·828 (0·0175)
Postprogression‡		
N	139	94
Mean	0·810 (0·0119)	0·783 (0·0138)
Adjusted least squares	0·809 (0·0290)	0·788 (0·0308)

Data are mean (SE), unless otherwise specified. For each patient, a HUI value is determined from the health states with the use of the US value set.
EQ-5D-5L=European QOL 5-Dimension 5-Level questionnaire.
ITT=intention-to-treat. NA=not applicable. HUI=health utility index. *Means adjusted by histology, region, prior treatment, age, duration of prior treatment, and baseline EQ-5D-5L score. †Average of all postbaseline preprogression EQ-5D-5L HUI scores among all patients with disease progression. ‡First postprogression EQ-5D-5L HUI score among all patients with disease progression.

Source: Reprinted from The Lancet Oncology, vol. 19 no. 8, Oza AM, Matulonis UA, Malander S, et al. Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOTOV16/NOVA): results from a double-blind, phase 3, randomised controlled trial, page no. 1121, Copyright (2018), with permission from Elsevier. [8]

EQ-5D-5L VAS

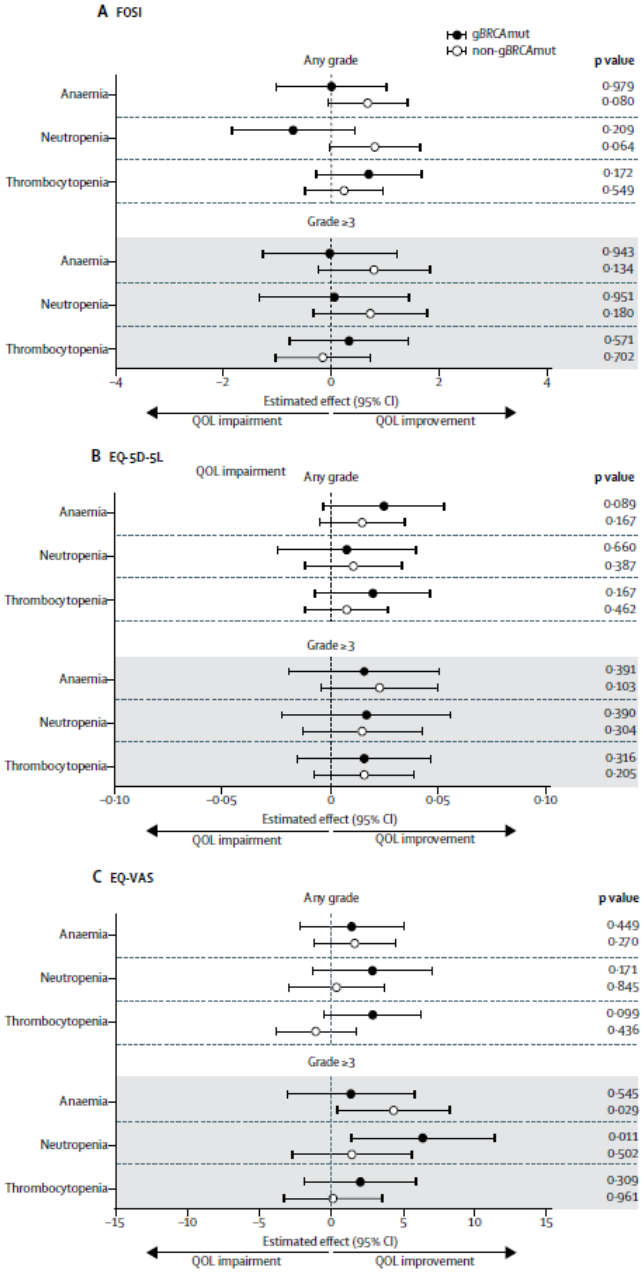
EQ-5D-5L VAS mean (SD) scores were similar between niraparib and placebo groups in both the gBRCAmut (niraparib: 74.6 [17.88]; placebo: 75.2 [16.29]) and the non-gBRCAmut cohort([niraparib: 75.2 [18.01]; placebo: 75.3 [18.22])[7] at baseline, throughout the study during the maintenance (treatment) period, and at post progression (MID not defined).

Analysis of Hematologic AEs on PRO Outcomes

The analysis performed to assess the relationship between hematologic AEs and response on the FOSI and EQ-5D-5L (HUI and VAS) scores demonstrated that hematological toxicity had no significant effect on scores in any of the cohorts for both the unadjusted

and adjusted FOSI models, or for disutility for the EQ-5D-5L HUI and VAS models (Figure 9).[8] The most common grade 3 or 4 AEs observed in patients receiving niraparib were thrombocytopenia in 34%, anemia in 25%, and neutropenia in 20% of patients.[8]

Figure 9: Adjusted Mixed Model Effects of AEs by Cohort in the NOVA trial



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CIPN

Neuropathy, which was measured by the degree of tingling or numbness in the feet and hands, was equivalent between treatment groups at baseline in both the gBRCAmut cohort (feet: 59% in the niraparib group versus 60% in the placebo group; hands: 80% versus 79%, respectively) and the non-gBRCAmut cohort (feet: 56% in the niraparib group versus 58% in the placebo group; hands: 76% versus 74%, respectively).[7] In the gBRCAmut cohort, the degree of neuropathy did not meaningfully change in either treatment group throughout the trial during the treatment (maintenance) period and at post-progression for either outcome (i.e., hands and feet); any between group differences were less than the MID (two to three points). In the gBRCAmut cohort, similar results were observed; however, at post-progression, a higher proportion of patients treated with niraparib had limited to no neuropathy in the feet compared to placebo (feet: 53% in the niraparib group versus 41% in the placebo group; hands: 62% versus 62%, respectively). It is unclear whether this difference met the MID.

Harms

Adverse Events

An overall summary of the incidence of TEAEs in the NOVA trial is provided in Table 22.[2,5] At least one TEAE occurred in all patients (100%) who received niraparib and in 95.5% of patients who received placebo; and any treatment-related TEAE occurred in 97.5% and 70.9% of patients, respectively. The incidence for all categories of TEAEs was higher in the niraparib group compared to the placebo group. No on-treatment deaths occurred in either treatment group; however, one patient in the niraparib group and two patients in the placebo group died from the MDS or AML during follow-up (one death in each group was assessed as treatment-related by the investigator).

Table 22: Summary of TEAEs in the NOVA trial (Safety Population)

Reported – n (%)	Niraparib (n=367)	Placebo (n=179)
Any TEAE	367 (100.0)	171 (95.5)
Any Related TEAE	358 (97.5)	127 (70.9)
Any CTCAE Grade ≥3 TEAE	272 (74.1)	41 (22.9)
Any Related CTCAE Grade ≥3 TEAE	237 (64.6)	8 (4.5)
Any Serious TEAE	110 (30.0)	27 (15.1)
Any Related Serious TEAE	62 (16.9)	2 (1.1)
Any TEAE Leading to Treatment Interruption	244 (66.5)	26 (14.5)
Any TEAE Leading to Dose Reduction	253 (68.9)	9 (5.0)
Any TEAE Leading to Treatment Discontinuation	54 (14.7)	4 (2.2)
Any TEAE Leading to Death	0	0

CTCAE =Common Terminology Criteria for Adverse Events; TEAE= treatment-emergent adverse event.

Data sources: Mirza et al. 2016,[2] EPAR 2017[5]

Table 23 provides a summary of the TEAEs occurring in at least 10% of patients in each treatment group of the NOVA trial.[2] The most common TEAEs of any grade that occurred in the niraparib group (versus the placebo group) were nausea (73.6% versus 35.2%), thrombocytopenia (61.3% versus 5.6%), fatigue (59.4% versus 41.3%), anemia (50.1% versus 6.7%), constipation (39.8% versus 20.1%), vomiting (34.3% versus 16.2%), and neutropenia (30.2% versus 6.1%). The most common grade 3 or 4 TEAEs in the niraparib group (versus the placebo group) were thrombocytopenia (33.8% versus 0.6%), anemia (25.3% versus 0%), neutropenia (19.6% versus 1.7%), fatigue (8.2% versus 0.6%), and hypertension (8.2% versus 2.2%).

Table 23: TEAEs occurring it at least 10% of Patients in the NOVA trial (Safety Population)

Event	Niraparib (N=367)		Placebo (N=179)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Nausea	270 (73.6)	11 (3.0)	63 (35.2)	2 (1.1)
Thrombocytopenia†	225 (61.3)	124 (33.8)	10 (5.6)	1 (0.6)
Fatigue‡	218 (59.4)	30 (8.2)	74 (41.3)	1 (0.6)
Anemia§	184 (50.1)	93 (25.3)	12 (6.7)	0
Constipation	146 (39.8)	2 (0.5)	36 (20.1)	1 (0.6)
Vomiting	126 (34.3)	7 (1.9)	29 (16.2)	1 (0.6)
Neutropenia¶	111 (30.2)	72 (19.6)	11 (6.1)	3 (1.7)
Headache	95 (25.9)	1 (0.3)	17 (9.5)	0
Decreased appetite	93 (25.3)	1 (0.3)	26 (14.5)	1 (0.6)
Insomnia	89 (24.3)	1 (0.3)	13 (7.3)	0
Abdominal pain	83 (22.6)	4 (1.1)	53 (29.6)	3 (1.7)
Dyspnea	71 (19.3)	4 (1.1)	15 (8.4)	2 (1.1)
Hypertension	71 (19.3)	30 (8.2)	8 (4.5)	4 (2.2)
Diarrhea	70 (19.1)	1 (0.3)	37 (20.7)	2 (1.1)
Dizziness	61 (16.6)	0	13 (7.3)	0
Cough	55 (15.0)	0	8 (4.5)	0
Back pain	49 (13.4)	2 (0.5)	21 (11.7)	0
Arthralgia	43 (11.7)	1 (0.3)	22 (12.3)	0
Dyspepsia	42 (11.4)	0	17 (9.5)	0
Nasopharyngitis	41 (11.2)	0	13 (7.3)	0
Urinary tract infection	38 (10.4)	3 (0.8)	11 (6.1)	2 (1.1)
Palpitations	38 (10.4)	0	3 (1.7)	0
Dysgeusia	37 (10.1)	0	7 (3.9)	0
Myalgia	30 (8.2)	1 (0.3)	18 (10.1)	0
Abdominal distention	28 (7.6)	0	22 (12.3)	1 (0.6)

* Listed are the adverse events of any grade that occurred in at least 10% of the patients in either study group, along with the corresponding incidence of grade 3 or 4 events. No grade 5 events were observed in either study group.
† The category of thrombocytopenia includes reports of thrombocytopenia and decreased platelet count.
‡ The category of fatigue includes reports of fatigue, asthenia, malaise, and lethargy.
§ The category of anemia includes reports of anemia and decreased hemoglobin count.
¶ The category of neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia.

Source: From The New England Journal of Medicine, Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer, Vol. no. 375, Issue No. 22, Page No. 2162. Copyright ©2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Adverse Events of Special Interest

The incidence of grade ≥ 3 TEAEs occurring in at least 5% of patients in either treatment group was 74.1% in in the niraparib group and 22.9% in the placebo group, of which most events were hematological laboratory abnormities (Table 24).[5] The most common grade ≥ 3 events were thrombocytopenia, occurring in 28.3% of patients in the niraparib group versus 0.6% in the placebo group, and anemia occurring in 24.8% of patients in the niraparib group and 0% in the placebo group.

The incidence of MDS/AML was similar in the treatment groups (1.4% versus 1.1%, respectively).[5] Most patients who developed MDS/AML had a prior history of myelosuppression (eight of nine patients), and had received other DNA damaging agents and radiotherapy.

Table 24: Grade 3/4 TEAE Reported in ≥5% of Patients in Either Treatment Group of the NOVA trial (Safety Population)

Event – n (%)	Niraparib (n=367)	Placebo (n=179)
Any CTCAE Grade 3 or 4 TEAE	272 (74.1)	41 (22.9)
Thrombocytopenia	104 (28.3)	1 (0.6)
Anaemia	91 (24.8)	0
Neutropenia	41 (11.2)	1 (0.6)
Neutrophil count decreased	32 (8.7)	2 (1.1)
Hypertension	30 (8.2)	4 (2.2)
Platelet count decreased	27 (7.4)	0
Fatigue	21 (5.7)	0

CTCAE = Common Terminology Criteria for Adverse Events and TEAE = Treatment-emergent adverse events.

Data Source: EPAR 2017[5]

The incidence of grade 3 or higher TEAEs decreased following a reduction in the dose of niraparib to 200 mg, with the exception of anemia and hypertension, which decreased at a dose of 100 mg (Table 25).[5] Most of the hematologic laboratory abnormalities occurred within the first three treatment cycles, after which the incidence of grade 3 or 4 thrombocytopenia, neutropenia, and fatigue was infrequent beyond the cycle following dose adjustments based on a patient's AE.[2]

Table 25: Grade 3/4 TEAEs Reported in ≥5% of Patients in the Niraparib Group by Dose at Onset of the AE (Safety Population)

Adverse Event – n (%)	Niraparib Dose		
	300 mg (n=367)	200 mg (n=254)	100 mg (n=128)
Thrombocytopenia	103 (28.1)	13 (5.1)	2 (1.6)
Anemia	55 (15.0)	40 (15.7)	8 (6.3)
Neutropenia	35 (9.5)	15 (5.9)	2 (1.6)
Neutrophil count decreased	31 (8.4)	6 (2.4)	0
Platelet count decreased	26 (7.1)	2 (0.8)	1 (0.8)
Hypertension	17 (4.6)	12 (4.7)	3 (2.3)
Fatigue	19 (5.2)	3 (1.2)	0

Data source: EPAR 2017[5]

At least one treatment interruption due to TEAEs occurred in 66.5% (n=244) of patients in the niraparib group and 14.5% (n=26) of patients in the placebo group; and at least one dose reduction due to TEAEs occurred in 68.9% (n=253) and 5.0% (n=9) of patients, respectively.[5] The majority of dose interruptions and dose reductions in the niraparib group were attributable to thrombocytopenia (30.8% and 30.5%, respectively) and anemia (19.6% and 17.7%, respectively).[3]

Treatment discontinuations attributable to TEAEs were also higher in the niraparib group at 14.7% (n=54) compared to 2.2% (n=4) in the placebo group.[2] Fatigue accounted for the majority of non-hematologic TEAEs leading to treatment discontinuation in the niraparib group at 2.7% (n=10) followed by nausea at 1.6% (n=6).[3] The treatment discontinuations due to myelosuppression TEAEs of any grade are summarized in Table 26. Thrombocytopenia accounted for the majority of hematologic TEAEs leading to treatment discontinuation at 3.3% (n=12).[2]

Table 26: Treatment Discontinuations due to Myelosuppression TEAEs of Any Grade in the NOVA trial (Safety Population)

Event — no (%)	Niraparib (N=367)	Placebo (N=179)
Thrombocytopenia[a]	12 (3.3)	1 (0.6)
Neutropenia[b]	7 (1.9)	0
Leukopenia[c]	7 (1.9)	0
Anemia[d]	5 (1.4)	0
Pancytopenia	3 (0.8)	0

[a]Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; [b]Neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia; [c]Leukopenia includes reports of neutropenia, neutrophil count decrease, white blood cell count decreased, leukopenia, lymphocyte count decreased, lymphopenia, febrile neutropenia, and monocyte count decreased; [d]Anemia includes reports of anemia and decreased hemoglobin counts.

Source: From The New England Journal of Medicine, Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer, Vol. no. 375, Issue No. 22, Supplement, Page No. 26. Copyright ©2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2]

Exploratory analyses based on baseline body weight and platelet count are presented in Table 27. These data show that the incidence of TEAEs during the first 30 days of the first dose of niraparib were higher in every category in patients with low body weight or platelet count when compared to patients with a higher weight and platelet count at baseline. [3]

Table 27: Summary of TEAEs within 30 Days of First Dose by Baseline Body Weight and Platelet Count in the NOVA trial (Safety Population)

TEAE – n (%)	≥ 77 kg and ≥150, 000/µL (n=85)	< 77 kg and <150, 000/µL (n=280)
Any TEAE with CTCAE toxicity Grade ≥ 3	27 (31.8)	139 (49.6)
Any related TEAE with CTCAE toxicity Grade ≥ 3	23 (27.1)	128 (45.7)
Any serious TEAE	1 (1.2)	46 (16.4)
Any related serious TEAE	1 (1.2)	41 (4.6)
Any TEAE leading to dose reduction	24 (28.2)	134 (47.9)
Any TEAE leading to dose interruption	27 (31.8)	137 (48.9)
Any TEAE leading to treatment discontinuation	1 (1.2)	16 (5.7)
Any TEAE leading to death	0	0
Grade 3/4 thrombocytopenia event	10 (11.8)	97 (34.6)
Grade 3/4 anemia event	1 (1.2)	7 (2.5)
Grade 3/4 neutropenia event	7 (8.2)	41 (14.6)

CTCAE = Common Terminology Criteria for Adverse Events and TEAE = Treatment-emergent adverse events.

Data source: pCODR Submission[3]

Subsequent Cancer Treatments Received Post-Progression

A summary of the most common (> 10% of patients in any treatment group) subsequent cancer treatments that patients received after disease progression in the NOVA trial is provided in Table 28.[87] [redacted] was the most common anti-cancer therapy received post-progression, followed by [redacted]. In the gBRCAmut cohort, [redacted] of patients received any subsequent anti-cancer therapy during trial follow-up in the niraparib and placebo groups, respectively. In the HRD-positive non-gBRCAmut cohort, [redacted] of patients received any subsequent anti-cancer therapy in the niraparib group and placebo groups, respectively; and in the overall non-gBRCAmut cohort there were [redacted] of patients, respectively. Of note, a total of [redacted] trial patients received [redacted] as subsequent treatment post-progression. All but [redacted] of these patients were in the gBRCAmut cohort, where [redacted] of patients in the niraparib and placebo groups, respectively, received [redacted] as post-trial treatment after disease progression. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the CADTH Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 28: Most Common (> 10% of patients) Subsequent Anti-cancer Treatments Received by Patients After Disease Progression in the NOVA trial (ITT Population)[87]

Anticancer Therapy, n (%)	gBRCAmut Cohort (n=203)		Non-gBRCAmut cohort (n=350)			
			HRD-positive (n=162)		Overall (n=350)	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=106)	Placebo (n=56)	Niraparib (n=234)	Placebo (n=116)
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

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

BRCA = breast cancer susceptibility gene; gBRCAmut = germline BRCA mutation; HRD = homologous recombination deficiency.

Data source: GlaxoSmithKline Inc Checkpoint Responses 2020[87]

6.4 Ongoing Trials

Table 29: Ongoing trials of niraparib in adult patients with platinum-sensitive, recurrent ovarian cancer

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: NORA NCT03705156 **Characteristics:** Phase III, double-blind, randomized (2:1) placebo-controlled trial n = 265[74] **Setting:** 27 sites in China **Patient Enrolment Start Date:** June 8, 2017 **Data cut-off:** Estimated primary completion date – April 15, 2021 **Sponsor** Zai Lab (Shanghai) Co., Ltd.	**Key Inclusion Criteria:** Female patients ≥ 18 years of age • High-grade serous or dominantly high-grade serous ovarian cancer • Prior receipt of two lines of platinum-containing chemotherapy with a CR or PR after the first-line platinum-containing chemotherapy, and receipt of at least 4 cycles of platinum-containing chemotherapy (must be carboplatin, cisplatin, or nedaplatin) in second line • ECOG PS 0-1 **Key Exclusion Criteria:** • Having undergone ascites drainage with the last two cycles of the last chemotherapy regimen • Symptomatic uncontrolled brain metastasis • Diagnosis of previous or current MDS or AML	**Intervention:** Niraparib (200 or 300 mg based on patient's weight) **Comparator:** Placebo (matched dose to niraparib (2 or 3 capsules)	**Primary:** • PFS **Secondary:** • CFI • TFST • OS

AML = acute myeloid leukemia; CFI = Chemotherapy-free interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MDS = myelodysplastic syndrome; PFS = Progression free survival; OS = Overall survival; TFST = Time to first subsequent therapy.

Data source: Clinicaltrials.gov[75]

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 female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy:

- Summary and critical appraisal of sponsor-submitted ITC/ NMA comparing niraparib with olaparib for the maintenance treatment of female adult patients with platinum-sensitive, recurrent ovarian cancer and a gBRCAmut [10]

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

7.1 Summary and Critical Appraisal of Sponsor-submitted ITC/NMA comparing Niraparib with Olaparib for the Maintenance Treatment of Female Adult Patients with Platinum-sensitive, Recurrent Ovarian Cancer and a gBRCAmut

7.1.1 Objective

Olaparib is currently an approved treatment in Canada for patients with platinum-sensitive, recurrent ovarian cancer and a BRCA mutation (somatic or germline). Accordingly, PAG has requested comparative data on niraparib to olaparib in these patients; however, the systematic review performed by CADTH (refer to section 6) did not identify any trials that directly compared niraparib to olaparib.

In the absence of a direct head-to-head comparison of niraparib and olaparib, the sponsor submitted evidence to CADTH from two ITCs, both available from conference proceedings, that compared niraparib to two different doses of olaparib in two different patient populations with platinum-sensitive relapsed ovarian cancer (300 mg twice daily in patients with gBRCAmut cancer[12] and 400 mg twice daily in patients with non-gBRCAmut cancer[11]). Both ITCs were conducted by the sponsor of olaparib. As these two ITCs remain unpublished in full in the peer-reviewed literature, a full critical appraisal of these reports was not possible; therefore, a summary of the methods and results of these analyses are summarized in Section 8. The CADTH Methods Team identified a third ITC/NMA conducted by the sponsor of niraparib for their submission to the NICE, which CADTH requested to review for this submission. This ITC/NMA, which was provided to CADTH as an unpublished report, compares olaparib to niraparib in patients with platinum-sensitive, recurrent ovarian cancer with a gBRCAmut.

The objective of this section is to summarize and critically appraise the methods and findings of the sponsor-submitted ITC/NMA[10] (originally submitted to NICE) comparing niraparib with olaparib for the maintenance treatment of female adult patients with platinum-sensitive, recurrent ovarian cancer and a gBRCAmut.

7.1.2 Findings

Methods

Systematic Review

The objective of the sponsor-submitted ITC/NMA[10] was to estimate the comparative efficacy and safety of niraparib to olaparib as maintenance therapy in patients with platinum-sensitive, recurrent ovarian cancer and a gBRCAmut. The ITC/NMA was based on a systematic literature review, in which the following databases were searched from inception to August 14, 2017: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The reference lists of included studies were also screened for additional relevant studies. The inclusion criteria of the SLR is provided in Table 30.

Table 30: Inclusion Criteria for the Systematic Literature Review

Criteria	Description
Population	• females 18 years or older • undergoing treatment for ovarian cancer, fallopian tube cancer, and primary peritoneal cancer • at least one recurrence of disease • platinum sensitive • in response (complete or partial) to chemotherapy with a platinum-based agent • germline BRCA mutation
Interventions	Maintenance therapy with one of the following: • niraparib • olaparib
Comparators	• Any comparator • Placebo
Outcomes	Primary outcome of interest: • PFS Secondary outcomes of interest: • discontinuations due AEs hematological AEs
Study Design	RCTs

AE = adverse event; BRCA = breast cancer susceptibility gene; gBRCAmut = germline BRCA mutation; PFS = progression-free survival; RCT = randomized controlled trials.

Data source: Sponsor-Submitted ITC/NMA[10]

All abstracts and proceedings identified by the literature search were screened for eligibility. Potentially eligible studies underwent a full-text article screen. Data were extracted from all eligible studies in duplicate. The quality of the included studies was assessed using The Cochrane Collaboration's Risk of Bias Tool. All screening, data extraction, and risk of bias assessments were performed by two independent reviewers; and a third reviewer was used to resolve any discrepancies between the two reviewers after reconciliation.

Indirect Treatment Comparison/Network Meta-Analysis

Feasibility Assessment

An assessment was conducted to determine the feasibility and appropriateness of performing an ITC/NMA with the eligible trials, which included: 1) a determination of whether the evidence for the interventions of interest formed one evidence network and 2) an assessment of the distribution of study and patient characteristics of included studies, as any imbalances between studies in characteristics known to be treatment effect modifiers may bias indirect treatment comparisons.

Analysis

Individual studies that formed part of one evidence network and were deemed sufficiently similar in terms of patient populations and outcomes of interest were included in the ITC/NMA according to a Bayesian framework using methods described in the NICE Decision Support Unit.[90]

The primary outcome of the ITC/NMA was PFS. Survival data for time-to-event outcomes were modeled using the methods of Ouwens et al., 2011 and Jansen (2011),[91,92] which do not assume constant proportional hazards. The report did not state whether or not the proportional hazards assumption was met in these analyses. The approach uses parametric survival functions or fractional polynomials, and the difference in these parameters are synthesized (and indirectly compared) across studies. Thus, treatment effects are represented by multiple parameters rather than a single parameter. Multiple survival distributions for PFS were considered and included the following: Weibull, Gompertz, and second order fractional polynomials including p_1= 0 or 1 and p_2= 0 or 1. For relative treatment effects in the 2nd order fractional polynomial framework, models were assessed based on the following

assumptions: 1) treatment only had an impact on two of the three parameters describing the hazard function over time (i.e. one scale and one shape parameter) and 2) treatment had an impact on all three parameters describing the hazard function over time (i.e. one scale and two shape parameters). Normal non-informative priors were used for all parameters (mean of 0 and a variance of 10,000).

The secondary outcomes of interest were hematological AEs and treatment discontinuations due to AEs. The analyses of AEs were performed using the full trial populations from all three trials irrespective of gBRCAmut status. These binary outcomes were analyzed based on the proportion of patients who experienced the event of interest using a regression model with a binomial likelihood and logit link. Normal non-informative prior distributions were used with a mean of 0 and a variance of 10 000 to estimate study and treatment effect parameters.

While both fixed and random-effects models were considered for analyses, the authors stated that there were often insufficient data to estimate between-study heterogeneity. In cases where there were sufficient data (all three trials were included in the evidence network), it was possible to use a random effects model; however, the authors' noted that the heterogeneity parameter may be unstable and poorly estimated. Consequently, only analyses using fixed effects models were performed.

The deviance information criterion (DIC) was used to compare the goodness-of-fit of competing survival models and was used to inform model selection. The model with the better trade-off between fit (of the model to data) and parsimony (fewer parameters) has a lower DIC and was preferred by the analysts; a difference in DIC between models of approximately five points was considered clinically meaningful. The plausibility of the obtained HR was also considered. A Markov Chains Monte Carlo method was used to estimate model parameters in OpenBUGS version 3.2.3 in R version 3.4.0. A first series of iterations from the OpenBUGS sampler were used as a burn-in and inferences were based on additional iterations using two chains.

The results of the ITC/NMA were presented as relative treatment effect estimates. The posterior distributions of relative treatment effects were summarized by calculating the median and 95% credible intervals (CrIs) which were constructed from the 2.5th and 97.5th percentiles of the posterior distributions. For binary outcomes, treatment effect estimates were presented as relative risks (RRs); and for time-to-event outcomes based on KM curves, treatment effect estimates were presented as HRs and survival estimates at three-month intervals with plots presented up to 24 months.

Results

Systematic Review

The SLR identified 450 citations based on the database search; of these, four citations representing three unique RCTs met the inclusion criteria and were included in the ITC/NMA: NOVA /ENGOT-OV16/, SOLO2/ENGOT-OV21, and Study 19. All three trials were double-blind, placebo-controlled, multi-centre, international trials. Two were phase III (ENGOT-OV16/NOVA and SOLO2/ENGOT-OV21) and the other was a phase II trial (Study 19). The NOVA /ENGOT-OV16 trial evaluated niraparib at a dose of 300 mg daily, SOLO2/ENGOT-OV21 evaluated olaparib (tablets) at a dose of 300 mg twice daily, and Study 19 evaluated olaparib (capsules) at a dose of 400 mg twice daily. The characteristics of the three RCTs are summarized in Table 31 (patient characteristics) and Table 32 (prior treatment). The authors acknowledged that differences in dosages (i.e. olaparib 300 mg or olaparib 400 mg), study phase (i.e. phase II or phase III trials), and follow-up durations (ranged from 15 months in Study 19 to 24 months in the NOVA and SOLO2 trials) between the included trials could be sources of heterogeneity across the trials.

All three trials included female patients who were 18 years of age or older with high-grade serous ovarian cancer or fallopian tube cancer that was platinum-sensitive (defined as having a CR or PR after completion of the last round of platinum therapy). The two olaparib trials only included patients with BRCA mutations; therefore, only those patients from the NOVA trial with a gBRCAmut were included in the ITC/NMA. In each trial, most patients had a tumour located in the ovaries (>80%), an ECOG PS of 0 (range, 65.9 to 83.8%), and had greater than 12 months time elapse from their previous platinum chemotherapy to disease progression (range, 58.1% to 62.2%). The median age of trial patients ranged from 55 to 58 years in the two trials reporting these data. In terms of prior treatment, the majority of patients had two or more prior lines of chemotherapy and in two trials some patients had prior bevacizumab therapy (range, 16.8% to 26.2%). Approximately half of the trial patients had achieved a complete response. The results of the authors' risk of bias assessment were presented and showed all three trials were appraised as having a low risk of bias on most of the domains of the Cochrane Risk of Bias Tool with the exception of the NOVA trial, which had 'unclear risk' for the domains of sequence generation and allocation concealment.

In terms of efficacy outcomes, the authors reported that PFS data were available from all three trials (as an HR and KM curves); NOVA/ENGOT-OV16 and SOLO2/ENGOT-OV21 trials provided PFS data for a follow-up period of 24 months, and Study 19 provided PFS data for over 15 months. For Study 19, a secondary publication that provided longer follow-up data (five years) from the trial was excluded from the ITC/NMA, as it did not provide data on PFS. No information was provided in the ITC/NMA report on outcome definitions, methods of outcome assessment (i.e. whether PFS was investigator or independent central review), or the frequency of outcome assessment in each trial. The efficacy results for PFS are summarized in Table 33.

In terms of safety outcomes, the authors stated that there was common reporting across the trials for the following AEs: nausea, abdominal pain, fatigue, anemia, neutropenia, and thrombocytopenia. Data on treatment discontinuation due to AEs were also available. The AE outcomes of the individual trials are summarized in Table 34.

Table 31: Baseline Characteristics of Patients in RCTs included in the ITC/NMA

Trial	Treatment	Patients, n	Age, median	ECOG PS, %			Primary tumour site, %				Objective response to most recent platinum-based regimen, %		Time-to-disease progression after previous platinum therapy, %	
				0	1	2	Fallopian tube	Ovary	Peritoneum	Fallopian tube or peritoneal	CR	PR	≥6 to ≤12 months	>12 months
NOVA/ ENGOT-OV16 [a]	Niraparib	138	57	65.9	34.1	-	6.5	88.4	5.1	-	51.4	48.6	39.1	60.9
	Placebo	65	58	73.8	26.2	-	9.2	81.5	9.2	-	50.8	49.2	40.0	60.0
Study 19[a]	Olaparib	74	57.5	83.8	14.9	0.0	-	87.8	-	12.2	48.6	51.4	37.8	62.2
	Placebo	62	55.0	72.6	24.2	1.6	-	87.1	-	12.9	54.8	45.2	41.9	58.1
SOLO2 / ENGOT-OV21	Olaparib	196	-	82.7	16.3	-	-	83.7	-	15.8	46.4	53.6	40.3	59.7
	Placebo	99	-	77.8	22.2	-	-	86.9	-	13.1	47.5	52.5	40.4	59.6

CR = complete response; gBRCAmut = germline BRCA mutation; ECOG PS = Eastern Cooperative Oncology Group performance status; PR = partial response.

[a] Data represent the subgroup of patients with gBRCAmut.

Data source: Sponsor-Submitted ITC/NMA[10]

Table 32: Prior Lines of Treatment of Patients in RCTs included in the ITC/NMA

Trial	Treatment	Patients, n	Prior bevacizumab therapy, %	Lines of prior chemotherapy, %			
				1	2	3	≥3
NOVA / ENGOT-OV16 [a]	Niraparib	138	23.9	0.7	50.7	-	48.6
	Placebo	65	26.2	0.0	46.2	-	53.8
Study 19[a]	Olaparib	74	-	0.0	35.1	37.8	64.9
	Placebo	62	-	0.0	45.2	29.0	54.8
SOLO2 / ENGOT-OV21	Olaparib	196	16.8	0.0	56.1	30.6	43.4
	Placebo	99	20.2	0.0	62.6	20.2	37.4

[a] Data represent the subgroup of patients with gBRCAmut.

Data source: Sponsor-Submitted ITC/NMA[10]

Table 33: PFS Results from Individual RCTs included in the ITC/NMA

Trial	Treatment	PFS, median (months)	Follow-up, median (months)
NOVA / ENGOT-OV16 [a]	Niraparib	21.0	16.9
	Placebo	5.5	
Study 19[a]	Olaparib	11.2	Over 15 months
	Placebo	4.3	
SOLO2 / ENGOT-OV21	Olaparib	19.1	22.1
	Placebo	5.5	22.2

PFS = progression-free survival.

[a] Data represent the subgroup of patients with gBRCAmut.

Data source: Sponsor-Submitted ITC/NMA[10]

Table 34: AE Data from Individual RCTs included in the ITC/NMA

Outcome	Study	Niraparib	Placebo	Olaparib
Discontinuations				
Discontinuation due to adverse events	NOVA / ENGOT-OV16	54/367 (14.7%)	4/179 (2.2%)	-
	SOLO2 / ENGOT-OV21	-	2/99 (2%)	21/195 (10.8%)
	Study 19	-	2/128 (1.6%)	7/136 (5.1%)
Hematologic events (overall)				
Anemia	NOVA / ENGOT-OV16	184/367 (50.1%)	12/179 (6.7%)	-
	SOLO2 / ENGOT-OV21	-	8/99 (8.1%)	85/195 (43.6%)
	Study 19	-	7/128 (5.5%)	29/136 (21.3%)
Neutropenia	NOVA / ENGOT-OV16	111/367 (30.2%)	11/179 (6.1%)	-
	SOLO2 / ENGOT-OV21	-	6/99 (6.1%)	38/195 (19.5%)
	Study 19	-	5/128 (3.9%)	7/136 (5.1%)
Thrombocytopenia	NOVA / ENGOT-OV16	225/367 (61.3%)	10/179 (5.6%)	-
	SOLO2 / ENGOT-OV21	-	3/99 (3%)	27/195 (13.8%)
	Study 19	-	-	-
Hematologic events (grades 3/4)				
Anemia	NOVA / ENGOT-OV16	93/367 (25.3%)	0/179 (0%)	-

Outcome	Study	Niraparib	Placebo	Olaparib
	SOLO2 / ENGOT-OV21	-	2/99 (2%)	38/195 (19.5%)
Neutropenia	NOVA / ENGOT-OV16	72/367 (19.6%)	3/179 (1.7%)	--
	SOLO2 / ENGOT-OV21	-	4/99 (4%)	10/195 (5.1%)
Thrombocytopenia	NOVA / ENGOT-OV16	124/367 (33.8%)	1/179 (0.6%)	-
	SOLO2 / ENGOT-OV21	-	1/99 (1%)	2/195 (1%)

Data Source: Sponsor-Submitted ITC/NMA[10]

Progression-free Survival

Three separate ITCs were performed based on the different doses of olaparib: 1) niraparib 300mg daily compared to olaparib 300 mg twice daily; 2) niraparib 300mg daily compared to olaparib 400 mg twice daily; and 3) niraparib 300mg daily compared to pooled data from the two olaparib trials. A sensitivity analysis NMA was also performed that combined the olaparib trials but considered the two doses as distinct treatments.

The overall evidence network, irrespective of dosage and outcomes of interest, is depicted in Figure 10. In all analyses, the best fitting models (according to the DICs) were the 2nd order fractional polynomial model with both powers equal to zero.

Figure 10: Evidence Network

Data source: Sponsor-Submitted ITC/NMA[10]

Analysis of niraparib 300 mg versus olaparib 300 mg: The evidence network for the analysis of niraparib 300 mg daily versus olaparib 300 mg twice daily is depicted in Figure 11. Two trials (NOVA and SOLO2) were included in the network. Data for PFS were available for 24 months for each of the two trials included in the NMA. The results of the ITC (estimated HRs and survival for each treatment at each timepoint) are summarized in Table 35.

Figure 11: Evidence Network for PFS - Niraparib 300 mg daily versus Olaparib 300 mg twice daily

Data source: Sponsor-Submitted ITC/NMA[10]

The results for PFS showed that both niraparib and olaparib were favoured over placebo up until the [redacted] (HR range: [redacted] for niraparib compared to placebo; [redacted] for olaparib compared to placebo). For the comparison of niraparib versus olaparib 300 mg, neither active treatment was favoured over each other at any timepoint throughout the follow-up period. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the CADTH Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 35: Estimates of Survival and Hazard Ratios from Fixed-effects ITC of PFS; Niraparib 300 mg daily versus Olaparib 300 mg twice daily

	Placebo (No Treatment)	Niraparib 300 mg QD		Olaparib 300 mg BID		Niraparib 300 mg QD versus olaparib 300 mg BID
Month	Survival	Survival	HR (CrI)	Survival	HR (CrI)	HR (CrI)
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

BID = twice daily; CrI = Credible interval; HR = Hazards ratio; QD = daily.

Modelled using second order fractional polynomials with p_1=0 and p_2=0.
All bolded values favour active treatment over placebo.

Data source: Sponsor-Submitted ITC/NMA[10]

Analysis of niraparib 300 mg versus olaparib 400 mg: The evidence network for the analysis of niraparib 300 mg daily versus olaparib 400 mg twice daily is depicted in Figure 12. Two trials were included in the network (NOVA and Study 19). Data for PFS were available for 24 months for niraparib and for 15 months for olaparib. The results of the ITC are summarized in Table 36.

Figure 12: Evidence Network for PFS - Niraparib 300 mg daily versus Olaparib 400 mg twice daily

Data source: Sponsor-Submitted ITC/NMA[10]

The results for PFS showed that niraparib was favoured over placebo up until the [redacted] timepoint (HR range: [redacted]), and olaparib was favoured over placebo up until the [redacted] timepoint (HR range: [redacted]). For the comparison of niraparib versus olaparib 400 mg, neither active treatment was favoured over each other at any point throughout the follow-up period. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the CADTH Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.*)

Table 36: Estimates of Survival and HRs from Fixed-effects ITC of PFS - Niraparib 300 mg daily versus Olaparib 400 mg twice daily

	Placebo (No Treatment)	Niraparib 300 mg QD		Olaparib 400 mg BID		Niraparib 300 mg QD versus olaparib 400 mg BID
Month	Survival	Survival	HR (CrI)	Survival	HR (CrI)	HR (CrI)
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

BID = twice daily; CrI = Credible interval; HR = Hazards ratio; QD = daily.

Modelled using second order fractional polynomials with p_1=0 and p_2=0.
All bolded values favour active treatment over placebo.
Data Source: Sponsor-Submitted ITC/NMA[10]

Analysis of niraparib 300 mg versus olaparib pooled data: The evidence network for the analysis of niraparib 300 mg daily versus pooled olaparib data is depicted in Figure 13. Three trials were included in the network (NOVA, SOLO2, and Study 19). The results of the ITC are summarized in Table 37 and showed that niraparib was favoured over placebo up until the [redacted] timepoint (HR range: [redacted]), and olaparib was favoured over placebo up until the [redacted] timepoint (HR range: [redacted]). For the comparison of niraparib to olaparib, neither active treatment was favoured over each other at any point throughout the follow-up period. The estimates of survival and hazard ratios for the pooled olaparib data led to HR values that were intermediate between the HR estimates obtained from the ITCs of niraparib compared to olaparib 300 mg and 400 mg. (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the CADTH Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.*)

Figure 13: Evidence Network for PFS - Niraparib 300 mg daily versus Pooled Olaparib Data

Data source: Sponsor-Submitted ITC/NMA[10]

Table 37: Estimates of Survival and HRs from Fixed-effects ITC of PFS - Niraparib 300 mg daily versus Olaparib Pooled Data

	Placebo (No Treatment)	Niraparib 300 mg QD		Olaparib pooled data		Niraparib 300 mg qd versus pooled olaparib data
Month	Survival	Survival	HR (CrI)	Survival	HR (CrI)	HR (CrI)
3						
6						
9						
12						
15						
18						
21						
24						

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

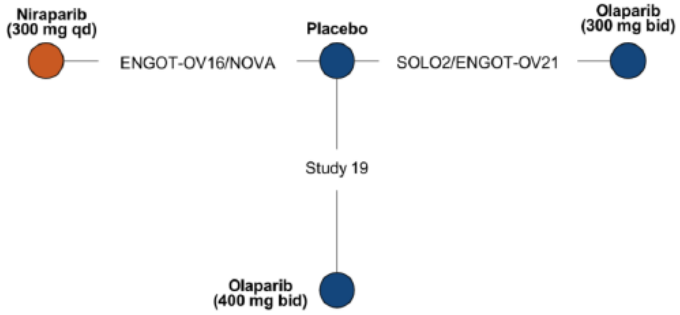
BID = twice daily; CrI = Credible interval; HR = Hazards ratio; QD = daily.

Modelled using second order fractional polynomials with p_1=0 and p_2=0.
All bolded values favour active treatment over placebo.

Data Source: Sponsor-Submitted ITC/NMA[10]

Sensitivity Analysis of niraparib 300 mg versus olaparib 300 mg versus olaparib 400 mg: The evidence network for the sensitivity analysis of niraparib 300 mg daily versus olaparib 300 mg twice daily versus olaparib 400 mg twice daily is depicted in Figure 14. This analysis included both olaparib trials but considered them as separate treatments to allow for comparison of both doses simultaneously. As there was only one trial per dose, results of the sensitivity analysis were similar to results of the analyses of each dose separately. Results of the NMA for the sensitivity analysis are summarized in Table 38 and showed that niraparib 300 mg was favoured over placebo up until the [redacted] timepoint (HR range: [redacted]), olaparib 300 mg was favoured over placebo up until the [redacted] timepoint (HR range: [redacted]), and olaparib 400 mg was favoured over placebo up until the [redacted] timepoint (HR range: [redacted]). No comparisons were made between the active treatments in the sensitivity analysis. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the CADTH Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Figure 14: Evidence Network for PFS Sensitivity Analyses - Niraparib 300 mg daily versus Olaparib 300 mg twice daily versus Olaparib 400 mg twice daily (as separate treatments)



Data source: Sponsor-Submitted ITC/NMA[10]

Table 38: HRs from Fixed-effects NMA of PFS Sensitivity Analyses - Niraparib 300 mg daily versus Olaparib 300 mg twice daily versus Olaparib 400 mg twice daily

Month	Niraparib 300 mg QD	Olaparib 400 mg BID	Olaparib 300 mg BID
	HR (CrI)	HR (CrI)	HR (CrI)
3	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]

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

BID = twice daily; CrI = credible interval; HR = hazards ratio; QD = daily.
Modelled using second order fractional polynomials with p_1=0 and p_2=0.
All bolded values favour active treatment over placebo.

Data source: Sponsor-Submitted ITC/NMA[10]

Adverse Events

The results of the NMA for safety outcomes are summarized in Table 39. The relative risk (RR) of experiencing hematological events (all grade; and grades 3/4) was higher for niraparib compared to placebo (RR range: [redacted]) for each AE evaluated (anemia, neutropenia, and thrombocytopenia). For the comparison of olaparib to placebo, the RR of experiencing hematological events of all grades was higher for olaparib for all three AEs (RR range: [redacted]). For grade 3/4 hematological events, the RR for experiencing anemia was higher for olaparib compared to placebo (RR=[redacted]) but not for neutropenia or thrombocytopenia. For the comparison of niraparib to olaparib, there was no difference in risk of experiencing hematological events of all grades. The risk of grade 3/4 hematological events was lower for olaparib compared to niraparib for neutropenia (RR=[redacted]) and for thrombocytopenia (RR=[redacted]). *(Non-disclosable information was used in this CADTH Guidance Report and the*

sponsor requested this clinical information not be disclosed pursuant to the CADTH Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

When compared to placebo, discontinuations due to AEs occurred more frequently for both niraparib (RR=[redacted]) and olaparib (RR=[redacted]); and neither active treatment group had a higher risk of treatment discontinuations due to AEs compared to each other (Table 39). *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the CADTH Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Table 39: Relative Risk of Hematologic AEs from Fixed-effects NMA models

Outcome	Niraparib versus Placebo	Olaparib versus Placebo	Olaparib versus Niraparib
	RR (CrI)	RR (CrI)	RR (CrI)
Discontinuations			
Discontinuation due to adverse events	[redacted]	[redacted]	[redacted]
Hematologic events (All grade)			
Anemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Hematologic events (grade 3/4)			
Anemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]

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

BID = twice daily; CrI = credible interval; QD = daily; RR = relative risk.

For comparisons with placebo, all bolded suggest a higher risk of adverse events with active treatment. For comparisons between olaparib and niraparib, bolded values less than 1.0 suggest a lower risk of adverse events with olaparib.

Data Source: Sponsor-Submitted ITC/NMA[10]

Critical Appraisal of Indirect Treatment Comparison / Network Meta-Analysis

The sponsor submitted ITC/NMA was critically appraised according to recommendations of the International Society for Pharmacoeconomics and Outcomes Research Task Force on Indirect Treatment Comparisons and Network Meta-Analyses.[93] Details of the quality appraisal are provided in Table 40.

The key limitations of the ITC/NMA include the small size and structure of the network, which had no closed loop, and potential sources of heterogeneity across the trials related to differences in patient and study characteristics. These limitations resulted in imprecision of estimates and uncertainty around the long-term extrapolation of fitted models. These limitations are summarized below.

The ITC/NMA was based on a SLR that identified studies according to prespecified inclusion criteria. The literature search appeared comprehensive but was performed in 2017; therefore, there is a possibility that recent eligible evidence may not be included in the NMA. The authors' risk of bias assessments concluded that all three trials were appraised as having a low risk of bias on most of the domains of the Cochrane Risk of Bias Tool, with the exception of the NOVA trial which had 'unclear risk' for the domains of sequence generation and allocation concealment. Overall, the outcomes assessed were appropriate; however, other important outcomes, including OS, HRQoL, and AEs leading to dose reductions or dose interruptions, were not considered despite the availability of evidence for some of these outcomes (HRQoL, and AEs leading to dose reductions and interruptions). Based on the NMA report, it is

unclear whether the outcomes assessed in the included trials were similar with respect to the definitions used and assessment methods (i.e. investigator versus centrally assessed). The authors also did not report the criteria of the trials used to determine response (complete or partial) to chemotherapy. Any differences in outcome assessment and the criteria used for chemotherapy response across included studies may be a source of heterogeneity between studies and have the potential to influence (bias) relative treatment effect estimates. There were other differences in study characteristics across the trials that may also be potential sources of heterogeneity; these included study design (phase III versus phase II), variability in the duration of patient follow-up (ranged from 15 months in Study 19 to 24 months in the NOVA and SOLO2), and the different doses and formulations of olaparib (300 mg tablets versus 400 mg capsules). The authors noted that longer follow-up data were available for Study 19 but not for the outcome of PFS. To address the possibility that dose may be a treatment effect modifier, and to account for the differences in durations of follow-up, the authors performed multiple ITCs comparing niraparib to each olaparib dose (300 mg and 400 mg) and irrespective of dose (pooled olaparib data). A sensitivity analysis was also performed that compared niraparib to both doses of olaparib analyzed as different treatments in the same network. Results of the sensitivity analysis were similar to results of the analyses of each dose separately, whereby the active treatments (niraparib and olaparib) were each favoured over placebo for the first few months of follow up, but not over each other. No information was provided on the treatment exposure of patients in each trial.

Overall, based on the reporting of the ITC/NMAs, the characteristics of included patients in the three trials appeared similar in terms of the distributions of patients by age, primary tumour site, time-to-disease progression after previous platinum therapy, and type of response (complete versus partial) to their most recent platinum-based regimen. However, some sources of clinical heterogeneity were noted, including differences in ECOG PS status, the number of prior lines of chemotherapy, and experience with bevacizumab. The baseline performance status of patients in SOLO2 and Study 19 trials of olaparib appeared better (% of patients ECOG PS 0 ranged from 72.6% to 83.8%) compared to that of patients in the NOVA trial (ECOG PS 0 ranged from 65.9% to 73.8%). Study 19 included a more heavily pretreated patient population (majority of patients had received three or more lines of chemotherapy (olaparib: 64.9% and placebo: 54.8%) and prior exposure to bevacizumab was not reported. Information on other important baseline characteristics were also unknown due to missing information for all or some trials (i.e., median age and tumour histology). No information was provided describing the standard of care provided to patients in the trials. Despite these differences, the authors' stated that the feasibility assessment that was performed concluded that patient and study characteristics of included trials were homogenous. The authors stated that the main limitation of the NMA was the small size of the evidence network, which did not permit the use of a random effects analysis model to account for heterogeneity or the use of meta-regression techniques to adjust for the influence of potential treatment effect modifiers. Therefore, the NMA results may be affected by differences in study and patient characteristics across the trials, and the direction of this potential bias is difficult to determine in light of missing information and imbalances in factors that bias in different directions.

The NMA was restricted to patients with a gBRCAmut. The SOLO2 trial only recruited patients with a gBRCAmut, while the NOVA trial randomized and analyzed patients with a gBRCAmut as a separate subgroup from patients who were categorized into the non-gBRCAmut cohort. However, in Study 19, the BRCA status of patients was not part of the original study design and mutation status was determined retrospectively. Therefore, the gBRCAmut patients from this trial comprise a post-hoc subgroup where within study randomization was not preserved, which can introduce bias into the NMA if any imbalances in patient characteristics exist between treatment groups.

The available trials formed a network with no closed loop; therefore, it was not possible to validate the transitivity assumption of NMA and check for consistency of results between direct and indirect comparisons. As previously noted, there was variation in the duration of follow-up across the included studies. The authors stated that follow-up data in the NOVA and SOLO2 trials were available for up to 24 months in these trials; however, 24 months reflects the maximum follow-up in these trials. The median follow-up was 16.9 months for the gBRCAmut cohort of the NOVA trial.[2] The median follow-up in the SOLO2 trial was 22.1 months for the olaparib group and 22.2 months for the placebo group.[34] The NMA results for PFS at later time points (i.e. 18 to 24 months) produced imprecise estimates (HRs with wide CrIs), which reflects the influence of patient attrition at these later time points and uncertainty in the extrapolation of survival. Given this uncertainty, the estimates at later time-points should be interpreted with caution.

Overall, the ITC/NMA results can be considered generalizable to the Canadian context since one of the included doses of olaparib (300 mg) is approved for use in Canada for the same patient population and separate analyses were performed according to dose.

Table 40: Summary of Critical Appraisal of Sponsor-submitted ITC/NMA using ISPOR criteria

ISPOR Questions	Details and Comments
1. Is the population relevant?	Yes, partially. The population is relevant to the patient population of the submission and specifically to the Canadian context. However, the indication for this review is not limited to germline BRCA mutated patients, which is the patient population of the olaparib trials and therefore does not address non-BRCA mutated patients.
2. Are any critical interventions missing?	No. The ITC/NMA included all relevant interventions for this patient population.
3. Are any relevant outcomes missing?	Yes. The ITC/NMA reported outcomes for PFS and AEs. Other important outcomes such as OS, HRQoL, and AEs leading to dose interruptions or dose reductions were not included.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Overall, the ITC/NMA results can be considered to be generalizable to the Canadian context since one of the included doses of olaparib (300 mg) is approved for use in Canada for the same patient population and separate analyses were performed according to dose.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	The researchers performed a SLR with prespecified PICO criteria to identify relevant trials. The ITC/NMA report described the information sources searched and the search strategies used. However, the literature search was performed in 2017; therefore, the results may be outdated, and recent trials may not have been included.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	The included trials formed a connected network; however, there was no closed loop available to evaluate consistency of direct and indirect evidence.
7. Is it apparent that poor quality studies were included thereby leading to bias?	The quality of the included studies was evaluated using the Cochrane Risk of Bias tool. The authors stated that the included trials had a low risk of bias.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Selective outcome reporting was evaluated as part of the risk of bias assessment and no selective outcome reporting was found for each included trial.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	The distributions of patients for most patient and study characteristics that were reported on (e.g., age, ECOG PS, primary tumour site, time to disease progression after previous platinum therapy, and objective response to most recent platinum-based regimen) were similar between the included studies; however, some differences were noted (e.g. follow-up time, prior lines of therapy, ECOG PS). There was also missing information for other characteristics (i.e. median age and histology); therefore, it is difficult to identify all potential sources of clinical heterogeneity. The ITC/NMA report did not provide a summary of the eligibility criteria used in each trial.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Yes. Different doses of olaparib were identified as potential treatment effect modifiers. The two doses were analyzed separately and as a pooled treatment in the sensitivity analysis. Due to the small size of the network, the authors reported that it was not possible to investigate the effect of imbalances in other potential effect modifiers.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Within-study randomization may not have been preserved for Study 19 given that the subgroup of patients that was included in the analysis from this study was defined post-hoc and was not based on a stratification factor (i.e. for patients with a gBRCAmut versus no gBRCAmut).
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Not applicable.

ISPOR Questions	Details and Comments
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	No. The authors reported that due to the small size of the network, it was not possible to statistically adjust for imbalances in potential treatment effect modifiers.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	The authors stated that both fixed and random-effects models were considered; however, an insufficient number of trials were available in each network to achieve stable estimates of between-study heterogeneity. Accordingly, only the fixed-effects analysis results were presented.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	Not applicable.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Evidence network diagrams were presented for the analyses of PFS. No networks diagrams were provided for the analyses of AEs.
19. Are the individual study results reported?	Individual study results were reported.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	No.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	No.
23. Is the impact of important patient characteristics on treatment effects reported?	No.
24. Are the conclusions fair and balanced?	Yes. The conclusions were fair and balanced. The authors concluded that results of the ITC/NMA demonstrated that niraparib appeared to be a favourable alternative for maintenance therapy in patients with platinum-sensitive, recurrent ovarian cancer and a gBRCAmut. Accordingly, PFS was improved with niraparib 300 mg daily relative to placebo and was comparable to olaparib 300 mg twice daily and 400 mg twice daily doses. The authors acknowledged that both therapies were associated with some hematological adverse events. They also reported limitations of the analyses such as the small network, which limited the assessment of potential effect modifiers.
25. Were there any potential conflicts of interest?	No conflict of interest information was reported; however, the ITC/NMA was commissioned by the sponsor.
26. If yes, were steps taken to address these?	No.

7.3 Summary

The CADTH review team identified an ITC/NMA conducted by the sponsor of niraparib for their submission to the NICE, which CADTH requested to review for this submission. The ITC/NMA was provided to CADTH as an unpublished report and compared olaparib to niraparib in patients with platinum-sensitive, recurrent ovarian cancer with a gBRCAmut. A systematic literature search identified three trials that met the eligibility criteria and were included in the ITC/NMA; the trials evaluated the following treatments, all compared to placebo: niraparib 300 mg daily, olaparib 300 mg twice daily, and olaparib 400 mg twice daily. Results of the ITC/NMA suggested that all active treatments were favoured over placebo for the efficacy outcome of PFS, however none of the active treatments were favoured over each other. Compared to patients treated with olaparib, patients treated with niraparib had a higher relative risk for grade 3/4 events of both neutropenia and thrombocytopenia. Results of the analyses for AEs suggested that both niraparib and olaparib had higher risk for treatment discontinuations due to AEs compared to placebo, but not over each other. The key limitations of the ITC/NMA include the small size and structure of the evidence network, which had no closed loop (therefore it was not possible to check for consistency of results between direct and indirect comparisons), and potential sources of heterogeneity across the trials related to differences in patient and study characteristics. The results of the ITC/NMA should be interpreted with consideration of these limitations.

8 Comparison with Other Literature

Two ITCs were included as part of the submission to CADTH and informed the PE model. Both ITCs were available as conference proceedings and their results remain unpublished in full in the peer-reviewed literature. These conference sources lacked important information on patient populations and methodology that is required to perform a thorough critical appraisal. As such, the available information from these reports has been summarized along with any potential limitations that could be identified.

1. Comparative efficacy and safety of olaparib 400 mg and Niraparib 300 mg as maintenance treatment after response to chemotherapy in patients with platinum-sensitive relapsed non-gBRCAmut ovarian cancer (available as conference poster)[11]

Objective:

The objective of this ITC was to compare the efficacy and safety of niraparib and olaparib as maintenance treatment after response to chemotherapy in patients with platinum-sensitive relapsed non-gBRCAmut ovarian cancer.

Methods:

This ITC compared niraparib 300 mg daily to olaparib 400mg twice daily as maintenance treatment after response to chemotherapy in patients with platinum-sensitive relapsed non-gBRCAmut ovarian cancer. A SLR was conducted of the following databases to identify relevant literature according to pre-defined eligibility criteria: Embase®, MEDLINE®, and COCHRANE (specific databases not specified). The ITC was performed in WinBUGS version 1.4.3 using Bayesian fixed model. The following efficacy outcomes were analyzed: investigator-assessed PFS, IRC-assessed PFS, and TFST. The following safety outcomes were analyzed: grade 3 or 4 AEs, and AEs leading to treatment discontinuation, dose interruption, or dose reduction (ITT data from the NOVA trial were used for safety outcomes as these data were not available by gBRCAmut status).

Results:

Two studies were identified that met the inclusion criteria for the ITC: NOVA and Study 19. A Bayesian ITC was performed to compare the two treatments using data from the NOVA trial for niraparib and Study 19 for olaparib. The analyses were restricted to patients who had non-gBRCAmut ovarian cancer. Baseline characteristics were reported as similar between the studies, with the exception of a higher proportion of patients in Study 19 who had an ECOG PS of 0 (versus 1) compared to NOVA, and a higher proportion of patients in NOVA who achieved a CR to the most recent chemotherapy compared to Study 19. For all efficacy outcomes analyzed, no differences in treatment effect were found between olaparib and niraparib: investigator-assessed PFS (HR= 0.94; 95% CrI, 0.54 to 1.65), IRC-assessed PFS (HR=1.25; 95% CrI, 0.67 to 2.30), and TFST (HR=0.78; 95% CrI, 0.47 to 1.30). For the analysis of safety outcomes, olaparib was favoured over niraparib, demonstrating lower odds of grade 3 or 4 AEs (OR=0.28; 95% CrI, 0.12 to 0.72) and AEs leading to dose interruption (OR=0.15; 95% CI, 0.04 to 0.59). Neither treatment was favoured over the other for the odds of AEs leading to discontinuation or dose reduction.

Limitations:

While the NOVA trial randomized and analyzed patients with non-gBRCAmut cancer separately from those with gBRCAmut cancer, this was not done in Study 19. As Study 19 included patients with and without BRCA mutations, if only those patients with a non-gBRCAmut were analyzed in this ITC and BRCA was not a stratification variable, randomization may not be maintained for the subgroup analysis. Additionally, the data for TFST in Study 19 was conducted as a post-hoc analysis, as no progression data based on RECIST were collected after the primary analysis of PFS.

2. Comparative efficacy and safety of olaparib 300 mg tablets and niraparib 300 mg tablets as maintenance treatment after response to chemotherapy in patients with platinum-sensitive relapsed gBRCAmut ovarian cancer (available as conference abstract)[12]

Objective:

The objective of this ITC was to compare the efficacy and safety of niraparib and olaparib as maintenance treatment after response to chemotherapy in patients with platinum-sensitive relapsed gBRCAmut ovarian cancer.

Methods:

This ITC compared niraparib 300 mg once daily to olaparib 300mg twice daily as maintenance treatment after response to chemotherapy in patients with platinum-sensitive relapsed gBRCAmut ovarian cancer. Analyses were restricted to patients who had gBRCAmut ovarian cancer. The following efficacy outcomes were analyzed: investigator-assessed PFS, IRC-assessed PFS, and TFST. The following safety outcomes were analyzed: grade ≥3 AE, and AEs leading to discontinuation, dose interruption, or dose reduction.

Results:

Two studies were included in the ITC: NOVA and SOLO2. A Bayesian ITC was performed to compare the two treatments using data from the NOVA trial for niraparib and the SOLO2 trial for olaparib. For all efficacy outcomes analyzed, no differences in treatment effect were found between olaparib and niraparib: investigator-assessed PFS (HR=1.11; 95% CrI, 0.67 to 1.83), IRC-assessed PFS (HR=0.93; 95% CrI, 0.53 to 1.61, and TFST (HR: 0.90; 95% CrI, 0.54 to 1.49). For the safety analyses, olaparib was favoured over niraparib, demonstrating lower odds of any grade ≥3 AE (OR=0.18; 95% CrI, 0.07 to 0.47), AEs leading to dose interruption (OR=0.30; 95% CrI, 0.11 to 0.79), and AEs leading to dose reduction (OR=0.13; 95% CrI, 0.02 to 0.85). Neither treatment was favoured over the other for odds of AEs leading to discontinuation.

Limitations:

None identified.

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 (Zejula) for ovarian cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

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

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Reviews - Cochrane Central Register of Controlled Trials January 2020**, Embase** 1974 to 2020 February 24**, Ovid MEDLINE(R)**

ALL 1946 to February 24, 2020

#	Search Strategy
1	(zejula* or niraparib* or MK 4827 or MK4827 or HMC2H89N35 or 195Q483UZD or 75KE12AY9U or L4JFC1PHCI).ti,ab,ot,kf,kw,hw,rn,nm.
2	1 use cctr
3	1 use medall
4	limit 3 to english
5	2 or 4
6	*niraparib/
7	(zejula* or niraparib* or MK 4827 or MK4827).ti,ab,kw,dq.
8	6 or 7
9	8 use oemezd
10	limit 8 to english
11	10 not conference abstract.pt.
12	5 or 11
13	remove duplicates from 12
14	10 and conference abstract.pt.
15	limit 14 to yr="2015-Current"
16	13 or 15

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Search Strategy
#3	Search: **#1 AND #2**
#2	Search: **publisher[sb]**
#1	Search: **zejula*[tiab] OR niraparib*[tiab] OR MK 4827[tiab] OR MK4827[tiab] OR HMC2H89N35[rn] OR 195Q483UZD[rn] OR 75KE12AY9U[rn] OR L4JFC1PHCI[rn] OR niraparib [Supplementary Concept]**

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

4. Grey literature search via:

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

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

Search: Zejula (niraparib)/ovarian, fallopian tube or peritoneal 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, fallopian tube or peritoneal 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, fallopian tube or peritoneal cancer — last five years

Literature Search Methods

The literature search for clinical studies was performed by an information specialist from the CADTH 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).[94]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. 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 concept was zejula (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 May 19, 2020.

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).[95]

Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the 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 one member of the CADTH Methods Team with input provided by the Clinical Guidance Panel and other members of the CADTH Review Team. Additional limitations and sources of bias were identified by the CADTH Methods Team.

Data Analysis

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

Writing of the Review Report

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

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

References

1. Zejula (niraparib capsules): 100 mg niraparib (as niraparib tosylate), oral antineoplastic agent [product monograph]. Mississauga (ON): GlaxoSmithKline Inc.; 2019. Accessed 2020 Jun 8.
2. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med.* 2016;375(22):2154-2164.
3. pan-Canadian Oncology Drug Review sponsor submission: zejula (niraparib), 300 mg, once-daily, oral. GlaxoSmithKline Inc. Mississauga (ON): GlaxoSmithKline Inc.; 2020 Feb 7.
4. Moore KN, Secord AA, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol.* 2019;20(5):636-648.
5. European Public Assessment Report (EPAR) Zejula (niraparib). London (GB): European Medicines Agency; 2017: https://www.ema.europa.eu/en/documents/assessment-report/zejula-epar-public-assessment-report_en.pdf. Accessed 2020 Jun 8.
6. Clinical Study Report [study protocol]: PR-30-5011-C. A phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum sensitive ovarian cancer. [internal sponsor's report]. Waltham (MA): TESARO Inc.
7. Clinical Study Report: PR-30-5011-C. A phase 3, randomized, double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer [internal sponsor's report]. Waltham (MA): TESARO, Inc.
8. Oza AM, Matulonis UA, Malander S, et al. Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomised controlled trial. *Lancet Oncol.* 2018;19(8):1117-1125.
9. GlaxoSmithKline Inc. response to pCODR checkpoint meeting questions on zejula (niraparib) for ovarian cancer [additional sponsor's information]. Mississauga (ON): GlaxoSmithKline, Inc.; 2020 Apr 6.
10. GlaxoSmithKline Inc. response to pCODR checkpoint meeting questions on niraparib (zejula) for ovarian cancer. Mississauga (ON): GlaxoSmithKline Inc.; 2020 Apr 1.
11. Sackeyfio A, Gill J, Hettle R, Siddiqui K, Friedlander M, Ledermann JA. Comparative efficacy and safety of olaparib 400 mg capsules BID and niraparib 300 mg tablets QD as maintenance treatment after response to chemotherapy in patients with platinum-sensitive relapsed non-germline BRCA-mutated ovarian cancer (PSROC). *Value Health.* 2017;20 (9):A412.
12. Hettle R, Sackeyfio A, Gill J, Siddiqui K, Nussey F, Friedlander M. Comparative efficacy and safety of olaparib 300 mg tablets bid and niraparib 300 mg tablets qd as maintenance treatment after response to chemotherapy in patients with platinum-sensitive relapsed germline BRCA-mutated ovarian cancer (PSROC). *Value Health.* 2017;20 (9):A412.
13. Quality of life in patients with recurrent ovarian cancer (OC) treated with niraparib: results from the ENGOT-OV16/NOVA Trial. *Ann Oncol.* 2017;Conference: 42nd ESMO Congress, ESMO 2017. Spain. 28(Supplement 5):v330.
14. Friedlander M, Matulonis U, Gourley C, et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. *Br J Cancer.* 2018;119(9):1075-1085.
15. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol.* 2014;32(13):1302-1308.
16. Timms KM, Abkevich V, Hughes E, et al. Association of BRCA1/2 defects with genomic scores predictive of DNA damage repair deficiency among breast cancer subtypes. *Breast Cancer Res.* 2014;16(6):475.
17. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2020;382(22):2091-2102.
18. Mateo J, Porta N, Bianchini D, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol.* 2020;21(1):162-174.
19. Pujade-Lauraine E, Colombo N, Glasspool R, et al. OREO/ENGOT OV-38: A phase IIIB trial of olaparib maintenance retreatment in patients with epithelial ovarian cancer. *Ann Oncol.* 2017;28:v330-v354.
20. AstraZeneca. NCT03106987: A study to examine olaparib maintenance retreatment in patients with epithelial ovarian cancer. (OReO). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2017: https://clinicaltrials.gov/ct2/show/NCT03106987. Accessed 2020 Jun 8.
21. Brenner DR, Weir HK, Demers AA, et al. Projected estimates of cancer in Canada in 2020. *CMAJ.* 2020;192(9):E199-E205.
22. Kanchi KL, Johnson KJ, Lu C, et al. Integrated analysis of germline and somatic variants in ovarian cancer. *Nat Commun.* 2014;5:3156.
23. Pennington KP, Walsh T, Harrell MI, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin Cancer Res.* 2014;20(3):764-775.
24. Cunningham JM, Cicek MS, Larson NB, et al. Clinical characteristics of ovarian cancer classified by BRCA1, BRCA2, and RAD51C status. *Sci Rep.* 2014;4:4026.

25. Sackeyfio A, Santi I, Friedlander M. PCN347 - exploring the impact of radiographic progressive disease and first subsequent therapy on health state utility values in germline-BRCA-mutated (GBRCAM) platinum-sensitive relapsed ovarian cancer (psroc) patients on olaparib tablets as maintenance monotherapy. *Value Health.* 2018;21:S73.
26. Moynahan ME, Chiu JW, Koller BH, Jasin M. Brca1 controls homology-directed DNA repair. *Mol Cell.* 1999;4(4):511-518.
27. Moynahan ME, Pierce AJ, Jasin M. BRCA2 is required for homology-directed repair of chromosomal breaks. *Mol Cell.* 2001;7(2):263-272.
28. Cerrato A, Morra F, Celetti A. Use of poly ADP-ribose polymerase [PARP] inhibitors in cancer cells bearing DDR defects: the rationale for their inclusion in the clinic. *J Exp Clin Cancer Res.* 2016;35(1):179.
29. Integrated genomic analyses of ovarian carcinoma. *Nature.* 2011;474(7353):609-615.
30. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2017;390(10106):1949-1961.
31. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med.* 2012;366(15):1382-1392.
32. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol.* 2014;15(8):852-861.
33. Matulonis UA, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive, relapsed serous ovarian cancer and a BRCA mutation: Overall survival adjusted for postprogression poly(adenosine diphosphate ribose) polymerase inhibitor therapy. *Cancer.* 2016;122(12):1844-1852.
34. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2017;18(9):1274-1284.
35. Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013;24 Suppl 6:vi24-32.
36. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011;365(26):2473-2483.
37. pCODR Epert Review Committee (pERC) final recommendation: olaparib (lynparza). Ottawa (ON): CADTH; 2017 Sep 20: https://cadth.ca/sites/default/files/pcodr/pcodr_olaparib_lynparza_resub_fn_rec.pdf. Accessed 2020 Jun 8.
38. Coleman RL, Spirtos NM, Enserro D, et al. Secondary Surgical Cytoreduction for Recurrent Ovarian Cancer. *N Engl J Med.* 2019;381(20):1929-1939.
39. Du Bois A, Vergote I, Ferron G, et al. Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: AGO DESKTOP III/ENGOT ov20. *J Clin Oncol.* 2017;35(15_suppl):5501-5501.
40. National Comprehensive Cancer Network. Ovarian cancer including fallopian tube cancer and primary peritoneal cancer. *NCCN clinical practice guidelines in oncology (NCCN guidelines)*. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2019.
41. Society of Gynecologic Oncology. Guidelines. https://www.sgo.org/clinical-practice/guidelines/. Accessed 2020 Jun 8.
42. Tesaro Inc. NCT01847274: A maintenance study with niraparib versus placebo in patients with platinum sensitive ovarian cancer. *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2013: https://clinicaltrials.gov/show/NCT01847274. Accessed 2020 Jun 8.
43. Del Campo JM, Matulonis UA, Malander S, et al. Niraparib Maintenance Therapy in Patients With Recurrent Ovarian Cancer After a Partial Response to the Last Platinum-Based Chemotherapy in the ENGOT-OV16/NOVA Trial. *J Clin Oncol.* 2019;37(32):2968-2973.
44. Abstracts Presented for the 50th Annual Meeting of the Society of Gynecologic Oncology March 16-19, 2019, Honolulu, HI. *Gynecol Oncol.* 2019;154 (Supplement 1):1-288.
45. Berek JS, Matulonis UA, Peen U, et al. Correction to: Safety and dose modification for patients receiving niraparib (Annals of Oncology (2018) DOI: 10.1093/annonc/mdy181). *Ann Oncol.* 2019;30(5):859.
46. Berek JS, Matulonis UA, Peen U, et al. Safety and dose modification for patients receiving niraparib. *Ann Oncol.* 2019;30(5):859.
47. Mirza MR, Dorum A, Benigno B, et al. Long-term safety assessment of niraparib in patients with recurrent ovarian cancer: Results from the ENGOT-OV16/NOVA trial. *Int J Gynecol Cancer.* 2019;29 (Supplement 4):A15-A16.
48. Ison G, Howie LJ, Amiri-Kordestani L, et al. FDA approval summary: niraparib for the maintenance treatment of patients with recurrent ovarian cancer in response to platinum-based chemotherapy. *Clin Cancer Res.* 2018;24(17):4066-4071.
49. Mirza MR, Benigno B, Dorum A, et al. Long-term safety of niraparib in patients with recurrent ovarian cancer (ROC): Results from the ENGOT-OV16/NOVA trial. *Int J Gynecol Cancer.* 2018;28 (Supplement 2):21-22.
50. Del Campo JM, Mirza MR, Berek JS, et al. The successful phase 3 niraparib ENGOT-OV16/NOVA trial included a substantial number of patients with platinum resistant ovarian cancer (OC). *J Clin Oncol.* 2017;35(15).

51. Oza AM, Matulonis UA, Malander S, et al. Quality of life in patients with recurrent ovarian cancer (OC) treated with niraparib: Results from the ENGOT-OV16/NOVA Trial. *Ann Oncol.* 2017;28 (Supplement 5):v330.
52. A randomized, double-blind phase 3 trial of maintenance therapy with niraparib vs placebo in patients with platinum-sensitive recurrent ovarian cancer (ENGOT-OV16/NOVA trial). *Clin Adv Hematol Oncol.* 2016;14(12):3-5.
53. A randomized, double-blind phase 3 trial of maintenance therapy with niraparib vs placebo in patients with platinum-sensitive recurrent ovarian cancer (ENGOT-OV16/NOVA trial). *Clinical Advances in Hematology and Oncology.* 2016;14(12 Supplement 14):3-5.
54. Matulonis U, Herrstedt J, Oza A, et al. Engot-ov16/nova: A maintenance study with niraparib versus placebo in patients with platinum-sensitive ovarian cancer. *Int J Gynecol Cancer.* 2016;26 (Supplement 3):19-20.
55. Mirza MR, Monk BJ, Oza A, et al. A randomized, double-blind phase 3 trial of maintenance therapy with niraparib vs placebo in patients with platinum-sensitive recurrent ovarian cancer (ENGOT-OV16/NOVA trial). *Ann Oncol.* 2016;27(Supplement 6).
56. Matulonis U, Mahner S, Wenham RM, et al. A phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer (ENGOT-OV16/NOVA trial). *J Clin Oncol.* 2014;32(5s):abstr TPS5625.
57. Mirza M, Berek JS, Vergote I, et al. Engot-ov16/nova: a phase 3 randomized double-blind trial of maintenance with PARP-inhibitor niraparib versus placebo in patients with platinum-sensitive ovarian cancer. *Int J Gynecol Cancer.* 2014;24(9 SUPPL. 4):33-34.
58. Matulonis UA, Herrstedt J, Tinker A, et al. Long-term benefit of niraparib treatment of recurrent ovarian cancer (OC). *J Clin Oncol.* 2017;35(15 Supplement 1).
59. Berek JS, Matulonis UA, Peen U, et al. Safety and dose modification for patients receiving niraparib. *Ann Oncol.* 2018;29(8):1784-1792.
60. Matulonis UA, Monk BJ, Secord AA, et al. Baseline platelet count and body weight as predictors of early dose modification in the quadra trial of niraparib monotherapy for the treatment of heavily pretreated (>=4th line), advanced, recurrent high-grade serous ovarian cancer. *Gynecol Oncol.* 2019;154 (Supplement 1):3.
61. Gonzalez A, Mirza MR, Vergote I, et al. A prospective evaluation of tolerability of niraparib dosing based upon baseline body weight (wt) and platelet (blplt) count: blinded pooled interim safety data from the PRIMA Study. *Ann Oncol.* 2018;29 (Supplement 8):viii335-viii336.
62. Moore KN, Secord AA, Geller M, et al. QUADRA: A phase II, open-label, single-arm study to evaluate niraparib in patients (pts) with relapsed ovarian cancer (ROC) in 4th or later line of therapy: Results from the tBRCAmut subset. *Ann Oncol.* 2018;29 (Supplement 8):viii337.
63. Moore KN, Secord AA, Geller MA, et al. QUADRA: A phase 2, open-label, single-arm study to evaluate niraparib in patients (pts) with relapsed ovarian cancer (ROC) who have received >=3 prior chemotherapy regimens. *J Clin Oncol.* 2018;36(15 Supplement 1).
64. Moore K, Rimel BJ, Achour H, et al. Safety and efficacy of niraparib in patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer (QUADRA). *Int J Gynecol Cancer.* 2016;26 (Supplement 3):784.
65. Moore KN, Rimel B, Agarwal S, Balser J, Martell RE, Monk BJ. A Phase 2, openlabel study of niraparib in women with advanced, relapsed, highgrade serous epithelial ovarian, fallopian tube or primary peritoneal cancer after 3 previous chemotherapy regimens. *J Clin Oncol.* 2015;33(15 SUPPL. 1).
66. Tesaro Inc. NCT02354586: A study of niraparib in patients with ovarian cancer who have received three or four previous chemotherapy regimens (QUADRA). Bethesda (MD): U.S. National Library of Medicine; 2015: https://clinicaltrials.gov/show/NCT02354586. Accessed 2020 Apr 21.
67. Fabbro M, Moore KN, Dorum A, et al. Efficacy and safety of niraparib as maintenance treatment in older patients (>=70years) with recurrent ovarian cancer: Results from the ENGOT-OV16/NOVA trial. *Gynecol Oncol.* 2019;152(3):560-567.
68. Matulonis UA, Walder L, Nottrup TJ, et al. Niraparib maintenance treatment improves time without symptoms or toxicity (TWiST) versus routine surveillance in recurrent ovarian cancer: A TWiST analysis of the ENGOT-OV16/NOVA trial. *J Clin Oncol.* 2019;37(34):3183-3191.
69. Matulonis UA, Walder L, Nottrup TJ, et al. Time without symptoms or toxicity in patients with recurrent ovarian cancer receiving niraparib maintenance treatment versus placebo: A TWIST analysis of the ENGOT24-OV16/NOVA trial. *Gynecol Oncol.* 2019;154 (Supplement 1):2.
70. Mirza MR, Walder L, Monk BJ, et al. A time without symptoms or toxicity analysis of niraparib compared with routine surveillance in the maintenance treatment of patients with recurrent ovarian cancer. *Value Health.* 2018;21 (Supplement 3):S16.
71. Fabbro M, Moore KN, Dorum A, et al. Safety and efficacy of niraparib in elderly patients (Pts) with recurrent ovarian cancer (OC). *Ann Oncol.* 2017;28 (Supplement 5):v332.

72. Mirza MR, Monk BJ, Gil-Martin M, et al. Efficacy of niraparib on progression-free survival (PFS) in patients (pts) with recurrent ovarian cancer (OC) with partial response (PR) to the last platinumbased chemotherapy. *J Clin Oncol.* 2017;35(15 Supplement 1).
73. Del Campo JM, Matulonis UA, Malander S, et al. Niraparib maintenance therapy in patients with recurrent ovarian cancer after a partial response to the last platinum-based chemotherapy in the ENGOT-OV16/NOVA trial. *J Clin Oncol.* 2019;37(32):2968-2973.
74. Wu X, Zhu J, Yin R, et al. A prospective evaluation of tolerability of niraparib dosing based on baseline body weight (BW) and platelet (plt) count: Blinded pooled interim safety data from the NORA study. *Ann Oncol.* 2019;30 (Supplement 5):v411.
75. Zai Lab (Shanghai) Co Ltd. NCT03705156: Clinical trial evaluating the efficacy and safety of ZL-2306 (niraparib) in ovarian cancer patient. Bethesda (MD): U.S. National Library of Medicine; 2018: https://clinicaltrials.gov/show/NCT03705156. Accessed 2020 Apr 21.
76. Concin N, Lorusso D, Braicu L, et al. EUDARIO/ENGOTov-48: a European multicenter randomised phase II trial on the combination of the HSP90 inhibitor ganetespib with carboplatin followed by maintenance treatment with niraparib (+/- ganetespib) compared to platinum-based combination-chemotherapy followed by niraparib in relapsed platinum-sensitive ovarian cancer patients. *J Clin Oncol.* 2019;37.
77. Gonzalez-Martin A, Colombo N, Heitz F, et al. ENGOT-Ov41/GEICO-69-O/ANITA trial: A phase III randomized, double-blinded trial of platinum-based chemotherapy (CT) with or without atezolizumab (ATZ) followed by niraparib maintenance with or without ATZ in patients with recurrent ovarian, tubal or peritoneal cancer (OC) and platinum treatment-free interval (TFIp) >6 months. *J Clin Oncol.* 2019;37(Supplement 15).
78. Universitaire Ziekenhuizen Leuven. NCT03783949: European trial on enhanced DNA repair inhibition in ovarian cancer (EUDARIO). Bethesda (MD): U.S. National Library of Medicine; 2018: https://clinicaltrials.gov/show/NCT03783949. Accessed 2020 Apr 21.
79. Wang S, Sun K, Xiao Y, et al. Elevation of immune cell infiltration and interferon-stimulated gene expression is associated with niraparib treatment in murine syngeneic tumor models. *Mol Cancer Ther.* 2017;17(1 Supplement 1).
80. Walsh CS. Latest clinical evidence of maintenance therapy in ovarian cancer. *Curr Opin Obstet Gynecol.* 2020;32(1):15-21.
81. Gourd E. Niraparib improves progression-free survival in ovarian cancer. *Lancet Oncol.* 2019;20(11):e615.
82. Mirza MR, Matulonis UA. Niraparib in recurrent ovarian cancer. *N Engl J Med.* 2017;376(8):801-802.
83. Niraparib slows ovarian cancer progression. *Cancer Discov.* 2016;6(12):OF2.
84. Tesaro Inc. EudraCT 2013-000685-11: A phase 3 randomized double-blind trial of maintenance study with niraparib versus placebo in patients with platinum sensitive ovarian cancer. 2013: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000685-11. Accessed 2020 Apr 21.
85. Heinzl S. Recurrent ovarian cancer: Niraparib extends progression-free survival. *Arzneimitteltherapie.* 2017;35(1-2):38-39.
86. Clinical Study Report [statistical analysis plan]: PR-30-5011-C. A phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum sensitive ovarian cancer. [internal sponsor's report]. Mississauga (ON): Tesaro, Inc.; 2016 May 18.
87. GlaxoSmithKline Inc. response to pCODR checkpoint meeting questions on zejula (niraparib) for ovarian cancer [additional sponsor's information]. Mississauga (ON): GlaxoSmithKline, Inc.; 2020 Apr 20.
88. Beaumont J, Yount S, Lalla D, et al. Validation of the functional assessment of cancer therapy-ovarian (FACT-O) symptom index (FOSI) in a phase II clinical trial of pertuzumab in patients with advanced ovarian cancer. *J Clin Oncol.* 2007;25:16021-16021.
89. Tesaro Inc. NCT00749502: A Study of MK4827 in participants with advanced solid tumors or hematologic malignancies (MK-4827-001 AM8). Bethesda (MD): U.S. National Library of Medicine; 2008: https://clinicaltrials.gov/ct2/show/NCT00749502. Accessed May 15, 2020.
90. Dias S, Welton N, Sutton A, Caldwell D, Lu G, Ades A. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. . *Med Decis Making.* 2013;33(5):641-656.
91. Ouwens M, Philips Z, Jansen J. Network meta-analysis of parametric survival curves. *Res Synth Methods.* 2011;1(3-4):258-271.
92. Jansen J. Network meta-analysis of survival data with fractional polynomials. *BMC Med Res Methodol.* 2011;11(61).
93. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health.* 2014;17(2):157-173.
94. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46.
95. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2020 Jun 8.