CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Initial Clinical Guidance Report

Olaparib (Lynparza) for Ovarian Cancer - Resubmission

August 31, 2017

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding olaparib (Lynparza) for 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 regarding olaparib (Lynparza) for ovarian cancer conducted by the Genitourinary Clinical Guidance Panel (CGP) and the pCODR 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 on olaparib (Lynparza) for ovarian cancer a summary of submitted Provincial Advisory Group Input on olaparib (Lynparza) for ovarian cancer, and a summary of submitted Registered Clinician Input on olaparib (Lynparza) for ovarian cancer, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of olaparib (Lynparza) as maintenance treatment for adult patients with platinum sensitive relapsed *BRCA*-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

The appropriate comparator for olaparib in this treatment setting is best-supportive care and close follow-up "watch and wait". Patients must have received at least one prior course of platinum-based chemotherapy and demonstrated platinum sensitivity in these courses (defined as disease progressing at least 6 months after completion of the penultimate platinum chemotherapy). They must have then experienced a relapse, and received an additional course of platinum-based chemotherapy (e.g., second line), to which they responded (complete or partial response). Patients would then be in the "maintenance phase", where they would be eligible to receive olaparib until disease progression. The patient population under review by pCODR is adult patients with platinum-sensitive relapsed BRCA-mutation epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy and is in line with the Health Canada approved indication. An NOC/c was issued by Health Canada for olaparib capsules for this indication on April 29, 2016, pending the results of trials to verify its clinical benefit.[1]

Olaparib (Lynparza) is a first-in-class, oral, potent inhibitor (ADP-ribose) polymerase (PARP). Olaparib represents the first targeted medicine in ovarian cancer. The recommended dosing for olaparib is 400 mg (8 x 50 mg capsules) taken orally, twice daily (Total daily dose of 800 mg). It is recommended that treatment be continued until progression of the underlying disease. In the maintenance setting, patients should start treatment with olaparib no later than 8 weeks after completion of their final dose of the platinum-containing regimen. A different non-bioequivalent formulation (tablet) of olaparib requires a complete regulatory review by Health Canada. At the time of this review, olaparib tablets do not have regulatory approval.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Two clinical trials were identified that met the eligibility criteria and are included in this systematic review. SOLO-2 is a randomized, international, multicentre Phase III confirmatory trial that evaluated maintenance treatment with olaparib 300 mg twice daily (tablet formulation) in patients with relapsed high grade serous ovarian cancer (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer with *BRCA* mutations who had responded following platinum-based chemotherapy. The results of SOLO-2 were not provided in the original olaparib submission to pCODR in 2016 as it was ongoing at the time.

Study 19 was a randomized, double-blind, multicentre Phase II international trial that evaluated olaparib 400 mg twice daily (capsule formulation) in patients with advanced platinum-sensitive high-grade serous ovarian cancer who had received 2 or more previous platinum-containing regimens and had demonstrated an objective response to their last platinum-based chemotherapy regimen. The pCODR review focused on the subgroup of patients with *BRCA* mutations and epithelial ovarian, fallopian tube or primary peritoneal cancer. Just over half (51.3%) of enrolled patients had the *BRCA*-m status. Subgroups analyses in the *BRCA*-m population were pre-planned, but these exploratory analyses were not powered to detect a statistically significant difference for any of the endpoints. Study 19 was included in the original olaparib submission to pCODR and previously reviewed in 2016.

The primary outcome of both trials was progression free survival (PFS) with secondary outcomes including overall survival, overall response rate, , adverse events, time to first subsequent treatment or death, time to second subsequent treatment or death, time to second progression or death (PFS2), health-related quality of life and patient reported outcomes.

Results:

PRIMARY OUTCOME: Progression-free Survival (PFS)

SOLO-2[2]

At 63% maturity, a statistically significant improvement in the median PFS for olaparib over placebo of 13.6 months (median PFS 19.1 vs. 5.5 months) was reported, translating into a 70% reduction in risk of disease progression or death with olaparib vs. placebo (HR 0.30; 95% CI 0.22-0.41; p<0.0001). The proportion of patients who had not experienced disease-progression at 12 months was 3.1 times greater in the olaparib group than in the placebo group (65.1% vs. 20.9%, respectively). At the 2 year mark, the proportion of patients who remained progression free was 2.8 times greater in the olaparib group than in the placebo group (43.0% vs. 15.1%, respectively). A sensitivity analysis of PFS, measured by blinded independent central review (BICR) at 51% maturity, also demonstrated a statistically significant improvement in PFS in patients receiving olaparib vs. placebo (HR 0.25; 95% CI 0.18 to 0.35; P<0.0001; median 30.2 months vs 5.5 months).

Study 19

BRCA-M Subgroup Analysis [3,5]

At 53% patients with BRCA-m tumours were reported to have 6.9 month prolongation of median PFS (11.2 compared to 4.3 months in the olaparib and placebo arms, respectively; HR 0.18; 95% CI 0.10-0.31; p<0.0001) at the 2012 data-cut off.

SECONDARY OUTCOMES: SOLO-2

Overall Survival (OS)[2,4]

At the September 19, 2016 data cut-off (DCO), OS data were only at 24% maturity and median OS was not reached in either treatment arm. The reported 20% reduction in the risk of death in olaparib treated patients compared with placebo treated patients is based on a total of 72 OS events in 295 patients. This did not reach statistical significance (HR 0.80; 95% CI 0.50-1.31; p=0.43). A total of 69% of patients were alive and continuing on the study.

Progression-free Survival 2 (PFS2, Time to second progression or death)[2,4]

At 40% maturity, there was a 50% reduction in risk of second progression or death with olaparib compared to placebo (HR 0.50; 95% CI 0.34-0.72; p=0.0002). The median PFS2, calculated using Kaplan-Meier techniques, was not yet reached in the olaparib group and 18.4 months in the placebo group. At 24 months, 59.2% of patients in the olaparib group and 37.3% of patients in the placebo group were second progression-free.

Time to Study Treatment Discontinuation or Death (TDT), Time to First Subsequent Therapy or Death (TFST) and Time to Second Subsequent Therapy or Death (TSST)[2,4]

There was a nominally statistically significant reduction in the time from randomization to discontinuation of treatment or death in the olaparib group compared with the placebo group. Median TDT was 19.4 months in the olaparib group compared to 5.6 months with placebo, corresponding to a hazard ratio of 0.31 (95% CI 0.23-0.42; nominal p<0.0001). There was a nominally statistically significant delay in both TFST and TSST in the olaparib group compared with the placebo group (TFST HR 0.28 95% CI 0.21-0.38; p<0.0001; TSST HR 0.37 95% CI 0.26-0.53; p<0.0001).

Patient Reported Outcomes: Functional Assessment of Cancer Therapy – Ovarian (FACT-O), Trial Outcome Index (TOI) and New patient-centric endpoints of the FACT-O

Using a mixed model for repeated measures (MMRM) analysis of all the post-baseline TOI scores for each visit, no statistically significant or clinically relevant difference between the treatment arms in the average change from baseline TOI score over 12 months was found [2]. The estimated average difference between the arms over 12 months was less than 1 point, in the context of a TOI scale of 100 points. There was no difference on average over a 12 month period between the treatment arms with respect to all patient-centric endpoints of the FACT-O (disease-related symptoms, common treated-related toxicities of cancer treatment, HRQoL and physical functioning). Over a 12 month period, the estimated average difference between the arms was less than 1 point for all 4 endpoints.[4]

Adverse Events and Safety[2]

The proportion of patients who experienced any AEs (all National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (CTCAE) grades) was similar between the olaparib and placebo groups, 98.5% and 94.9%, respectively (Please see Tables 9 and 10 in section 6 of the systematic review for further details). Serious AEs were reported in 17.9% vs 8.1% of patients in the olaparib and placebo group, respectively. The incidence of any grade ≥3 AEs was 36.9% in the olaparib group and 18.2% in the placebo group. Anemia, identified by Ovarian Cancer Canada (OCC) as an AE of particular interest, was the most common grade ≥3 AE in the olaparib group (n=38, 19.5%), but the majority of cases were low grade. In approximately one-fifth of patients, AEs of anaemia led to temporary dose interruptions, and to dose reduction in approximately one-tenth of patients. Anaemia was reported as an SAE in a low proportion of patients and a low proportion of patients permanently discontinued study treatment as a result of anaemia AEs.[4]

SECONDARY OUTCOMES: STUDY 19[3]

Overall Survival (OS) FOR *BRCA*-m Subgroup Analysis[6]

In an updated analysis of the BRCA-m population at 70% maturity (95/136 events), OS was 34.9 months versus 30.2 months in the olaparib treated patients compared to placebo treated, respectively. The median improvement in OS was 4.7 months longer for olaparib versus placebo (HR=0.62, 95% CI: 0.41-0.94, p=0.02480). It is notable that threshold was not set to determine statistical significance for OS in the *BRCA*-m subgroup. Therefore the reported p-values are nominal.

Patient Reported Outcomes: FOSI, Total Functional Assessment of Cancer Therapy - Ovarian (FACT-O) and Trial Outcome Index (TOI).

Within the subgroup of patients with the *BRCA*-m, minimally important differences in improvement rates were observed in 25.0% and 18.9% of patients based on the TOI analysis, 27.0% and 20.8% of patients based on the FACT-O analysis, and 21.2% and 16.1% of patients based on the FOSI analysis in the olaparib and placebo groups, respectively. The majority of patients experienced no change from baseline in both the olaparib and placebo groups for all three scales. A greater proportion of patients in the placebo group (18.9% and 26.4%, respectively) experienced worsening in the TOI and FACT-O scales as compared to the olaparib group (10.9% and 15.9%). None of these differences were however statistically significant.

[Table 1]: Highlights of Key Outcomes[2,4-6]

	SOLO-2 (tablet formulation, 300 mg bd)		STUDY 19 (capsule formulation, 400 mg bd)	
	DCO 19 September 2016 Full Analysis Set (n=295)		DCO 2015 BRCAm Subset (n=136)	
	Olaparib	Placebo	Olaparib	Placebo
PFS				
Number of events: total number of patients (%)	107:196 (54.6%)	80:99 (80.8%)	26:74 (35%)*	46:62 (74%)*
Median PFS (months)	19.1	5.5	11.2*	4.3*
HR (95% CI)	0.30 (0.22-0.41)		0.18 (0.10-0.31)*	
P-value (2-sided)	p<0.0001		p<0.0001*	
PFS2				
Number of events: total number of patients (%)	70:196 (35.7%)	49:99 (49.5%)	NA	NA
Median PFS2 (months)	Not reached	18.4	NA	NA
HR (95% CI)	0.50 (0.34-0.72)		NA	
P-value (2-sided)	p=0.0002		NA	
OS				
Number of events: total number of patients (%)	45:196 (23.0%)	27:99 (27.3%)	47:74 (64%)	48:62 (77%)
Median OS (months)	Not reached	Not reached	34.9	30.2
HR (95% CI)	0.80 (0.50-1.31)		0.62 (0.41-0.94)	
P-value (2-sided)	p=0.4267		p=0.02480	
TDT				
Number of events: total number of patients (%)	112:196 (57.1%)	86:99 (86.9%)	66:74 (89%)	61:62 (98%)
Median time (months)	19.4	5.6	11.0	4.6
HR (95% CI)	0.31 (0.23-0.42)		0.36 (0.25-0.52)	
P-value (2-sided)	p<0.0001 (nominal p-value)		p<0.00001	
TFST				
Number of events: total number of patients (%)	92:196 (46.9%)	79:99 (79.8%)	53:74 (72%)	59:62 (95%)
Median time (months)	27.9	7.1	15.6	6.2
HR (95% CI)	0.28 (0.21-0.38)		0.32 (0.22-0.48)	
P-value (2-sided)	p<0.0001		p<0.00001	

	SOLO-2 (tablet formulation, 300 mg bd)		STUDY 19 (capsule formulation, 400 mg bd)	
	DCO 19 September 2016 Full Analysis Set (n=295)		DCO 2015 BRCAm Subset (n=136)	
	Olaparib	Placebo	Olaparib	Placebo
TSST				
Number of events: total number of patients (%)	68:196 (34.7%)	60:99 (60.6%)	52:74 (70%)	56:62 (90%)
Median time (months)	Not reached	18.2	22.0	15.3
HR (95% CI)	0.37 (0.26-0.53)		0.41 (0.28-0.62)	
P-value (2-sided)	p<0.0001		p=0.00001	

Note: *PFS data-cut 2012 for Study 19; bd Twice daily; CI Confidence interval; CSR Clinical study report; DCO Data cut-off; HR Hazard ratio; OS Overall survival; PFS Progression free survival; PFS2 Time to second progression or death; TDT Time to discontinuation of treatment or death; TFST Time to first subsequent therapy or death; TSST Time to second subsequent therapy or death; Nominal p-value: No adjustments were made for analyses within the BRCA subgroup in Study 19. Control of type I error for the exploratory endpoints was not defined and, as such, where p-values <0.05 are observed for these endpoints, we can say nominal significance was met.

Adverse Events and Safety:
In the *BRCA*-m subgroup, all grade AEs between the olaparib and placebo groups was 97% and 94%, respectively. However, grade ≥3 AEs were 38% compared to 18% in the olaparib and placebo BRCA-m subgroup, respectively.

Important Limitations

<u>SOLO-2</u>
The following are some limitations and potential sources of bias from the SOLO-2 trial. The complete list appears in section 6.

- Selected predefined subgroup analyses of PFS were reported in the trial, however the trial was not sufficiently powered to detect differences in subgroups. Thus, the interpretation of these results is challenging due to the lack of statistical power. Moreover, statistically significant differences should be interpreted with caution due to the small number of patients in the subgroups.

- For patients randomized to the placebo group, [redacted] received a PARP inhibitor as a subsequent therapy after progression; of these, [redacted] patients received a PARP inhibitor as their first subsequent therapy. [redacted] ([redacted]) patients in the olaparib group received a PARP inhibitor as a subsequent therapy. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until May 20, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*). There will likely be confounding from subsequent use of other PARP inhibitors, in the placebo arm with the use of a subsequent PARP inhibitor after progression.

- At the time of the data analysis, OS data were immature (24% maturity) (HR 0.80; 95% CI 0.50 to 1.31; P=0.4267; median not reached) making the actual degree of long term benefit unknown. With sufficient follow-up OS could be evaluated, but any benefit will be confounded by post trial treatments.

<u>Study 19</u>
Sources of bias for Study 19 have previously been discussed[3] and only an abbreviated list appears below:

- The primary efficacy analyses of Study 19 were based on the ITT population and not the BRCA subgroup.

- The sample size calculation, conducted only in the overall population for PFS, allowed for a type 1 error-rate of 20%. Therefore interpretation of results should be done with caution given that the trial has a 20% chance of detecting a false positive. None of the secondary outcomes (e.g., OS) in the ITT analysis nor the exploratory endpoints in the subgroup analysis of patients with the *BRCA*-m (e.g., PFS, OS) were powered to detect a statistically significant difference. Therefore all interpretation of testing for significance within these analyses should be done with caution.

- Adjustments were made for multiple testing for OS in the ITT population and OS was not significant at any interim analysis based on this analysis plan. No adjustments were made for multiple testing within any of the exploratory endpoints or analyses within the BRCA subgroups. At the latest OS analysis, in patients with the BRCAm and with 70% maturity, the median OS was 34.9 months compared with 30.2 months in the olaparib and placebo arms, respectively (HR = 0.62; 95% CI, 04.1 to 0.94; p=0.02480, not adjusted for multiple testing).

- Baseline characteristics were mostly balanced between treatment arms in the ITT and *BRCA*-m-positive subgroup. However, stratification of patients was based on complete or partial response to the most recent platinum-based regimen and this has the potential to introduce a degree of imbalance to the population at baseline. It is not clear what impact these imbalances may have had on the direction or magnitude of benefit.

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

From a patient perspective, the impact of ovarian cancer is significant for women diagnosed with this disease and their caregivers. Because early symptoms can be non-specific and generally there is no screening test, ovarian cancer is usually detected in its later stages resulting in a poor prognosis. Surgery and chemotherapy have been the mainstays; however, as most women are likely to face a recurrence, the patient advocacy group believes it is helpful to have a greater spectrum of agents with which to treat this type of cancer. The patient advocacy group reported that 13 patients and two caregiver respondents had direct experience with olaparib. The primary treatment side effects of olaparib included tiredness/weakness, nausea, taste changes, blood problems and dizziness, which were found to be similar in the larger in the respondents who had not received olaparib.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- No treatment option currently for maintenance therapy
- New treatment option that is an oral drug
- The clinical benefits, safety and therapeutic equivalence of 400mg twice daily in capsules compared to 300mg twice daily in tablets
- Guidance on switching from tablets to capsules or from capsules to tablets, when the tablets become available

- Clarity on whether patients previously treated with three or more lines of chemotherapy are considered in the trial and in the funding request

Economic factors:

- Resources for BRCA testing
- Additional therapy that is maintenance therapy and does not replace intravenous chemotherapy when patients progress on maintenance therapy

Registered Clinician Input

The clinicians providing input noted that olaparib is a well-tolerated oral drug, providing this group of patients an opportunity to extend remission significantly and potentially delay time to next chemotherapy. It is felt there is a huge unmet need, specifically targeted therapy in ovarian cancer, and the improvement in progression-free survival is significant, given the high rate of relapse. It was noted that the funding request for maintenance treatment of patients after platinum-based chemotherapy, regardless of specific number of relapses or timing, is the appropriate indication.

Summary of Supplemental Questions

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of olaparib (Lynparza) monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy.

- What is the clinical effectiveness, safety and therapeutic equivalence of olaparib at 300 mg tablet PO BID (as in SOLO2) vs. 400 mg capsule PO BID (as in Study 19)?

At the currently approved 400 mg BID capsule dose, patients are required to consume eight 50 mg large size capsules twice daily. In an attempt to improve dosing constraints of the capsule formulation, an alternative tablet formulation with improved bioavailability has been developed to facilitate olaparib administration to patients. Comparisons of the bioavailability of these two different oral formulations was investigated.[7]

Findings

Study 24 investigated the relative bioavailability of the tablet formulation of olaparib used in SOLO-2 and other ongoing Phase III trials compared to the currently approved capsule formulation. AstraZeneca's Clinical Summary Report explains that, "crystalline olaparib has low solubility across the physiological pH range relative to the desired dose so the development of dosage forms was directed towards solubility enhancing technologies".[4] They further explain that "the tablet formulation has greater bioavailability due to improved solubility milligram to milligram compared to the capsule formulation enabling a lower 300 mg dose to achieve comparable clinical efficacy and similar tolerability to 400 mg capsules."

Trial

Study 24 was an open-label, multicentre, multistage, Phase I trial (Study D0810C00024- Study 24 [NCT00777582])[7] to compare the pharmacokinetics (PK), efficacy, and tolerability of different doses and schedules of the olaparib capsule and tablet formulations with a goal of determining an optimal tablet dosing strategy for Phase III studies of olaparib (See Table 13 for details). The study included two stages of sequentially enrolled cohorts: stage 1, pharmacokinetic properties of tablet and capsule formulations were compared in patients with

advanced solid tumours; stage 2, tablet dose escalation with expansion cohorts at doses/schedules of interest in patients with solid tumours and *BRCAm* breast/ovarian cancers.

Outcomes

Bioavailability Assessment

The capsule showed a slower rate of absorption (lower dosed normalized Cmax) at doses of up to 100 mg in vivo, but similar extent of absorption (similar dosed normalized AUC). At doses above 100 mg, the extent of absorption was higher for the tablet formulation.

Analyses based on geometric least squares mean (gLSmean), Cmax and AUC ratios and 90 % CIs from the patients in the study, determined that the tablet and capsule formulations cannot be considered bioequivalent. The relative bioavailability of tablet doses compared with capsules was higher based on Cmax ratios. Additional assessments of steady-state PK were conducted and determined olaparib tablet ≥ 300 mg matched or exceeded that of the olaparib 400 mg capsule.

A total of 65% of randomized patients in the expansion phase required dose reduction to 300 mg after dose escalation of up to 400 mg twice daily (tablet maximum tolerated dose based on haematological toxicity). An improvement in tolerability was observed with the olaparib 300 mg BD tablet formulation and was similar to that with capsules. The most common adverse events (AEs) leading to olaparib dose modification were nausea, fatigue and vomiting.

Objective Response Rate (ORR)

Objective response rate based on radiological assessment was 30% (16/53; 95% CI 18.3–44.3) across cohorts of g*BRCA*m carriers with serous ovarian carcinoma, although it appeared higher for patients receiving 300 mg tablets BD (5/13, 38%; 95% CI 13.9–68.4) and 400 mg tablets BD (5/12, 42%; 95 % CI 15.2–72.3). The ORR based on a RECIST and/or CA-125 was 40% (21/53, 95% CI 26.5–54.0).

Limitations

Investigators did note some potential issues and limitations with the analysis that are worth discussing further.[4] For the change in tumour size analysis, a number of tumour size assessments were either missing or performed outside of the scheduled visit window. These were thereby imputed according to prespecified imputation rules. An increase in imputations over time, believed to be reflective of the number of patients withdrawing from the study, suggests change in tumour size comparisons for week 16 should be interpreted with caution.[4]

See section 7.1 for more information.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

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

[Table 2]: Assessment of generalizability of evidence for Olaparib[2,4,5,7]

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>ECOG PS</td><td>Inclusion criteria for Study 19 and SOLO-2 specified patients were required to have an ECOG PS ≤2.
<table><tr><td colspan="3">SOLO-2</td></tr><tr><th>ECOG Status</th><th>Olaparib</th><th>Placebo</th></tr><tr><td>(0) Normal activity</td><td>162 (82.7)</td><td>77 (77.8)</td></tr><tr><td>(1) Restricted activity</td><td>32 (16.3)</td><td>22 (22.2)</td></tr></table>
1.0% of patients in the olaparib arm had an unknown ECOG PS in SOLO-2.
<table><tr><td colspan="3">Study 19</td></tr><tr><th>ECOG Status</th><th>Olaparib</th><th>Placebo</th></tr><tr><td>(0) Normal activity</td><td>62 (84)</td><td>45 (73)</td></tr><tr><td>(1) Restricted activity</td><td>11 (15)</td><td>15 (24)</td></tr></table>
1.4% of patients in the olaparib arm and 1.6% of patients in the placebo arm had an unknown ECOG PS in Study 19.</td><td>Do the results apply to patients with ECOG PS ≥2?</td><td>If PS ≥ 2 due to recent chemotherapy side effects or treatment related fatigue or other toxicities, then patients may be considered eligible to switch to olaparib. If PS ≥ 2 due to progressive disease, then the patient would not be eligible for olaparib.</td></tr>
<tr><td>Intervention</td><td>Drug Formulation and dosing</td><td>The current Health Canada approval and the funding request indicates the dose is 400 mg (8 x 50 mg capsules) twice daily. The SOLO-2 trial submitted for review used a dose of 300mg (2 x 150 mg tablets) twice</td><td>Are the results of SOLO-2 (olaparib at a dose of 300 mg in tablet formulation) generalizable to the Canadian population, where the funding</td><td>The current Health Canada indication of olaparib is for adult patients with platinum sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		daily. At the time of the review, the 50mg capsules are on the Canadian market but not the 150 mg tablets. PAG is seeking information from the manufacturer on when the 150 mg tablets will be available in Canada, what the plans on transitioning capsules to tablets would be and whether the capsules will remain available for patients already on it. PAG is seeking data demonstrating that dose using capsules is therapeutically equivalent to dose using tablets. PAG is also seeking bioequivalence data and safety of the two different formulations and doses.	request, and Health Canada regulatory approval is for a dose of 400mg in capsule formulation?	platinum-based chemotherapy with a dose of 400 mg (8 x 50 mg capsules) twice daily. The olaparib tablets studied in SOLO-2 with a dose of 300 mg (2 x 150 mg) twice daily are not available in Canada at the time of the review but are expected to be available in the future. Until the tablets are approved, the CGP considers that the results from Study 19, using olaparib capsules at 400 mg PO BD, demonstrated high clinical efficacy. Study 24 demonstrated that patients' exposure following tablet doses ≥300 mg BID matched or exceeded that of the approved 400 mg BID capsule formulation (8×50 mg capsules BID). The bioavailability of the tablet appears to be greater due to improved solubility compared to the capsule. The 300 mg BID tablet dose was better tolerated than higher doses and it showed similar effectiveness in tumour shrinkage. Therefore, the CGP recommend that until the olaparib tablets are approved, the olaparib capsules should be used as bioavailability is similar. Furthermore, if olaparib is funded, patients currently on olaparib capsules should be transitioned to the tablet formulation when they become available.
	Line of Therapy	SOLO-2 required patients to have completed at least 2 previous lines of platinum-based chemotherapy and begin maintenance therapy within 8 weeks of completion of the final dose of the last platinum-containing regimen, with a minimum of 4 treatment cycles.	Do the results apply to patients who: 1) have only completed 1 previous course of platinum containing therapy? ? 2) had shorter or longer than 4 treatment cycles of chemotherapy? 3) have completed platinum-based chemotherapy more than 8 weeks prior?	1) Results do not apply to patients after first-line treatment with platinum-based therapy. This is subject on an ongoing phase III trials (SOLO 1). 2) Any patient with BRCA mutation and response to 2nd or later platinum-based therapy is eligible. Four cycles of platinum are required to switch to olaparib, unless the patient is allergic to platinum, in which case non-platinum therapy to 4 cycles can be substituted. To be eligible for olaparib, patients with measurable disease must demonstrate response to treatment (by clinical or radiologic evaluation) and patients without measurable disease cannot have evidence of a rising CA125.) 3) Patients must have completed platinum-based chemotherapy within 8 weeks of completion of the final dose of the last-platinum containing regimen. If there is a delay in initiating treatment beyond the 8 weeks, under rare circumstances beyond the control of the patient and physician, it is reasonable that olaparib be initiated so long as there is no evidence of disease progression at the time of starting olaparib as determined by the clinician.
	Treatment with olaparib beyond	Patients in SOLO-2 received olaparib maintenance therapy until disease progression or until investigator deemed	Should patients continue on treatment with olaparib following disease progression?	The CGP agree that there would be few patients who still receive olaparib after progression in actual practice.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	disease progression	that a patient was no long benefitting from treatment. If required, toxicities could be managed by treatment interruptions and dose reductions. In Study 19, patients received olaparib until objective disease progression (defined by Response Evaluation Criteria in Solid Tumours [RECIST] guidelines), provided they did not meet any criteria for discontinuation (any grade 3 or 4 adverse event [AE]).		In the opinion of the CGP, in cases where a patient temporarily stops maintenance treatment with olaparib (e.g., drug holiday), clinicians should confirm there is no evidence of disease progression before re-starting treatment with olaparib. If there is evidence of progression, the CGP agree that olaparib should not be re-started.

1.2.4 Interpretation

Burden of Illness and Need

Ovarian cancer is the eighth leading cause of cancer in Canadian women and fifth leading cause of cancer death.[8] Unfortunately, the death rate is high as most women present with advanced stage disease. According to the Canadian Cancer Society, in 2014 2,700 women in Canada developed ovarian cancer which is approximately 11 per 100,000 (age standardized rate). Approximately 1,750 women will die as a result of this disease for a mortality rate of 6.4 per 100,000 women.[8] As the disease often strikes women in their 50s and 60s, it removes them from the work force and leads to a substantial loss of productive life years.

Only 1% of patients with recurrent ovarian cancer are curable. Hence, therapy for patients with a recurrence is often dictated by their response to previous chemotherapy. Selection of therapy for women with recurrent disease is in large part determined by response to first-line therapy. Hence, we have divided recurrent disease into either platinum-sensitive (progression-free interval [PFI] > 6 months) or platinum-resistant (PFI ≤ 6 months) disease. The main goals of therapy should focus on palliation of cancer-related symptoms, delaying subsequent disease recurrence, prolongation of life, and optimization of quality of life.

The goals mentioned above, should provide guidance on the initiation and selection of therapy. In patients who are symptomatic immediate institution of treatment is justified and warranted to improve cancer-related symptoms. With asymptomatic recurrences (rising CA-125 level, radiologic evidence of disease) the timing of therapy is far more controversial. Those advocating immediate treatment argue that treating small-volume disease is more likely to succeed in achieving a complete response. Physicians who believe in delaying therapy emphasize that the goal of therapy in the recurrent setting is palliation, such that intervention should only be carried out at the onset of symptoms particularly as there is a lack of data to show that early treatment improves overall survival with potential worsening patient's quality of life.[9]

Recurrent high grade serous ovarian/fallopian tube/peritoneal carcinoma remains a significant disease burden and treatment challenge. Lacking clearly defined molecular drivers of disease progression, there are no defined treatment targets for the majority of women afflicted by this disease. The BRCA mutation subgroup is currently the only molecular subgroup that can be consistently and reliably identified through molecular testing,

Recurrent ovarian cancer has been traditionally been treated with chemotherapy to improve on progression free survival with the added benefit of an improvement in quality of life. Unfortunately, traditional chemotherapy drugs have been associated with significant toxicity and may worsen quality of life.

Olaparib is a new class of drugs, PARP inhibitor, and has been shown to improve on progression free survival with a manageable toxicity profile in patients with a germline BRCA 1/2 mutation in the recurrent ovarian cancer setting. Although, data are not mature as yet for overall survival, the introduction of olaparib will delay subsequent disease progression in these patients, allowing for further delay in introducing subsequent salvage chemotherapy with minimal impacts on patient's quality of life.

Effectiveness

Previously only one trial, Study 19, met the eligibility criteria for inclusion and was reviewed by pCODR in 2016.[10]. Study 19 was a phase II randomized, double-blind, multi-centre study to assess the efficacy of olaparib in the treatment of patients with platinum-sensitive serous ovarian cancer following treatment with two or more platinum containing regimens. The pCODR review focused on the subgroup of patients with BRCA-m, germline or somatic, epithelial ovarian, fallopian tube or primary peritoneal cancer. The primary efficacy outcome was PFS in the larger intention-to-treat population. Subgroup analysis

for PFS in the BRCAm population was a pre-planned exploratory end point. In the BRCAm subgroup of patients, median PFS was 11.2 versus 4.3 months (hazard ratio [HR] = 0.18; 95% confidence interval [CI], 0.10 to 0.31; P < 0.0001) in the olaparib compared with placebo groups. This translated into a 6.9-month gain in PFS in the BRCAm-positive subgroup. The conclusion from that review was that Study 19 was not powered to detect a statistically significant difference for any endpoints in the BRCA-m subgroup. Additionally, the small sample size and multiple testing can lead to an increase in Type I error rate leading to uncertainty in the internal validity of the study. Lastly, the samples size calculation for PFS allowed for a Type I error rate of up to 20%.

The Final Recommendation from pERC on September 29, 2016 was to not reimburse olaparib, but suggested the possibility of resubmission to support reimbursement once the results of the phase III SOLO-2 trial were available.[11]

Preliminary results from the SOLO-2 trial, a double blind, placebo controlled randomized trial confirmed that the primary endpoint of PFS was improved compared to placebo when used as maintenance treatment in platinum-sensitive, relapsed ovarian cancer patients with mutations in *BRCA1* and/or *BRCA2* (germline and somatic). This was presented at the 2017 Society of Gynecology Oncology meeting in Maryland, USA in March 2017.[12] This trial met the inclusion criteria for this review. SOLO-2 evaluated the olaparib tablet with a dosage of 300 mg twice daily compared to Study 19 which evaluated the olaparib capsule at 400 mg twice daily.

Median follow-up for PFS was 22.1 months in the olaparib arm and 22.2 months for the placebo arm. Investigator assessed PFS was 19.1 months in the olaparib arm and 5.5 months in the placebo arm (HR 0.30; 95% CI 0.22-0.41; p<0.0001)). PFS assessed by BICR was 30.2 months in the olaparib arm and 5.5 months in the placebo arm (HR 0.25, 95% CI 0.18 to 0.35, p<0.0001).

Secondary endpoints including TSST, PFS and PFS 2 all favoured olaparib. Patients who had not experienced disease progression with olaparib after 12 and 24 months was 65.1% and 43% respectively, compared to 20.9% and 15.1% with placebo.

Due to short follow-up, the overall survival data are still immature. Although not statistically significant, the immature OS data (24% maturity) showed no detriment for patients receiving olaparib and an HR that numerically favored olaparib treatment (HR 0.80; 95% CI 0.50 to 1.31; P=0.4267; median not reached). Furthermore, progression-free survival is considered a clinically important and valid primary endpoint in studies of recurrent ovarian cancer therapy.[13]

Patient reported health related quality of life was similar in both groups in the first 12 months.

Prior to SOLO-2, Study 24, an open-label, multicentre, multi-stage, Phase I trial to compare the pharmacokinetics, efficacy, and tolerability of different doses and schedules of the olaparib capsule and tablet formulations with a goal of determining an optimal tablet dosing strategy for Phase III studies of olaparib was conducted. This study investigated the relative bioavailability of the tablet formulation of olaparib used in SOLO-2 and other ongoing Phase III trials compared to the currently approved capsule formulation. Study 24 demonstrated that patients' exposure to olaparib following tablet doses ≥300 mg BID matched or exceeded that of the approved 400 mg BID capsule formulation (8×50 mg capsules BID). In addition, the 300 mg BID tablet dose was better tolerated than the higher doses and showed similar effectiveness in tumour shrinkage. As such, continuous dosing of olaparib tablets 300 mg BID (2 × 150 mg tablets BID) is recommended for olaparib Phase III clinical trials, thereby simplifying drug administration from 16 capsules to four tablets per day.

Safety

Adverse events were more commonly observed with olaparib than with placebo. Common toxicities experienced by patients in the SOLO-2 trial include nausea (76%), fatigue (66%), vomiting (38%) and diarrhea (33%).[2] Serious adverse events occurred in 18% of the olaparib group compared to 8.1% of placebo. There was one death secondary to acute myeloid leukemia with olaparib. Secondary malignancies occurred in 3.6% of the olaparib group versus 5.1% of the placebo group. Acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML) occurred in 2.1% of the olaparib group compared to 4.0% of the placebo group. This raises the possibility that previous chemotherapy may have a potential role in these serious adverse events.

Dose interruptions were common, with an incidence of 45.1% with olaparib versus 18.2% in the placebo group. Toxicity leading to discontinuation of olaparib occurred in 10.8% of patients. Anemia (3.1%) and neutropenia (1.0%) were the most common adverse events leading to discontinuation of olaparib. Dose reductions following adverse events occurred in 25.1% of patients receiving olaparib.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to olaparib (Lynparza) as maintenance treatment for adult patients with platinum sensitive relapsed BRCA-mutated (*BRCA1 or BRCA2* and germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy. This is based on the results of the phase II randomized controlled trial, Study 19, and the preliminary results of the confirmatory SOLO-2 phase III randomized controlled trial that demonstrated a clinically and statistically significant benefit in progression-free survival for olaparib compared with placebo.

In making this conclusion the Clinical Guidance Panel also considered that:

- The observed benefit in ***BRCA*** is consistent with the known biologic mechanism of action of PARP inhibitors. The results of the trial are generalizable to patients with recurrences who are sensitive to a platinum based therapy in the second or later lines of therapy.
- The results of Study 19 and SOLO-2 are not generalizable to patients following first-line therapy, those with disease progression during or shortly after (within 6 months) platinum based therapy for disease recurrence, or patients who do not have a germline or somatic ***BRCA***-mutation.
- Patient reported outcomes did not suggest any significant deterioration of quality of life while on maintenance olaparib as compared to placebo.
- Although the inclusion criteria of Study 19 and SOLO-2 was limited to patients who have an ECOG $\leq$2, the CGP agreed that a decline in ECOG PS >2 due to recent chemotherapy or treatment related fatigue or other toxicities should not preclude patients from eligibility to receive olaparib. However, patients with a decline in PS due to progressive disease should not be eligible for olaparib.
- OS data in the SOLO-2 trial were immature at the time of data analysis. With sufficient follow-up, OS could be evaluated but any benefit may be confounded by subsequent treatments post-trial.
- The current Health Canada approved indication of olaparib is for adult patients with platinum sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy with a dose of 400 mg capsules (8 x 50 mg) twice daily. Olaparib tablets studied in SOLO-2 with a dose of 300 mg (2 x 150 mg) twice daily are currently not available in Canada but is expected to be available in the future. Until the tablets are approved by Health Canada, the CGP considered that the evidence from Study 19 (demonstrating efficacy for the capsule

formulation) and results from Study 24 (demonstrating that the capsules at 400 mg BID and the tablets at 300 mg BID have similar effectiveness and bioavailability) to be sufficient such that the capsules should be used in the place of tablet until Health Canada approval for the olaparib tablets is granted.

2. BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Genitourinary Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Ovarian cancer is the deadliest of all gynecologic malignancies with a high case fatality ratio as over 75% of present at an advanced stage. According to the 2015 Canadian Cancer Statistics,[14] there is an estimated lifetime risk of 1.4% to develop the disease in Canadian women. There will be 2800 new ovarian cancer cases diagnosed in Canada with 1750 deaths directly attributable to the disease in 2015 using the same estimate. Standard recommended primary treatment includes a full staging procedure in clinically apparent early stage cancer and primary debulking followed by adjuvant chemotherapy or neoadjuvant chemotherapy followed by interval debulking surgery and then further adjuvant chemotherapy in the advanced setting. The aim of surgery in advanced cases is to reduce the tumor burden preferably to microscopic disease.[15-17] Standard chemotherapy is a combination of Carboplatin with a Taxane.[18-20] Expected response rate to this combination therapy is in the range of 75% to 85%. Unfortunately, a majority of patients will recur requiring further therapy At the time of recurrence, patients are often classified as being 'platinum sensitive' if the time from their last platinum based chemotherapy was at least 6 months or more and 'platinum resistant' if the recurrence was within 6 months of completing chemotherapy.[21,22]

Serous ovarian cancer is the most common epithelial tumor. mBRCA and other important defective components of the homologous recombination (HR) pathway can be detected in between 20 % to 30% of high grade serous ovarian cancer[23,24] that can predict increased platinum sensitivity and improved survival. Furthermore, The Cancer Genome Atlas (TCGA) project had shown that up to 50 % of high-grade serous ovarian cancers might have some defect in the HR pathway. Poly-ADP-ribose polymerase (PARP) is a family of enzymes composed of 17 members. PARP-1 is the best-characterized member of this family that plays an important role in the repair of single-strand breaks (SSB) by base excision repair. It has also been implicated in other roles involving DNA repairs. In cells that are deficient in double-strand break repair due to defects in homologous recombination (HR) pathways, inhibition of PARP and SSB repair often resulted in severe cellular damage and death. While inhibition of the enzymatic function of PARP was initially postulated to be the primary mechanism by which PARP inhibitors is mediated, subsequent research has suggested that a number of different mechanisms are also at work causing cells death.[25-28] Olaparib (Lynparza) is one of the most well studied PARP inhibitor. In 2014, based on the demonstration of its anti-cancer activity, the European Medicines Agency (EMA) granted its approval as maintenance therapy in patients with BRCA mutated ovarian cancer with platinum-sensitive recurrence The US Food and Drug Administration approved olaparib for the treatment of recurrent germ line BRCA-mutated (gBRCAm) ovarian cancer after at least three prior chemotherapy regimens in 2016.

2.2 Accepted Clinical Practice

Ovarian cancer recurrence is considered incurable and the goals of any therapy going forward are to delay time to subsequent progression, improve quality of life 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 illness. Management of platinum sensitive recurrences can include any combination of platinum based systemic therapies +/- bevacizumab and secondary cytoreductive surgery as appropriate.[29,30] Treatment plans need to be individualized taking into account each patient's current performance status, prior treatment related residual toxicities, overall disease burden and distribution at time of recurrence diagnosis. The general accepted clinical practice is to retreat with a platinum drug either as a single agent or as part of a combination regimen until platinum resistance develops defined as disease progression during therapy or within 6 months of the last platinum

treatment. In these sensitive patients, platinum based combination therapy[31,32] can have an expected response rate of around 50% - 60%. It is expected that each subsequent progression free interval will be shorter than previously experienced progression free time.

Due to the high-expected recurrence rate in advanced cases (stage III and IV), maintenance strategies had been studied in an effort to delay and also prevent recurrences. Prolonged uses of alkylating agents, platinum agents, and paclitaxel have not been shown to significantly increase overall survival although there has been an increase in PFS. However, maintenance therapy is associated with increased toxicities.[33-36] Hence, maintenance therapy after response to cytotoxic chemotherapy is not currently standard clinical practice. The SWOG study on maintenance taxane was associated with alopecia and neuropathy leading to impaired QoL. The improvement in median PFS was 8 months (improvement from 14 to 22 months) with no increase in OS .The study was stopped early due to toxicity. Hence there is no role of maintenance chemotherapy at the present moment after recurrence. Eventually, all patients with recurrent disease will develop resistance to platinum drugs with increasingly shortened progression free interval. [37] Further non-platinum chemotherapy can be considered at that time with an expected response rate between 15% and 25%.

More recently, a large number of potential therapeutic targets have been identified and a number of biologic agents designed to block receptors, ligands or pathways were studied in large phase III clinical trials with very encouraging preliminary results after first line chemotherapy as maintenance and in the recurrence settings.[38]

PARP (poly (ADP-ribose) polymerase) inhibitors, belong to a novel class of medication that works by preventing cancer cells from repairing their DNA once it have been damaged by chemotherapy agents. Olaparib is the most well studied of all PARP inhibitors. Pooled data from recent Olaparib monotherapy trials in germ line BRCA mutated patients with recurrent ovarian cancer who had received multiple lines of prior chemotherapy was summarized in a recent publication.[39] Data from two Phase I trials (NCT00516373 [Study 2]; NCT00777582 [Study 24]) and four Phase II trials (NCT00494442 [Study 9]; NCT00628251 [Study 12]; NCT00679783 [Study 20]; NCT01078662 [Study 42]) that recruited women with relapsed ovarian, fallopian tube or peritoneal cancer treated with Olaparib 400 mg monotherapy twice daily (capsule formulation) were aggregated. Of the 300 patients in the pooled population, 273 had measurable disease at baseline, of whom 205 (75%) had received ≥3 lines of prior chemotherapy. In the pooled population, the overall response rate was 36% (95% CI: 30, 42) and the median duration of response was 7.4 months (95% CI: 5.7, 9.1). The overall response rate among patients who had received ≥3 lines of prior chemotherapy was 31% (95% CI: 25, 38), with a duration of response of 7.8 months (95% CI: 5.6, 9.5). Of interest, olaparib treatment benefits were observed both in platinum-sensitive (platinum sensitive, but ineligible to receive further platinum-based chemotherapy) and platinum-resistant patients. The overall response rate declined as the number of prior lines of treatment increased e.g. the overall response rate for patients treated with one prior regimen was 50% and dropped to 24% for patients who had received ≥6 prior regimens. There was also a reduction in duration of response as the number of prior lines of treatment increased.

The safety profile of olaparib was similar in patients who had received ≥3 lines of prior chemotherapy compared with the pooled population. In the overall pooled analysis, a total of 113 (38%) patients had adverse events (AEs) leading to dose interruptions, with the most common causes being vomiting (21 [7%] patients) and anemia (12 [4%] patients). For the subset of patients who had received ≥3 lines of prior chemotherapy, 89 (40%) patients had AEs leading to dose interruptions; the most common causes were vomiting (18 [8%] patients) and anemia (11 [5%] patients). Overall, 15 patients (5%) experienced at least one AE that led to discontinuation of study treatment. All of these patients had received ≥3 lines of prior chemotherapy (7% in this subgroup). In the overall pooled analysis, eight patients (3%) had an AE leading to death, either on treatment or within 30 days of discontinuing treatment, and all had received ≥3 lines of prior chemotherapy. The AEs leading to death were: sepsis, intestinal perforation, suture rupture, acute leukemia in a patient who had a diagnosis of myelodysplastic syndrome at study entry, acute myeloid leukemia (AML), cerebrovascular accident, chronic

obstructive pulmonary disease and pulmonary embolism. The incidence of AE leading to death was 0.3% in the overall pooled set (0.4% in the subgroup of patients who had received ≥3 lines of chemotherapy). None of the AEs leading to death was considered causally related to Olaparib. This was part of the evidence the FDA considered before approving olaparib for the treatment of recurrent germ line BRCA-mutated (gBRCAm) ovarian cancer after at least three prior chemotherapy regimens.

2.3 Evidence-Based Considerations for a Funding Population

The expected patient population will be those with platinum-sensitive relapsed BRCA-mutated (germline or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have responded (complete response or partial response) to platinum-based chemotherapy (second line or beyond) for disease recurrence. Olaparib will be used in a maintenance setting as monotherapy until further clinical disease progression or intolerable toxicities occur.

It is estimated that about 15% to 20% of all patients with ovarian, fallopian tubes, and primary peritoneal cancers would be considered for this therapy during the course of their illness.

The clinician using standard criteria will easily define platinum sensitive recurrence. The presence of *BRCA* gene mutation will require additional genetic testing. Universal *BRCA* testing is currently recommended for all patients with high grade serous cancers. Utilization of olaparib should be limited to patients with proven germ line or somatic *BRCA1 or BRCA2* gene mutations based on existing data.

In 2014, olaparib has been approved by the European Medicines Agency to be used as maintenance therapy in patients with BRCA mutated ovarian cancer with platinum-sensitive recurrence and the US Food and Drug Administration for the treatment of recurrent germline BRCA-mutated ovarian cancer after at least three prior chemotherapy regimens. In January of 2016, the National Institute for Health and Care Excellence (NICE) also recommended that olaparib can be used as a maintenance treatment option for patients with relapsed, platinum-sensitive ovarian cancer, fallopian tube cancer, or peritoneal cancer who have *BRCA1* or *BRCA2* mutations and whose disease has responded to subsequent platinum-based chemotherapy. Olaparib was recommended only for people who have had three or more courses of platinum-based chemotherapy and the drug cost of olaparib for people who remain on treatment after 15 months is met by the company by NICE guideline.

In a 2016 review with pCODR-CADTH, evidence from Study 19 was evaluated. At the time, the pCODR Expert Review Committee (pERC) recommendation was not to fund olaparib as the Committee was not confident that there was a net clinical benefit of olaparib maintenance treatment compared with placebo, due to limitations in the evidence from the available multiple subgroup analysis.[11] pERC noted that although olaparib produces some anti-tumor activity, the Committee concluded that there was considerable uncertainty in the magnitude of clinical benefit of olaparib compared with placebo in regards to outcomes important to decision-making, including overall survival, progression-free survival, and quality of life. As potential next steps for stakeholders, pERC noted the possibility of a resubmission to support reimbursement. The Committee acknowledged that a phase III randomized controlled trial (RCT), SOLO-2[2], comparing olaparib maintenance monotherapy with placebo in patients with platinum-sensitive relapsed *BRCA*-mutated ovarian cancer with complete or partial response following platinum-based chemotherapy and who have documented *BRCA 1* or *BRCA 2* mutation, is currently ongoing. The current review is a resubmission for olaparib based on the confirmatory results of the SOLO-2 trial.

2.4 Other Patient Populations in Whom the Drug May Be Used

Other than the use of olaparib either as maintenance therapy or as monotherapy for relapsed ovarian cancers, potential uses that are being actively investigated in many ongoing clinical trials including its use in combination with chemotherapy to achieve better clinical response[40,41] or in combination with other anti angiogenic, immunomodulatory agents to increase the effectiveness of olaprib in a broader patient base and prevention of PARPi resistance.[42,43]

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Ovarian Cancer Canada (OCC), provided input for olaparib (Lynparza) as a maintenance monotherapy treatment for adult patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy, and their input is summarized below.

OCC conducted an anonymous online survey that was promoted to those living with ovarian cancer and their caregivers through the organization's database, website, social media sites and partners. OCC targeted the survey to those who: (1) were diagnosed with epithelial ovarian, fallopian tube or primary peritoneal cancer and; (2) have been treated with chemotherapy and; (3) had at least one recurrence of ovarian cancer at least six months after end of treatment and; (4) tested positive for a BRCA gene mutation and; 5) may or may not have taken olaparib as a treatment for their recurrent ovarian cancer. OCC reported receiving responses from 40 respondents, where 31 of the responses were from ovarian cancer patients and nine (9) responses were from caregivers. The sample included 21 patients with epithelial ovarian cancer, four (4) with fallopian tube cancer, three (3) with primary peritoneal cancer and three (3) who designated their ovarian cancer as 'other'. Among the ovarian cancer patients who responded, the majority (68% of the 31 respondents) were diagnosed between 2010 and 2015, and ten respondents were diagnosed between 2000 and 2009. Furthermore, these patients were more likely to be diagnosed at stage III or IV (74%) and had a *BRCA 1* gene mutation (64.5%). Respondents ranged in age from 35 to 72 years, and approximately 68% of respondents were 50 years and older. These responses were predominantly received from Canadian respondents, but there were no respondents from New Brunswick, Newfoundland, Prince Edward Island, Northwest Territories, Nunavut or the Yukon. There were also four respondents from the United States. Fifteen respondents indicated that they or those they were caregiving for had used olaparib as a treatment for ovarian cancer.

From a patient perspective, the impact of ovarian cancer is significant for women diagnosed with this disease and their caregivers. Because early symptoms can be non-specific and generally there is no screening test, ovarian cancer is usually detected in its later stages resulting in a poor prognosis. Surgery and chemotherapy have been the mainstays; however, as most women are likely to face a recurrence, OCC believes it is helpful to have a greater spectrum of agents with which to treat this type of cancer. Patients who have not taken olaparib indicated that the most important factors that olaparib should and address include prolonging survival, lengthening time until recurrence, improving their quality of life, and reducing visits to the cancer centre as this is an oral therapy. OCC reported that 13 patient and two caregiver respondents had direct experience with olaparib. The primary treatment side effects of olaparib included tiredness/weakness, nausea, taste changes, blood problems and dizziness, which were found to be similar in the larger group of women with ovarian cancer who had received olaparib. It was reported that a majority of respondents who have experienced with olaparib stated that they had experienced improved quality of life compared to previous treatments.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission and have not been corrected. OCC indicated that the number of respondents differs for each question given that some survey participants chose to skip questions.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Ovarian Cancer

OCC reported that the impact of ovarian cancer is enormous for those diagnosed with this disease and their caregivers.

The OCC asked respondents to describe overall how their lives had been affected by their diagnosis of ovarian cancer. Responses (N = 31/40) indicated that their lives were profoundly affected by ovarian cancer, such as significant psycho-social impacts, including fear, depression, worry and anxiety. Other negative impacts also included, but were not limited to, decreased sexual relationships, sleep disruptions, work life, lack of physical activity and well-being. Some of the key responses recorded were as follows:

- *"My memory and cognition has been negatively impacted. I have had to end my career earlier than planned due to treatment..."*
- *"I don't go to places I love because my blood counts are always low and I don't want to catch the colds & flu germs in crowded environments. This means I live a very isolated life..."*
- *"I am not the same person. I no longer teach - all the chemo has changed my brain so that I am unable to be in a crowd, to think on my feet, to plan, to make decisions... my world has been changed..."*
- *"The thought of recurrence is always in the back of your mind - not 'if' it will come back, but 'when'. The knowledge that chemotherapy may not be effective next time is very stressful..."*
- *"Sleep is adversely affected, as is the ability to enjoy life. Surgery and chemotherapy are debilitating, preventing you from working, caring for your family and even exercising..."*
- *"I am a 35-year-old woman. After my recurrence in my brain, I have been severely impacted. Today I am unable to work. I also lost my driver's license in the last year, which has severely limited my independence..."*

Respondents were also asked to rate the impact of ovarian cancer on their lives on a scale from 1 (no effect) to 5 (extremely negative). Below were the specific areas where respondents (N = 31/40) rated a score of 4 (very negative) or 5 (extremely negative):

- Sexual relationship = 18
- Sleep = 14
- Work life = 12
- Physical activity =9
- Well-being = 9

3.1.2 Patients' Experiences with Current Therapy for Ovarian Cancer

According to OCC, respondents' reported that their current treatments included chemotherapy and surgery. OCC also reported that 37 respondents replied to the question that their current treatment managed their ovarian cancer, which included chemotherapy and surgery. Seventeen of the 37 respondents reported that they agreed or strongly agreed that their current (or past) treatments were able to manage their ovarian cancer (based on a weighted average of 3.78). However, the OCC has indicated that that some of the comments noted below may demonstrate that their treatment was not as effective as the score would suggest:

- *"The treatments have kept me alive but it comes at a cost of not fully being able to live life fully..."*
- *"While on chemo, yes it worked - took all tumor markers down. Did what it was supposed to do. But 6 months later I started all over again..."*
- *"Since I have had four relapses, traditional chemo has failed to stop the cancer from returning. It has also harmed my hearing..."*
- *"The initial treatments did control the tumour growth, but she has the recurrence of ovarian cancer and now receiving chemotherapy..."*

According to respondents, their ovarian cancer treatments negatively affected them. Respondents were asked to rate the effect of treatments they received, on a scale from 1 (no effect) to 5 (extremely negative effect), on aspects of their life. Respondents (N = 37) reported on a number of areas that were rated as having a negative influence on their lives. The areas that the respondents, including caregivers rated as a score of 4 (very negative) or 5 (extremely negative) are noted below:

- Fatigue = 23
- Bowel problems = 20
- Hair loss = 18
- Blood problems = 15
- Neuropathy = 13
- Nausea/vomiting = 11
- Aching joints = 11
- Ascites = 7
- Skin irritations = 5
- Loss of fertility = 3

A majority of respondents noted that fatigue had a major impact. Specifically, 67% of respondents rated their fatigue as having a large effect or extremely large effect on their quality of life.

- *"I am very tired, not able to do what I used to do, not a lot of energy..."*
- *"I find now I tire easier so I need my rest or nap in the afternoons. I feel exhausted at times when I guess I overdo it..."*
- *"I am trying to be more active, however, the chemo I am currently on for my recurrence is completely wiping out my energy..."*

Another key area of impact that was mentioned included bowel issues.

- *"I have gone through chemo 4 times, radiation once, and surgery. I have a narrow rectum as a result of surgery, partial bowel obstruction and where my cancer keeps returning. This means I have to have a very rigid morning schedule in order to keep my bowels very soft. My oncologist tells me I will eventually have a colostomy if I live long enough. I can't travel with friends very well because of my morning routine..."*
- *"I have not been cancer free for the last 2 1/2 years and have been in constant treatment. I've had several hospital stays for partial bowel obstructions due to adhesions so have totally changed my diet to prevent these..."*

Respondents also described their experience with side effects, such as:

- *"Headaches are more frequent and currently experiencing mouth and throats sores..."*
- *"Fluid in lungs..."*
- *"Neutropenia; blood clot after inserting picc line; occasional acid reflux..."*
- *"My hearing has deteriorated significantly every time I have been on traditional chemo, requiring hearing aids, at additional cost. I have stiffness in my joints and some neuropathy in my feet. I also suffer from chemo brain (aka brain fog) where I can have difficulty remembering words while speaking and typing incorrect words..."*

According to the OCC, the majority of respondents were willing to tolerate additional side effects if the benefits of the treatment were considered to be short term (n = 27/37). The respondents provided the following comments:

- *"I would tolerate until my quality of life diminished to where I could no longer care for my family..."*

- *"Anything short of being bedridden 24/7..."*
- *"If it would give me more time with my family I would tolerate as much as I could..."*
- *"I have a fairly high tolerance of side effects - willing to put up with a lot short term for long term gain..."*
- *"Prête à tout..."*

Below are additional comments gathered from caregiver respondents on whether their family or friends would be willing to tolerate other side effects:

- *"These are not life threatening and the doctor will prescribe medications to take care of it. Exercise can improve tiredness..."*
- *"She wants to live..."*

Respondents were asked about the barriers to accessing treatments (e.g. financial difficulties, treatment not available). According to OCC, respondents (n=29) indicated that the top barriers are:

Respondents were asked to rate the effect of treatments they received, on a scale from 1 (no effect) to 5 (extremely negative effect), on aspects of their life. The responses indicate the number of respondents that chose four (4) or five (5) on the scale, which are the two highest ratings for significance.

- Travel = 5
- treatment not available = 3
- Financial issues = 1

Below are key comments gathered from OCC respondents:

- *"We travel nearly 4 hrs one way for treatment. We do spend a lot of money on travel, meals and accommodations..."*
- *"Lucky that I live in Toronto and being cared for at...and...Also lucky my employee insurance is helping to cover some costs on expensive meds to treat neutropenia and a blood clot discovered after inserting a picc line..."*
- *"We determined to seek help where we found it. Took extreme physical and financial effort which I did. Eventually could no longer do this when I was on a 2nd trial out of Toronto and became very debilitated..."*

3.1.3 Impact of Ovarian Cancer and Current Therapy on Caregivers

OCC reported that nine (9) caregivers responded to this survey: five respondents were a spouse/partner; two respondents were mothers; and two respondents were other family members. OCC indicated that these caregivers have been providing care between less than 2 years to more than three years for women with ovarian cancer. The time spent on caregiving ranges between 1 – 12 hours per day. Caregivers reported sleep, sexual relationships, work life, and self-esteem as being the most significant negative impact. Some of the key responses recorded were as follows:

- *"Travel plans have been put on hold. Some household chores are now my responsibility..."*
- *"I now try to keep work only to the hours of 9-5 on workdays. We make plans only a month in advance at a time; this is very difficult to do and to manage well..."*
- *"Substantial worry; daily routines are substantially affected by medicinal requirements..."*

Respondents were asked to rate how caregiving has impacted the following issues in your life, on a scale from 1 (no effect) to 5 (extremely negative effect), on aspects of their life. Respondents (N = 7) reported on a number of areas that were rated as having a negative influence on their lives. The areas that the caregiver respondents rated as a score of 4 (very negative) or 5 (extremely negative) are noted below:

- Sleep pattern = 4
- Sexual relationship = 3
- Work life = 3
- Self-esteem = 2

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Olaparib

Patient Expectations with Olaparib

Twenty-one respondents who have not been treated with olaparib responded to the survey about their expectations with the drug under review. Among the 15 respondents who considered taking olaparib, the majority stated that they would consider taking it because it would prolong a recurrence (n=15/15) while others also considered that it can be taken at home (n=9/15) and it does not cause hair loss (n=6/15).

OCC asked respondents to indicate the most important factors that olaparib should and address, and 16 respondents indicated the following:

- Expect the drug to prolong their survival = 16
- Lengthen time until recurrence = 16
- Improve their quality of life = 15
- Reduce visits to the cancer centre = 12

The OCC indicated that the majority of respondents were willing to deal with many side effects. The side effects that respondents (n=17) were the most willing to deal with are indicated below:

- Nausea = 17
- Tiredness = 15
- Taste changes = 14
- Blood problems = 12
- Bruising and bleeding easily = 9
- Pain under the ribs = 9
- Sore Mouth = 9
- Diarrhea = 11
- Headaches = 10
- Dizziness = 9
- Infections = 8

Respondents also stated that they would be less willing to tolerate the following side effects: blood disorders or blood cancer (N=5/21) and inflammation of lungs (n=5/17).

Below are some of the key comments gathered from the respondents on their willingness to tolerate olaparib's side effects:

- *"They can be controlled..."*

- *"Because I am tolerating many of them now (although I would like to get RID of the pain under my ribs, which can be debilitating). Nausea and fatigue would depend on degree..."*
- *"Because the drug works to extend time between relapses..."*
- *"With Stage 4 terminal cancer I would be willing to try anything to prolong my life..."*

OCC reported that fourteen respondents (n=14) expressed that the benefit of taking olaparib was to increase the length of time before recurrence (n=8); prolong life (n=7); and improved quality of life (n=2). Furthermore, among these respondents, one foresaw no risks of taking olaparib, while four were not sure about potential risks, seven considered the side effects and quality of life to be risks and two were concerned about side effects with no benefits. However, the majority of these respondents stated that the benefits of olaparib outweighed risks (n=10), whereas three were not sure and one stated that the benefits did not outweigh risks.

Patient Experiences with Olaparib

OCC indicated that fifteen (15) respondents, including patients and caregivers, had direct experience with olaparib. Respondents stated that treatment with olaparib was able to prolong survival; improve quality of life; and lengthen the time of recurrence.

Respondents reported that they experienced the following side effects with olaparib:

- Tiredness/weakness = 13
- Nausea = 8
- Taste changes = 8
- Blood problems (e.g. anemia) = 6
- Dizziness = 6
- Diarrhea = 5
- Headaches = 2
- Pain under the ribs = 2
- Bruising/bleeding easily = 2
- Sore mouth = 1
- Blood disorder or blood cancer = 1
- Infections = 0
- Inflammation of the lungs = 0
- None = 2

In terms of side effects, the most common unacceptable side effect reported by three respondents were blood problems. Other unacceptable side effects, including tiredness, bowel issues, blood disorders, pain, inflammation in the lungs, infections and elevated creatinine were each mentioned once by respondents. The OCC noted that four (4) respondents said no side effects were unacceptable.

OCC reported that among the 12 respondents, seven (N =7) respondents agreed or strongly agreed that olaparib had improved their quality of life compared to previous treatments. However, three of these respondents rated treatment with olaparib as neither positive nor negative. More specifically, patients stated that:

- *"It was great to take an oral chemo although the amount of pills required daily was a bit much..."*
- *"No negative impact....other than remembering to take the pills..."*
- *"I now feel cancer free and have evidence of being cancer free. I also have no negative side effects and have no trouble taking the medication..."*
- *"Allowed me to stay alive without chemo and enjoy my quality of life, though reduced..."*

- *"I was starting to struggle with day to day function as signs of returning disease were present. I then started Olaparib and within 3 months all signs of disease were gone..."*
- *"My positive response to Olaparib came quicker than any of the other treatments I have endured..."*

OCC noted that the majority of respondents (patients and caregivers) indicated that olaparib should be available as a treatment option for women in Canada who have a BRCA gene mutation and platinum-sensitive recurrent ovarian cancer. The following statements were reported:

- "*Even though it didn't work for me, I believe it should be an option for women with BRCA mutations*..."
- "*I had a positive response to Olaparib in less than 4 weeks (my very high CA125 number dropped nearly 40%). In less than 4 months, I was NED. In less than 6 months, my CA125 was in the normal range for the first time in nearly 2 years*..."

3.3 Additional Information

The OCC indicated that the lower number of respondents that provided feedback on this new treatment does not reflect a lack of interest from women who are living with ovarian cancer. In fact, the OCC noted that in Canada, the low response rate was most likely due to the restrictive criteria since approximately 20% of high grade serous ovarian cancer is caused by a BRCA gene mutation.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- No treatment option currently for maintenance therapy
- New treatment option that is an oral drug
- The clinical benefits, safety and therapeutic equivalence of 400mg twice daily in capsules compared to 300mg twice daily in tablets
- Guidance on switching from tablets to capsules or from capsules to tablets, when the tablets become available
- Clarity on whether patients previously treated with three or more lines of chemotherapy are considered in the trial and in the funding request

Economic factors:

- Resources for BRCA testing
- Additional therapy that is maintenance therapy and does not replace intravenous chemotherapy when patients progress on maintenance therapy

Please see below for more details.

4.1 Factors Related to Comparators

PAG identified that there is currently no maintenance treatment available for patients with platinum sensitive disease. The standard of care is best supportive care or observation.

4.2 Factors Related to Patient Population

PAG noted that olaparib would be additional therapy as it is maintenance therapy and does not replace chemotherapy.

The SOLO2 trial allowed patients who have received at least two previous lines of platinum containing therapy prior to randomisation. PAG is seeking clarity whether the review is intended for patients who have received only two lines of platinum-based therapy (and remain platinum-sensitive) or whether patients who have received more than two lines of platinum-based therapy and remain platinum-sensitive are included. PAG seeking data on number of patients in trial with two previous lines of therapy compared to those with three or more lines of therapy. If the submission (and model) is intended only for patients who remain platinum-sensitive after second line platinum, then the time-limited may be needed for patients who are already on more than 3 lines of therapy.

In the SOLO2 trial, treatment with olaparib started within eight weeks of completion of last dose of chemotherapy. PAG is seeking guidance on whether olaparib could be considered for patients who have completed platinum based chemotherapy more than eight weeks ago and what maximum time between completion of chemotherapy and commencement of olaparib would be.

PAG has concerns for indication creep for use in first-line in combination with chemotherapy, in maintenance therapy after one line of platinum based chemotherapy, for BRCA positive platinum sensitive relapsed ovarian cancer or for BRCA positive platinum resistant ovarian cancer, including patients treated with bevacizumab. PAG noted these patients would be out of scope of this review.

4.3 Factors Related to Dosing

In the SOLO2 trial, the dose of olaparib is 300mg (2 x 150mg tablets) twice daily. The funding request indicates the dose is 400mg (8 x 50mg capsules) twice daily. PAG is seeking data demonstrating that dose using capsules is therapeutically equivalent to dose using tablets. PAG is also seeking bioequivalence data and safety of the two different formulations and doses.

PAG noted there is pill burden associated with the capsules: at a dose of 400mg twice daily, patients are taking 16 capsules per day.

PAG also noted that there are patient participating in clinical trials using the tablets and is seeking guidance on the transition from tablets to capsules, when the patient completes the clinical trial and if olaparib capsules are funded.

4.4 Factors Related to Implementation Costs

There will be costs associated the BRCA testing as BRCA mutation is not routinely tested at this time. In addition, PAG noted that the BRCA test results can take a long time and there would be a delay in the initiation of treatment from completion of platinum-based chemotherapy. PAG noted that there will be a large number of patients requiring BRCA testing to identify the 20% who would be eligible for treatment with olaparib. This adds tremendous strain to limited resources in genetic testing.

Olaparib is a new class of drug and health care professionals will need to become familiar with monitoring adverse events and drug-drug interactions. PAG has concerns that the high rate of grade 3 and 4 anemia could impact quality of life significantly at this stage of disease and would require resources to manage. PAG also noted that the risks of developing Myelodysplastic syndrome/Acute Myeloid Leukemia and pneumonitis are not insignificant and additional resources would be required to monitor monthly and treat these serious adverse event.

4.5 Factors Related to Health System

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

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

4.6 Factors Related to Manufacturer

The current Health Canada approval and the funding request indicates the dose is 400mg (8 x 50mg capsules) twice daily. The SOLO2 trial submitted for review used a dose of 300mg (2 x 150mg tablets) twice daily. At the time of the PAG input, the 50mg capsules are on the Canadian market but not the 150mg tablets. PAG is seeking information from the manufacturer on when the 150mg tablets will be available in Canada, what the plans on transitioning capsules to tablets would be and whether the capsules will remain available for patients already on it. PAG is requesting bioequivalence data demonstrating the dose of 400mg using 8 x 50mg capsules is therapeutic equivalently to the dose of 300mg using 2 x 150mg tablets.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Four clinician inputs were received. Two clinician inputs were provided as a joint submission from a total of ten oncologists. Two clinician inputs were received from two individual oncologists.

The clinicians providing input noted that olaparib is a well-tolerated oral drug, providing this group of patients an opportunity to extend remission significantly and potentially delay time to next chemotherapy. It is felt there is a huge unmet need, specifically targeted therapy in ovarian cancer, and the improvement in progression-free survival is significant, given the high rate of relapse. It was noted that the funding request for maintenance treatment of patients after platinum-based chemotherapy, regardless of specific number of relapses or timing, is the appropriate indication.

Please see below for a summary of specific input received from the registered clinicians.

5.1 Current Treatment(s) for Ovarian Cancer

All clinicians providing input identified that there are currently no approved medications or comparable monotherapy with evidence for maintenance therapy of ovarian cancer after induction of remission with chemotherapy.

One joint clinician input also noted:

- A subpopulation of patients with ovarian cancer will carry a BRCA mutation either as the inherited (i.e. germ line mutation) (10%) or secondary to acquired, such as somatic mutation (5%). The majority (70%) of these patients have stage III or IV disease and 90% will relapse post first line chemotherapy. Of the patients with stage I and II disease, 60% will relapse. Of all these relapses, 66% will fulfil the criteria of being platinum sensitive (i.e. recur greater than six months after discontinuing first line therapy). The registered clinician noted that these patients can benefit from olaparib.

- There is no curative therapy available in this scenario and multiple consecutive treatment lines are usually administered. Therapy at the time of first relapse usually consists of a combination of carboplatinum plus paclitaxel, docetaxel, gemcitabine or liposomal doxorubicin. Subsequent relapses are usually treated with single-agent chemotherapy with any of the following: platinum analogues, taxanes, gemcitabine, liposomal doxorubicin, vinorelbine, topotecan or etoposide.

- As such there is a need for additional therapies that can increase the chemotherapy-free interval with the opportunity to improve overall survival. The PARP inhibitors are targeted therapies inducing synthetic lethality that in the BRCA population can achieve about 50% response. Some (10 to 15%) patients have benefitted from three or more years of cancer-free survival with olaparib single agent treatments, which is not seen with standard chemotherapy.

5.2 Eligible Patient Population

One group of clinicians noted that the eligible patient population would be BRCA positive patients who have received three or greater lines of therapy. The potential number of patients per year over the next five years across Canada would probably number about 1000.

Another group of clinicians providing input indicated that approximately 85% of patients with BRCA mutation will develop recurrent-platinum sensitive disease and be treated with second-line platinum therapy. Of these patients, 75% will have response and be eligible for maintenance therapy. Therefore, approximately 25% of new advanced stage cases per year will eventually qualify for olaparib maintenance.

One clinician providing input noted that this is not a large population but it is one of the first drugs that leverage our expanding knowledge of the molecular genetics of this disease and

allows us to show direct benefit to identified patients. Given the overall poor prognosis for these patients, this is an incredibly significant impact clinically and for the patient.

Another clinician providing input indicated that about 75-80% of women with this cancer type will relapse after first-line therapy, so there will be high demand, as this is often a fairly rapidly lethal condition, with progressive loss of quality of life due to cancer relapses and frequent re-exposure to chemotherapy. There won't be as high a prevalent population because this would generally be started in women who have relapsed ovarian cancer, and who have fairly recently completed a course of chemotherapy to bring cancer symptoms under control. Patients who are symptomatic from regrowing cancer will not be good candidates for this maintenance type approach, and often symptomatic relapse occurs within months of completion of prior chemotherapy.

5.3 Identify Key Benefits and Harms with Olaparib

One group of clinicians identified the key benefits and harms as follows:

Benefits

- Significantly improves PFS (11.2 months vs. 4.3 months, HR = 0.18 in germline positive BRCA patients; Ref: Study19)
- Easy to administer
- Convenient for patients as an oral take-home cancer drug
- Good tolerability

Harms

- Minimal clinically significant side effects

Another group of clinicians noted that PARP inhibitors have a significantly improved toxicity profile compared to chemotherapy. Fatigue, anaemia and nausea being the predominant side-effects which do not require significant assessment and are easily managed by dose interruption alone or dose reduction. Their patients report that their quality-of-life is better on PARP inhibitors than any standard cytotoxic chemotherapy.

They noted that the only potential harm is myelodysplastic syndrome. The rate is low (about 1%) and the association between PARP inhibitors and myelodysplastic syndrome is not clearly established, making it not significant in the balance of values for patients with relapsed incurable cancer.

The individual clinician inputs reiterated similar benefits and harms:

- The main benefits are that this drug may be quite reasonably tolerated and could extend remission significantly after completion of chemotherapy for relapse, thus potentially delaying the next needed chemotherapy course, improving QOL, and extending survival in those who are long-term responders. The longer disease can be kept at bay, also, the more possibility a woman may have the option to consider clinical trial agents that may be promising, or may benefit from the conduct of those trials, that we hope may allow us to expand the options available for ovarian cancer management.

- The main harms include the small possibility that PARP inhibitor therapy may increase the risk of myelodysplasia or leukemia, though thus far the data from studies don't show a significant excess of such occurrences, compared to women simply with chemotherapy exposure of a similar degree. Women may have negative impacts on QOL from such toxicities as stomach upset/diarrhea/fatigue and reversible cytopenias, but these may be reasonably managed with dose adjustments.

5.4 Advantages of Olaparib Over Current Treatments

The clinicians providing input noted that there is currently no maintenance therapy available. Olaparib would be an oral option, with low and manageable toxicity profile, for maintenance to improve progression-free survival and delay time to next chemotherapy for this group of

patients.

Specifically, in one of the clinician inputs:

- There is currently no therapy known to extend off-chemo remissions, and the durations of remission are generally progressively shorter over time, with increasing symptoms of cancer and/or increasing chemotherapy exposure.
- There is a huge unmet need for therapies which may extend remission and thus improve QOL, and as well hopefully extend survival.
- These drugs are now being studied in the first line setting to determine whether they can impact on relapse rate, or simply time to relapse.
- An improved cure rate, if achieved, would fill a huge unmet need, given the high relapse rates.

5.5 Sequencing and Priority of Treatments with Olaparib

The clinicians providing input identified that olaparib would be an additional therapeutic option as single agent maintenance therapy. Olaparib would not displace any current therapies and may reduce chemotherapy use over time for patients who have long response.

Although out of scope of this review, one clinician input noted that if the first line trials demonstrate a reduction in relapse, this would of course be the most exciting displacement of the need for chemotherapy at relapse. Patients achieving longer term remissions may require less intervention with paracenteses and palliative surgeries over time, as well.

In addition, one clinician noted that the indication sought was after first or subsequent relapse, with no specified requirement for a particular time window since prior therapy. This is an appropriate indication and the clinician is pleased that there did not seem to be an arbitrary limitation of availability to a particular relapse number or timing.

5.6 Companion Diagnostic Testing

The clinicians providing input indicated that BRCA mutation (somatic and germline) testing is essential to determine susceptibility to PARP inhibition and thus, response to treatment with olaparib. One group of clinicians felt that BRCA mutation testing would ideally be done as reflex testing at the time of diagnosis in the provinces.

5.7 Additional Information

One group clinician input was surprised by the negative recommendation from the previous submission for olaparib. The current submission answers the question of degree of benefit, based upon high level phase III data.

- The impact of ovarian cancer is considerable for patients and their caregivers. Timely access to emerging cancer therapies profoundly affects the lives of women with ovarian cancer and their families. There has been a lack of progress in treatment options for ovarian cancer for several decades, heightening the urgent unmet need that must be addressed for patients with this disease.
- Olaparib delays disease progression and extends the time before requiring subsequent cytotoxic chemotherapy, and maintains the quality of life of patients. This is achieved with minimal toxicity and the convenience of an oral medication.
- Canadian women with ovarian cancer remained at a distinct disadvantage as Lynparza was being marketed in over 45 countries worldwide
- The large clinical benefit and safety data from the randomized phase III trial, SOLO-2 (with the new tablet formulation), was consistent with the findings from Study 19 (capsule formulation)
- Both, Study 19 and the confirmatory SOLO-2 trial results, clearly establish the net clinical benefit of olaparib for patients with ovarian cancer and BRCA mutations, who have a platinum sensitive relapse. Olaparib achieves the primary goals of

maintenance therapy (PFS and OS), maintains quality of life, and addresses the high unmet need and gap in treatment that is present in patients with ovarian cancer.

6 SYSTEMATIC REVIEW

6.1 Objectives

The primary objective of this review is to evaluate the efficacy and safety of olaparib (Lynparza) monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic and as detected by approved testing) epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial, defined as at least a 30% decrease in the sum of the diameters of TL, taking as a reference the baseline sum of diameters) to platinum-based chemotherapy. As there is currently no maintenance treatment strategy recommended for patients with platinum sensitive disease after treatment for relapse, Olaparib is to be compared to the current standard of care, namely best supportive care or observation, although comparisons to placebo is suitable. The outcomes of interest include survival (progression-free, overall), response rate, time to treatment failure, quality of life, and adverse events.

A Supplemental Question, covered in detail in Section 7, asks what is the clinical effectiveness, safety and therapeutic equivalence of olaparib tablets at 300 mg PO BID (as in SOLO2) versus 400 mg capsules taken PO BID (as in Study 19)?

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the Table 3. 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 pCODR Methods Team are provided in Appendix A.

[Table 3]. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished phase I to III RCTs. In the absence of RCTs, fully published non-comparative clinical trials evaluating olaparib.	Adult patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic) epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy.	Olaparib (oral)	Best supportive care, observation, placebo	• **PFS** • **OS** • ORR • **HRQoL** • AEs • SAEs • WDAE • DLT • TFST • TSST • PFS2 • Rate of treatment discontinuation • Rate of dose de-escalation • BoR • DCR • PRO • Time to earliest progression • Long term-treatment benefit • Subsequent therapies

- [Abbreviations] RCT = randomized controlled trial; BRCA= breast cancer susceptibility genes; OS=overall survival; PFS = progression-free survival; ORR = overall response rate; HRQoL = health-related quality of life; AE = adverse events; SAE = serious adverse events; WDAE = withdrawals due to adverse events; DLT = dose-limiting toxicities; TFST = Time to first subsequent treatment or death; TSST = Time to second subsequent treatment or death; PFS2 = time to second progression or death; BoR = Best overall response; DCR = disease control rate; PRO = patient reported outcomes

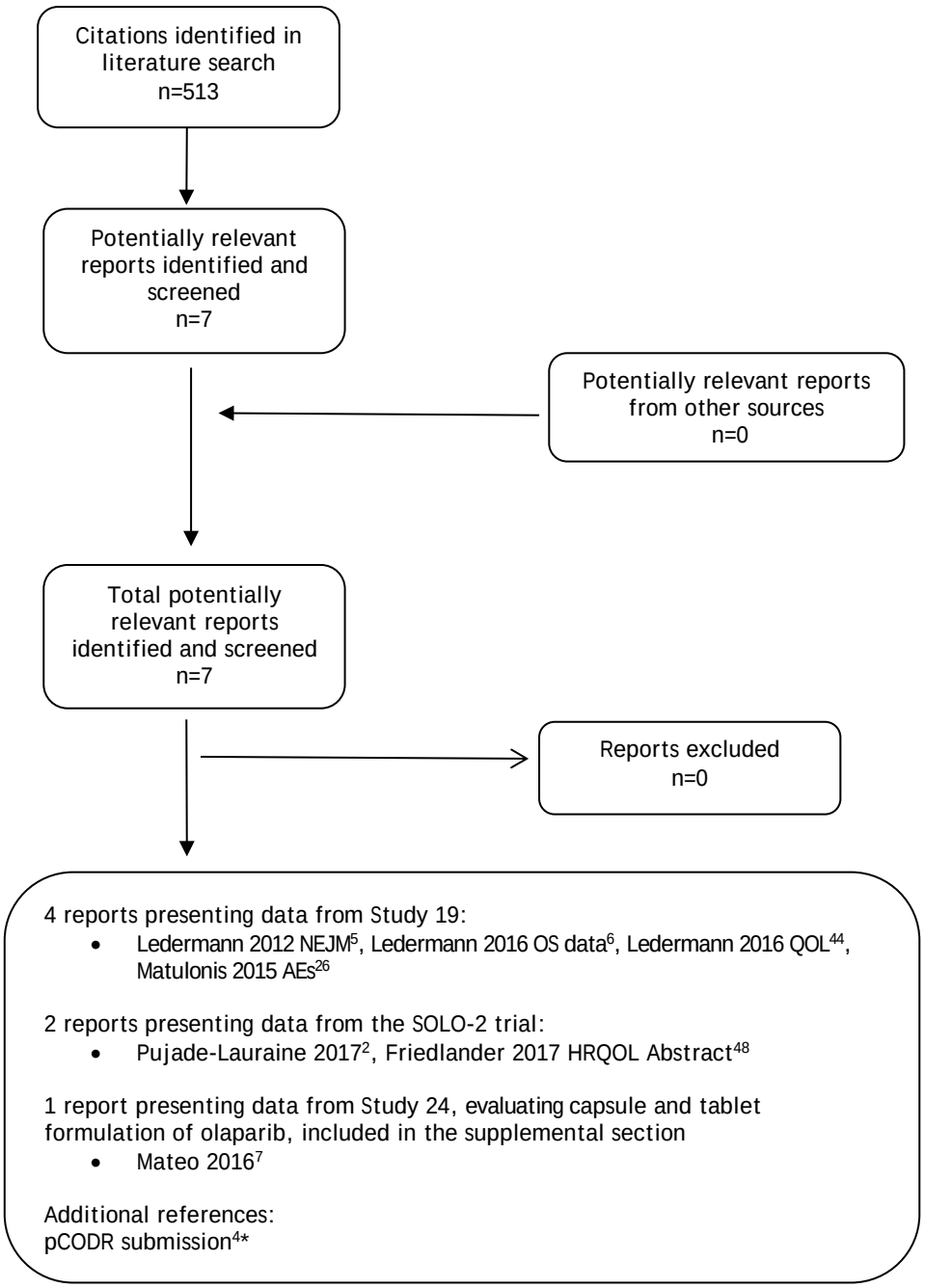
* *Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 513 potentially relevant reports identified, 2 trials with data presented in 6 reports were included in the pCODR systematic review[2,5,6,26,44,48] along with one Phase I trial [7] evaluating the capsule and tablet formulation of olaparib which was included in the supplemental section of this report.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



**Note: Additional data related to SOLO-2 were also obtained through requests to the Submitter by pCODR*

6.3.2 Summary of Included Studies

Two clinical trials were identified that met the eligibility criteria and are included in this systematic review (Please see Table 4). SOLO-2 is a randomized, international, multicentre Phase III trial that evaluated maintenance treatment with olaparib tablets in patients with relapsed high grade serous ovarian cancer (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer with *BRCA* mutations who had responded following platinum-based chemotherapy.

Study 19 was a randomized, double-blind, multicentre Phase II international trial that evaluated olaparib capsules in patients with advanced platinum-sensitive high-grade serous ovarian cancer who had received 2 or more previous platinum-containing regimens and had demonstrated an objective response to their last platinum-based chemotherapy regimen.

6.3.2.1 Detailed Trial Characteristics

[Table 4]: Summary of Trial Characteristics of the Included Studies[2,4,5]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
SOLO2/ENGOT Ov-21/GCIG, NCT01874353, D0816C00002 Randomized, double-blind, placebo-controlled, Phase III study 295 randomized ; 294 received study treatment (olaparib n=195; placebo n=99) 123 sites in 16 countries Patient Enrolment Dates: Sept 3, 2013 to Nov 21, 2014 Data cut-off: Sept 19, 2016 Funding: AstraZeneca	Key Inclusion Criteria: • Age ≥18 years or older • Recurrent ovarian or fallopian tube or peritoneal cancer • Platinum-sensitive disease • Patients had completed ≥2 courses of platinum-based chemotherapy with objective response • CA-125 measurements below the upper limit of the normal range • Normal organ and bone marrow function within 28 days prior to administration of study treatment • ECOG performance status 0 to 1 • Life expectancy of ≥16 weeks • Required to have a predicted deleterious, or suspected deleterious, *BRCA*m based on blood or tumor testing. Key Exclusion Criteria: • Previous treatment with a PARP inhibitor, including olaparib • Persistent toxicities (with the exception of alopecia) caused by previous cancer therapy • Concomitant use of known potent CYP3A4 inhibitors • Myelodysplastic syndrome or acute myeloid leukemia	Intervention: Olaparib (tablet formulation) orally at 300mg bid (maintenance therapy until objective disease progression) (2 x 150mg tablets) Comparator: Matching placebo tablets bid	Primary: PFS Secondary: OS PFS2 Time to first subsequent therapy or death (TFST) Time to second subsequent therapy or death (TSST) HRQoL Safety Tolerability
NCT00753545 Other Study ID numbers: D0810C00019 Study 19	Key Inclusion Criteria: • Adults (aged ≥ 18) • Female patients with histologically diagnosed recurrent ovarian or fallopian tube cancer or primary peritoneal cancer with high	Intervention: Olaparib (capsule formation) orally at 400 mg bid continually throughout a 28 day cycle	Primary: PFS Secondary: OS

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Randomized, double-blind, phase II study Enrollment: 265 Start date: August 2008 Primary Completion Date: June 2010 (November 2012) (final data collection date for primary outcome measures) Sept 30, 2015 for updated OS analysis (77% OS data maturity) Funding: AstraZeneca	grade (grade 2 or 3) serous features • Completed at least two courses of platinum-based chemotherapy and their most recent regimen induced an objective response as defined by RECIST version 1.0 or a cancer antigen 125 (CA-125) response, according to Gynecological Cancer Intergroup criteria. • BRCA1/2 mutation status was not required (Pre-planned retrospective analysis was conducted and published based on BRCA status) • Patients must be treated on the study within 8 weeks of completion of their final dose of the platinum containing regimen. <u>Key Exclusion Criteria:</u> • Previous treatment with PARP inhibitors including olaparib • Patients with low grade ovarian carcinoma • Patients receiving any chemotherapy, radiotherapy (except for palliative reasons), within 2 weeks from the last dose prior to study entry (or a longer period depending on the defined characteristics of the agents used).	(Eight 50 mg olaparib capsules) <u>Comparator:</u> Matching placebo capsules	ORR (RECIST or RECIST + CA-125) DCR (RECIST) DOR (RECIST) Change in tumour size at weeks 12 and 24 TTP (RECIST or CA-125) Safety <u>Exploratory:</u> Time to discontinuation Time to first subsequent therapy or death (TFST) Time to second subsequent therapy or death (TSST)

[Table 5]: Select quality characteristics of included studies of Olaparib in patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube or primary peritoneal cancer.[2,5,6,45]

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
SOLO 2	Olaparib vs. matching placebo	PFS	192 events of progression or death Two-sided significance level of 5% declared for PFS2 if one-sided P<0.0125.	Olaparib (196) and Placebo (99)	IVRS/ IWRS	Yes	Double -blind	Yes	Yes*	No	Yes
Study 19	Olaparib vs. matching placebo	PFS	137 PFS events Overall type 1 error rate 20% (1-sided, p<0.2)	Olaparib (136) and Placebo (129)	IVRS	Yes	Double -blind	Yes	Yes	No	Yes

Notes: IVRS/IWRS = interactive voice and web response system
* Final analysis for PFS, but OS data are still immature (24%) and a further analysis of OS is planned to be performed when the OS data are approximately 60% mature (approximately 177 deaths)

a) Trials

SOLO-2

SOLO-2 is a randomized, international, multicentre Phase III trial that evaluated maintenance treatment with olaparib in patients with relapsed high grade serous ovarian cancer (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer with *BRCA* mutations who had responded following platinum based chemotherapy. Patients received treatment until disease progression or until the investigator deemed that they were no longer benefiting from treatment.

SOLO-2 was conducted by the European Network for Gynaecological Oncological Trial groups (ENGOT) and funded by AstraZeneca. Eligible patients were randomized in a 2:1 ratio to receive either oral olaparib maintenance monotherapy (300 mg tablets twice daily,) (n=195) or placebo (twice daily, tablets) (n=99). Randomization and treatment masking was facilitated through an interactive voice and web response system (IVRS/IWRS) and was completed within 8 weeks of the patients' last dose of chemotherapy. The randomization was stratified by response to previous chemotherapy (CR or PR) and time to disease progression from the penultimate platinum-based chemotherapy (6-12 months or ≥12 months).

192 events of progression or death. In order to strongly control the Type I error at 2.5% 1-sided, a multiple testing procedure was employed across the primary endpoint (PFS) and key secondary endpoints (PFS2 and OS). All other variables that were tested (TFST, TSST, TDT, time to earliest progression by CA-125 or RECIST and change from baseline in TOI score) were tested at a 2-sided significance level of 5%.

Study 19

Details on Study 19 were reported previously[3]. Briefly, Study 19 was a randomized, double-blind, multicentre Phase II international study, globally distributed across 16 countries, in patients with advanced platinum-sensitive

(disease progression >6 months after completion of their penultimate platinum regimen) high-grade serous ovarian cancer who had received 2 or more previous platinum-containing regimens and had demonstrated an objective response (CR or PR) to their last platinum-based chemotherapy regimen. Patients were randomized within 8 weeks of completion of their final dose of a platinum-containing regimen in a 1:1 ratio to receive either olaparib capsules 400 mg twice daily (n=136) or matching placebo twice daily (n=129). The trial was sponsored by AstraZeneca.

Patients were stratified according to the interval between disease progression and the completion of their penultimate platinum-based regimen (from 6 to 12 months vs. > 12 months), and ancestry (Jewish vs. non-Jewish). A blocked randomization was generated and all centres used the same list to minimize possible imbalances in the number of patients assigned to each treatment group. The randomization was stratified based on the time to disease progression from completion of the penultimate platinum-containing therapy prior to enrolment, or to the last platinum-containing regimen therapy and the patient's ethnicity. Patients continued assigned treatment until objective disease progression (defined by Response Evaluation Criteria in Solid Tumours [RECIST] guidelines), provided they did not meet any criteria for discontinuation (any grade 3 or 4 adverse event [AE]).

Of note, *BRCA*1/2 mutation status was not required and was not known at study entry for all patients, but was determined in the blinded post-study period for the majority of patients (*a priori* planned analysis), such that *BRCA* mutation status was known for approximately 95% of women.

Patients receiving placebo were not permitted to crossover to treatment with olaparib after disease progression. However, patients were able to access other PARP inhibitors outside of the study and PARP inhibitor use was documented. For *BRCA* mutated patients randomized to the placebo group, 23% (n= 14/62) went on to received post-discontinuation PARP inhibitor treatment (olaparib n=10, rucaparib n=1; veliparib n=1; other PARP inhibitors n=2).[6] One publication [46] was identified that reported an exploratory post hoc analysis that excluded all patients from sites where 1 or more placebo patients received post-progression PARP inhibitor treatment. However, due to the inherent limitations associated with this post-hoc analysis, the Clinical Guidance Panel did not explore this further.

b) Populations

SOLO-2

SOLO-2 randomized 295 patients, of which 294 received study treatment. One patient in the olaparib arm was randomised in error. This patient was randomised on the final day of dosing of her 23 platinum-based chemotherapy, which was the final day that the study was open to accrual. However, after being randomised it became apparent that she did not fulfil the eligibility criteria, including not having a baseline RECIST scan and not having a minimum chemotherapy-free interval of 21 days; therefore, because the patient was randomised in error, she did not receive treatment on the study and is included in the full analysis set but not the safety analysis set[4]. Eligible patients were ≥18 years with histologically confirmed, relapsed high grade serous ovarian cancer (HGSOC) or high-grade endometrioid cancer, including primary peritoneal and/or fallopian tube cancer, or high-grade endometrioid cancer. Patients had received at least two previous lines of platinum-based chemotherapy and were in radiological response (either complete response or partial response) to their most recent regimen. In addition, patients were required to have platinum-sensitive disease (disease progression occurring at least 6 months after completion of platinum chemotherapy)

following the penultimate line of platinum-based chemotherapy before enrollment. For the course of chemotherapy immediately before randomization on the study, patients must have received at least four cycles of platinum-based chemotherapy. Furthermore, patients must have been randomized within 8 weeks of their last dose of chemotherapy (last dose was defined as the day of the last infusion). Patients were not allowed to receive bevacizumab or any investigational agent during this course of treatment nor could they have had previous treatment with PARP inhibitors, including olaparib. Eligible patients must have had normal organ and bone marrow function, measured within 28 days prior to randomization. Any patients with persistent toxicities grade 2 or higher caused by previous cancer therapy, with the exception of alopecia, or patients with myelodysplastic syndrome (MDL) or acute myeloid leukemia (AML) were not permitted in the trial.

Patients were required to have a predicted deleterious, or suspected deleterious, BRCA mutation based on blood or tumor testing. Patients also consented to provide two blood samples for BRCA mutation testing using Myriad BRCA*Analysis*®. Patients who had a known BRCA mutation before randomization were able to enter the trial based on this information and were required to provide blood samples for a confirmatory test.

Baseline characteristics of patients such as age, race, primary tumour location and platinum free interval were somewhat balanced between groups. See Table 6 below for further details. However, notable imbalances were observed between study arms for histology type, ECOG performance status, BRCA gene mutation and number of prior platinum regimens. There was a 5% and 6% difference between arms for the proportion of patients with an ECOG performance status of 0 and 1, respectively. More patients in the olaparib arm had an ECOG performance status of 0 and more patients in the placebo arm had an ECOG performance status of 1. The difference in histology types between arms was also apparent. The olaparib arm had 6.5% more serous types and the placebo arm had 3.5% more endometriod and 4.5% more of other non-specified histology types. Approximately 6% more patients in the placebo group entered the study with a known BRCA status and overall more patients in the olaparib arm had a *BRCA1* gene mutation and more patients in the placebo arm had a *BRCA2* gene mutation. Finally, the number of prior platinum regimens was also unbalanced between arms, with 6.5% more patients in the placebo arm having 2 prior regimens and 10% more patients in the olaparib arm having 3 prior regimens. However, differences in baseline characteristics were not statistically significant.

The median age in both treatment arms was 56 years and patients were predominately white (olaparib 88.3%; placebo 91.9%). The location of the tumour in the vast majority of the patients was the ovary (olaparib 82.7%; placebo 86.9%), followed by fallopian tubes or primary peritoneal (olaparib 15.8%; placebo 13.1%). Overall, 80% of randomized patients had a known *BRCA* mutation status previously tested in a local laboratory; the remaining 20% of patients had a *BRCA* mutation identified via the central Myriad CLIA Integrated BRAC*Analysis*® test.

Table 6: Demographics and Baseline Characteristics of Patients in SOLO-2[2,4]

	Olaparib 300 mg bd (n=196)	**Placebo** (n=99)
Demographics		
Age (years)		
Mean (SD)	57.0 (9.2)	56.6 (8.9)
Median (range)	56.0 (28-83)	56.0 (39-78)
Age group (years), n (%)		
<50	38 (19.4)	25 (25.3)

	Olaparib 300 mg bd (n=196)	**Placebo** (n=99)
≥50 to <65	118 (60.2)	52 (52.5)
≥65	40 (20.4)	22 (22.2)
Race, n (%)		
White	173 (88.3)	91 (91.9)
Black/African American	1 (0.5)	0
Asian	22 (11.2)	7 (7.1)
Other	0	1 (0.1)
Ethnic group, n (%)		
Hispanic or Latino	10 (5.1)	1 (1.0)
Disease Characteristics		
ECOG Performance status, n (%)		
(0) Normal activity	162 (82.7)	77 (77.8)
(1) Restricted activity	32 (16.3)	22 (22.2)
(2) In bed <50% of the time	0	0
Unknown	2 (1.0)	0
Histology type, n (%)		
Serous	183 (93.4)	86 (86.9)
Endometroid	9 (4.6)	8 (8.1)
Mixed, Epithelial	3 (1.5)	4 (4.0)
Other	0	1 (1.0)
Serous, pappilliferum, endometrioid	0	1 (1.0)
Missing	1 (0.5)	0
Tumour Characteristics		
Primary tumour location, n (%)		
Ovary	162 (82.7)	86 (86.9)
Fallopian tube	13 (6.6)	4 (4.0)
Primary peritoneal	18 (9.2)	9 (9.1)
Other	2 (1.0)	0
Missing	1 (0.5)	0
Previous Treatments		
Response to previous platinum chemotherapy (recorded at randomization by IVRS), n (%)		
PR	105 (53.6)	52 (52.5)
CR	91 (46.4)	47 (47.5)
Time to disease progression in the penultimate platinum-based chemotherapy prior to enrolment (recorded at randomization by IVRS), n (%)		
>6 to ≤12 months	79 (40.3)	40 (40.5)
>12 months	117 (59.7)	59 (59.6)
Number of prior chemotherapies, n (%)		
2	108 (55.1)	60 (60.6)
3	54 (27.6)	21 (21.2)
4 or more	33 (16.8)	17 (17.2)
Median (range)	2.0 (2-7)	2.0 (2-13)
Number of prior platinum-containing chemotherapies, n (%)		
2	110 (56.1)	62 (62.6)
3	60 (30.6)	20 (20.2)
4 or more	25 (12.8)	17 (17.2)
Median (range)	2.0 (2-7)	2.0 (2-7)

bd Twice daily; CR Complete response; CSR Clinical study report; ECOG Eastern Cooperative Oncology Group; FAS Full analysis set; IVRS Interactive voice response system; PR Partial response; SD Standard deviation

Study 19

Baseline characteristics of patients enrolled in Study 19 were somewhat balanced across arms in the ITT and BRCA-m-positive subgroup. There was a greater than 5%

difference observed between arms in both the ITT and BRCA-m subgroup for the proportion of patients with an ECOG performance status of 1 and 2 with more patients having an ECOG PS of 1 in the olaparib arm and more patients having an ECOG PS of 2 in the placebo arms. Adjustments for imbalances were applied in the full analysis set, but it is unclear if adjustments were made in the BRCAm subgroup analyses. See Table 7 below.

Furthermore, patients in both arms had a median of 3 prior chemotherapy regimens and a median of 2 prior platinum-based chemotherapy regimens. There were less than 2% of patients in each arm who had an ECOG performance status of 2 or of unknown performance status.

Table 7. Select Baseline Characteristics in Study 19[3]

	BRCA-m	
	Olaparib, n=74	Placebo, n=62
Median age (range)	57.5 (38-89)	55 (33-84)
Ancestry, n (%)		
Non-Jewish	60 (81%)	48 (77%)
Jewish	14 (19%)	14 (23%)
ECOG PS		
0	62 (84%)	45 (73%)
1	11 (15%)	15 (24%)
Time to progression with penultimate platinum-based regimen, n (%)		
>6–12 months	28 (38%)	26 (42%)
>12 months	46 (62%)	36 (58%)
Objective response to most recent platinum-based regimen, n (%)		
Complete	36 (49%)	34 (55%)
Partial	38 (51%)	28 (45%)
BRCA-germline-mutation status, n (%)		
BRCA 1 or BRCA 2 mutation	100%	100%
Negative	N/A	N/A
Unknown	N/A	N/A

c) Interventions

SOLO-2

Patients in the SOLO-2 trial were randomized to receive either olaparib 300 mg twice daily tablet formulation or a matching placebo. Patients were to continue receiving blinded treatment until they met the criteria for disease progression or until the investigator deemed that they were no longer benefiting from treatment. Dose reductions and interruptions were permitted during the trial as a result of adverse events.

Key protocol deviations, defined as those that either affected eligibility into the study or potentially affected the efficacy analysis, were fairly low with 15.6% of patients having at least 1 key deviation[4]. Key protocol deviations were generally balanced between the treatment groups. The most common key deviations observed in the olaparib and placebo treatment groups, respectively, were in the category relating to pre-treatment CA-125 levels. Five olaparib-treated patients and 1 placebo-treated patient were reported as having taken an overdose of study

treatment. In the olaparib group, none of the overdoses were intentional and none were associated with AEs.[4]

Study 19

Patients in Study 19 were randomly assigned to receive olaparib capsules, at a dose of 400 mg twice daily or matching placebo within 8 weeks after completion of their last dose of platinum-based chemotherapy. Patients continued the assigned treatment until objective disease progression, as defined by RECIST guidelines, or until any grade 3 or 4 adverse event that did not resolve completely or to grade 1 within 28 days after onset, according to CTCAE. Patients could continue to receive study treatment following objective progression provided that, in the opinion of the investigator, the patient was benefiting from the treatment and did not meet any other discontinuation criteria.[4]

d) Patient Disposition

SOLO-2

At the time of the data-cut off (DCO) for the SOLO-2 trial, there was a greater proportion of patients in the olaparib arm still receiving treatment than in the placebo arm. A total of 198 (67%) patients had discontinued the study, of which 112 (57%) were in the olaparib arm and 86 (87%) in the placebo arm. Worsening of disease was a top reason for study treatment discontinuation in many study patients, with a higher proportion in the placebo (76.8%) than the olaparib group (38.5%) discontinuing for this reason. However, there were more patients who discontinued study treatment due to AEs in the olaparib arm (11.3%) than in the placebo arm (2.0%). There was a similar number of patients in the olaparib and placebo arm who voluntarily discontinued treatment and a similar number of patients in both groups who had "Other" reasons for discontinuing study treatment (5.1% olaparib arm vs 4.0% placebo arm). Again, in most cases this was due to disease progression. At the time of DCO for the primary PFS analysis, a small number of patients (5 [2.6%] patients in the olaparib arm and 4 [4.0%] patients in the placebo arm) had withdrawn consent prior to progression. The total number of deaths was 45 (23.0%) in the olaparib arm versus 27 (27.3%) in the placebo arm. [47] In 42 patients (21.4%) in the olaparib arm and 25 patients (25.3%) in the placebo arm, the death was related to the disease under investigation only (i.e. death > 30 days after last treatment dose). A summary of patient disposition is provided in Table 8.

Overall, the total median study treatment exposure was greater than 3 times longer in the olaparib arm (19.4 months) than in the placebo arm (5.6 months). In the olaparib arm, the median total treatment duration was similar to the actual treatment duration, suggesting any interruptions did not have much impact on treatment duration.

Table 8. Summary of SOLO-2 patient disposition[4,47]

	Number (%) of patients		
	Olaparib (n=196)	Placebo (n=99)	Total (n=295)
Patients screened	602		
Patients randomized	196 (100.0)	99 (100.0)	295 (100.0)
Efficacy (ITT) analysis (FAS)	196 (100.0)	99 (100.0)	295 (100.0)
Patients who received treatment	195 (99.5)	99 (100.0)	294 (99.7)

Patients ongoing study treatment at data cut-off†	83 (42.6)	13 (13.1)	96 (32.7)
Safety analysis (SAS)	195 (99.5)	99 (100.0)	294 (99.7)
Patients who discontinued study treatment†	112 (57.4)	86 (86.9)	198 (67.3)
• Adverse events	22 (11.3)	2 (2.0)	24 (8.2)
• Objective disease progression	75 (38.5)	76 (76.8)	151 (51.4)
• Patient decision	5 (2.6)	4 (4.0)	9 (3.1)
• Other	10 (5.1)	4 (4.0)	14 (4.8)
Patients who terminated study†	55 (28.1)	37 (37.4)	92 (31.2)
• Patient decision	7 (3.6)	9 (9.1)	16 (5.4)
• Death	45 (23.0)	27 (27.3)	72 (24.4)
• Patient lost to follow up	1 (0.5)	1 (1.0)	2 (0.7)
• Other	2 (1.0)	0	2 (0.7)
Severe non-compliance to CSP	0	0	0

Notes: † Percentages are calculated from the number of patients who received treatment.

FAS= Full analysis set
SAS=Safety analysis set
CSP=Clinical Study Protocol
Data cut-off: 19 September 2016

Study 19[6]

Of the total 136 patients randomized to the olaparib arm at the September 30, 2015 data cut-off, 15 patients had ongoing treatment and 121 patients discontinued treatment due to AEs (n=8), worsening of condition (N=93), severe protocol non-compliance (n=3), lost to follow-up (n=1), subject withdrawal (n=14), and other reasons not specified (n=2). A total of 94 patients discontinued from the study due to death, 2 were lost to follow-up and 7 due to subject decision. At the 30 September 2015 data cut-off, 33 patients were ongoing the study. Of the 128 patients treated in the placebo arm, 1 had ongoing treatment and 127 discontinued treatment due to AEs (n=2), worsening of condition (n=116), severe protocol non-compliance (n=1), lost to follow-up (n=0), and subject withdrawal (n=8).A total of 114 patients discontinued from the study due to death (n=108), 3 were lost to follow-up and 3 due to subject decision. At this latest data cut-off, 14 patients were ongoing the study.

e) Limitations/Sources of Bias

SOLO-2

The following are limitations and potential sources of bias from the SOLO-2 trial:

- While baseline characteristics were generally well-balanced between treatment groups, several differences were observed between patients in the olaparib and placebo arms. The extent to which these differences impact the direction or magnitude of benefit or the generalizability of trial results is unknown.

- Selected predefined subgroup analyses of PFS were reported in the trial, however the trial was not sufficiently powered to detect differences in subgroups. Thus, the interpretation of these results is challenging due to the lack of statistical power. Moreover, statistically significant differences should be interpreted with caution due to the small number of patients in the subgroups.

- The differences in adverse events leading to dose interruptions, reductions and discontinuations observed between treatment arms had the potential to unmask patients in the olaparib group. The extent to which spontaneous unblinding of patients and investigators occurred is unknown, but the possible influence on greater quality of life and other patient-reported outcomes should be considered. A sensitivity analysis of PFS by BICR was conducted to account for any potential bias from investigator assessments.

- The sponsor AstraZeneca funded the trial and was involved in all aspects of conducting the trial including design of the study, data collection, performing data analysis, and interpreting results. The extent to which the sponsor involvement may have influenced the results and reporting of the trial is unknown.

- For patients randomized to the placebo group, [redacted] received a PARP inhibitor as a subsequent therapy after progression; of these, [redacted] patients received a PARP inhibitor as their first subsequent therapy. [redacted] ([redacted]) patients in the olaparib group received a PARP inhibitor as a subsequent therapy. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until May 20, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*). There will likely be confounding from subsequent use of other PARP inhibitors, in the placebo arm in SOLO-2 with the use of a subsequent PARP inhibitor.

- At the time of the data analysis, OS data was immature (24% maturity) (HR 0.80; 95% CI 0.50 to 1.31; P=0.4267; median not reached) making the actual degree of long term benefit unknown. With sufficient follow-up OS could be evaluated, but any benefit will be confounded by post trial treatments.

Study 19

Sources of bias for Study 19 have previously been discussed[3] and only an abbreviated list appears below:

- The primary efficacy analyses of Trial 19 were based on the ITT population and not the BRCA subgroup.

- The sample size calculation, conducted only in the overall population for PFS, allowed for a type 1 error-rate of 20%. Therefore interpretation of results should be done with caution given that the trial has a 20% chance of detecting a false positive. None of the secondary outcomes (e.g. OS) in the ITT analysis nor the exploratory endpoints in the subgroup analysis of patients with the BRCA-m (cg. PFS, OS) were powered to detect a statistically significant difference. Therefore all interpretation of testing for significance within these analyses should be done with caution.

- Baseline characteristics were mostly balanced between treatment arms in the ITT and *BRCA*-m-positive subgroup. However, stratification of patients was based on complete or partial response to the most recent

platinum-based regimen and this has the potential to introduce a degree of imbalance to the population at baseline. It is not clear what impact these imbalances may have had on the direction or magnitude of benefit.

- Adjustments were made for multiple testing for OS in the ITT population and OS was not significant at any interim analysis based on this analysis plan. No adjustments were made for multiple testing within any of the exploratory endpoints or analyses within the BRCA subgroups. At the latest OS analysis, in patients with the BRCAm and with 70% maturity, the median OS was 34.9 months compared with 30.2 months in the olaparib and placebo arms, respectively (HR = 0.62; 95% CI, 04.1 to 0.94; p=0.02480, not adjusted for multiple testing).

6.3.2.2 Detailed Outcome Data and Summary of Outcomes[2,4]

This section will focus on outcome data from the SOLO-2 trial. Key efficacy outcomes are summarized in Table 9 and Figure 2. Outcomes from Study 19 have been previously reported [3] and are not presented here.

SOLO-2 Efficacy Outcomes

PRIMARY OUTCOME

Progression-free Survival (PFS)
Analyses for PFS were performed based on the September 19, 2016 DCO (63% maturity) in which 187 investigator-assessed (according to RECIST 1.1) events of disease progression or death had occurred (olaparib group, 107/196 [54.6%]; placebo group, 80/99 [80.0%]). This met the sample size requirements for the study and provided adequate power to detect the differences the study was designed for. A statistically significant improvement in the median PFS for olaparib over placebo of 13.6 months (median PFS 19.1 vs. 5.5 months) was reported, translating into a 70% reduction in risk of disease progression or death with olaparib vs placebo (HR 0.30; 95% CI 0.22-0.41; p<0.0001). The proportion of patients who had not experienced disease-progression at 12 months was 3.1 times greater in the olaparib group than in the placebo group (65.1% vs 20.9%, respectively). At the 2 year mark, the proportion of patients who remained progression free was 2.8 times greater in the olaparib group than in the placebo group (43.0% vs. 15.1%, respectively).

A sensitivity analysis of PFS, measured by blinded independent central review (BICR) at 51% maturity, also demonstrated a statistically significant improvement in PFS in patients receiving olaparib vs placebo (HR 0.25; 95% CI 0.18 to 0.35; P<0.0001; median 30.2 months vs 5.5 months). The discrepancy in median PFS point estimates obtained from BICR and investigator-assessment was explained by the investigators as possibly resulting from informative censoring.[2] Study authors reported that some patients who were deemed to have progressed by investigator assessment had not had their repeating 12 week scans available for BICR and thus not shown to have progressed.[2] A sensitivity analysis adjusting for this informative censoring, where potentially informatively censored patients (14% in olaparib arm and 14% in placebo arm) were assumed to have an event at the next 12 week scan, resulted in a PFS that remained significantly longer with olaparib over placebo (HR 0.26, 95% CI 0.19 to 0.35, p<0.0001; median 19.6 vs 5.5 months).

The following subgroups were analysed for PFS[4]:

- Response to last platinum chemotherapy (CR or PR).

- Time to disease progression in the penultimate platinum based chemotherapy prior 5 to enrolment (>6 to 12 months or >12 months).
- *gBRCAm* status, confirmed by Myriad BRACAnalysis CDx® test or *gBRCA* wildtype or *gBRCA* variant of uncertain significance (VUS) or missing by Myriad BRACAnalysis CDx® test (some patients were unable to be tested using the Myriad BRACAnalysis CDx® test due to sample availability. Additionally, some mutations identified at screening were unable to be confirmed by the BRACAnalysis CDx® test).
- Mutations observed in SOLO2 that were not reported in the previously approved companion diagnostic submission (novel mutation subgroup).
- ECOG performance status at baseline (normal activity or restricted activity).
- Prior cytoreductive surgery for most recent progression (Yes or No).
- Lines of prior platinum therapy (2, 3 or 4+).
- Baseline CA-125 value (≤ULN or >ULN).
- *BRCA* mutation type (*BRCA1*, *BRCA2* or *BRCA1/2* [both]).
- Age at randomisation (<65 or ≥65 years).
- Prior use of bevacizumab (Yes or No).
- Region 1 (North America or Rest of World).
- Region 2 (Brazil, Poland, Russia, Japan, Korea or Rest of World).
- Race (White or Black/African-American or Asian or Native Hawaiian/Pacific Islander or American Indian/Alaska Native or Other).

Overall, across all predefined subgroups, the subgroup analysis showed a statistically significant reduction in the risk of progression or death in olaparib-treated patients that ranged from 48% to 86%. One exception was for patients with an ECOG performance status of restricted activity, where the PFS benefit did not reach statistical significance (95% CI 0.26-1.03).

The AstraZeneca Clinical Summary Report [4] offered several reasons to explain the longer median PFS seen in the olaparib group in the SOLO-2 trial compared to that reported in the *BRCAm* subgroup of Study 19. Among these was the higher proportion of more heavily pretreated patients (≥3 or more lines of prior chemotherapy) in Study 19 compared with SOLO-2. In Study 19, patients were allowed a non-platinum regimen between the penultimate and last platinum regimen, whereas this was not allowed in SOLO-2. This may potentially worsen the PFS outcome for patients in Study 19. Secondly, the report notes that the definition of PFS was not the same in both studies. In the SOLO-2 trial, progression could only be declared based on the results of the RECIST scans, which were conducted in strictly defined periods regardless of the CA-125 values. However, in Study 19, CA-125 progression could trigger an unscheduled tumour assessment to determine progression by RECIST. This resulted in placebo subjects in particular being declared to have progressed earlier than they would have been if they had only been declared as having progressed based on the scheduled RECIST scan assessments.

SECONDARY OUTCOMES

Progression-free Survival 2 (PFS2)

PFS2 was defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death. At 40% maturity, there was a 50% reduction in risk of second progression or death with olaparib compared to placebo (HR 0.50; 95% CI 0.34-0.72; p=0.0002). The median PFS2, calculated using Kaplan-Meier techniques, was not yet reached in the olaparib group and 18.4 months in the placebo group .[4] At 24 months, 59.2% of patients in the olaparib group and 37.3% of patients in the placebo group were second progression-free .[4] The AstraZeneca Clinical Summary Report [4] notes that as of the September 19, 2016 DCO, 83 (42.6%) patients in the olaparib arm were

censored as they were still undergoing treatment versus 13 (13.1%) patients in the placebo arm.

Overall Survival (OS)[2]

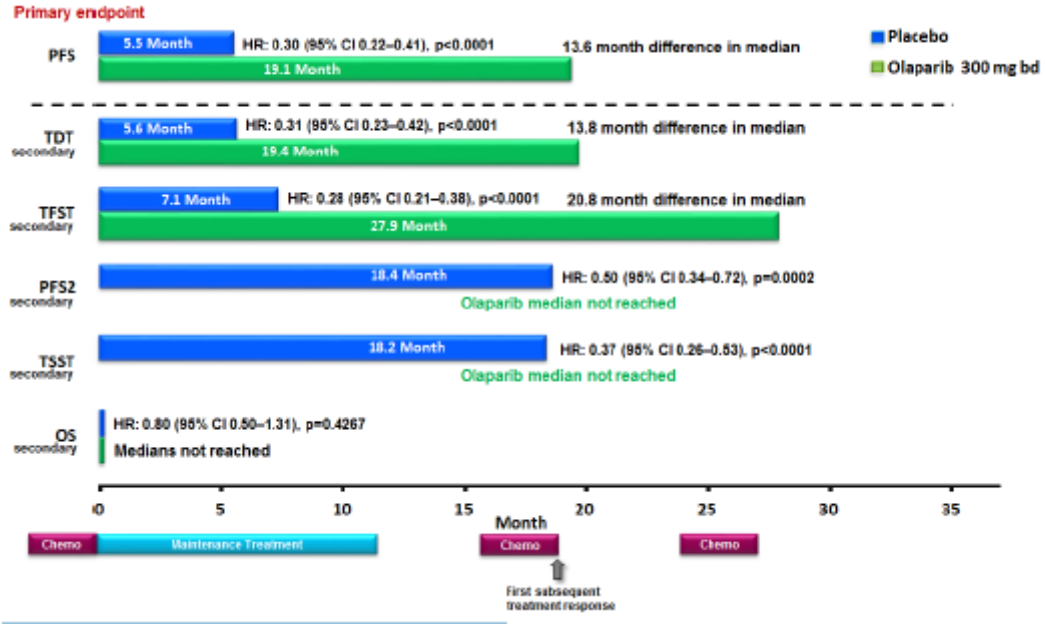
At the September 19, 2016 DCO, OS data were only at 24% maturity and median OS was not reached in either treatment arm. OS was defined as the time from the date of randomisation until death due to any cause. The reported 20% reduction in the risk of death in olaparib treated patients compared with placebo treated patients is based on a total of 72 OS events in 295 patients. This did not reach statistical significance (HR 0.80; 95% CI 0.50-1.31; p=0.43). The number of patients alive at 6 (99.5% vs 100%), 12 (96.9% vs 97.9%), 18 (89.5% vs 85.1%) and 24 months (76.3% vs 73.8%) was similar for patients in the olaparib and placebo groups, respectively. A total of 69% of patients were alive and continuing on the study. OS times are long relative to PFS times and are confounded by multiple subsequent lines of therapy.

Time to Study Treatment Discontinuation or Death (TDT) [4]
There was a nominally statistically significant reduction in the time from randomization to discontinuation of treatment or death in the olaparib group compared with the placebo group. Median TDT was 19.4 months in the olaparib group compared to 5.6 months with placebo, corresponding to a hazard ratio of 0.31 (95% CI 0.23-0.42; nominal p<0.0001).

The PFS2, TFST, and TSST data together demonstrate that the PFS benefit of olaparib treatment is maintained beyond the immediate treatment period and that olaparib provides a meaningful delay to the time when patients require further anticancer therapy.

Time to First Subsequent Therapy or Death (TFST) and Time to Second Subsequent Therapy or Death (TSST)[4]
Reporting on intermediate clinical endpoints such as TFST (defined as the time from randomisation to the earlier of first subsequent therapy start date following study treatment discontinuation, or death) and TSST (defined as the time from randomisation to the earlier of the second subsequent therapy start date following study treatment discontinuation, or death) help to demonstrate efficacy when post-progression survival can be long and include multiple lines of subsequent therapies.[4] There was a nominally statistically significant delay in both TFST and TSST in the olaparib group compared with the placebo group (TFST HR 0.28 95% CI 0.21-0.38; p<0.0001; TSST HR 0.37 95% CI 0.26-0.53; p<0.0001) The Clinical Summary Report form AstraZeneca noted that the median TFST in the olaparib arm (27.9 months) was substantially longer than the median PFS (19.1 months), suggesting clinical benefit with olaparib continues beyond the strict criteria of radiological progression and delays the need to start the next round of chemotherapy.[4] Furthermore, the report points out that patient censoring could also be a factor contributing to the difference. They report that the proportion of patients who did not require first subsequent cancer therapy at 24 months was higher in the olaparib group than the placebo group.[4]

Figure 2: SOLO-2 Graphical summary of efficacy results[2,4]



Coloured bars represent the medians for the endpoints
bd Twice daily; Chemo Chemotherapy; CI Confidence interval; CSR Clinical study report; DCO Data cut-off; HR Hazard ratio; OS Overall survival; PFS Progression-free survival; PFS2 Time to second progression or death; TDT Time to discontinuation of treatment or death; TFST Time to first subsequent therapy or death; TSST Time to second subsequent therapy or death

Time to Earliest Progression[4]

The time from randomization to earliest progression identified by modified RECIST 1.1 or CA-125 or death was nominally statistically significantly longer in the olaparib group compared with the placebo group. The median time to earliest progression or death was 16.9 months in the olaparib group compared to 4.9 months with placebo, corresponding to a HR of 0.30 (95% CI 0.23-0.41).

Objective response rate (ORR)[4]

For patients with measurable disease at baseline, the ORR was 41.1% for the olaparib group and 17.1% in the placebo group (odds ratio 3.52; 95% CI 1.34-10.59, p=0.0097). There were 12.3% of patients in the olaparib group and 5.7% of patients in the placebo group whose best objective response corresponded to a complete response. The best objective response of a partial response was observed in 28.8% and 11.4% of patients in the olaparib and placebo groups, respectively.

Long term-treatment benefit[4]

[redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until May 20, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*). The median daily dose, defined as the total dose divided by the actual duration of treatment (total duration of treatment excluding any dose interruptions), was 597.6 (IQR 541.3–600.0) mg for olaparib-treated patients and 598.4 (IQR 593.0–600.0) mg in the placebo group.[2] The number of patients remaining on treatment over time in the olaparib group was [redacted] and [redacted] compared with [redacted] and [redacted] in the placebo group, respectively. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this*

information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until May 20, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier).

Subsequent Therapies[4]

Subsequent anticancer therapy after treatment discontinuation was administered to [redacted] ([redacted]) olaparib-treated patients and [redacted] ([redacted]) placebo-treated patients. The proportion of patients who subsequently received [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until May 20, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).

[redacted].[47] (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until May 20, 2018 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).

Health-related quality of life (QoL)[4,48]

Functional Assessment of Cancer Therapy – Ovarian (FACT-O) and Trial Outcome Index (TOI)

The FACT-O questionnaire, is comprised of physical, social/family, emotional and functional well-being subscales, as well as the additional concerns scale consisting of specific ovarian cancer symptoms. The TOI, derived from the FACT-O, targets the most relevant symptoms together with functional and physical well-being and can be directly related to signs and symptoms and AEs.

Using a mixed model for repeated measures (MMRM) analysis of all the post-baseline TOI scores for each visit, no statistically significant or clinically relevant difference between the treatment arms in the average change from baseline TOI score over 12 months was found.[4] The estimated average difference between the arms over 12 months was less than 1 point, in the context of a TOI scale of 100 points. Compliance rates for planned visits of FACT-O were high in both groups. Secondary planned analyses investigated the duration of 'good quality of life' by time without symptoms of disease or toxicity (TWiST) and quality-adjusted PFS

(QAPFS; a single measure of PFS and HRQOL outcomes). No significant detrimental effect of olaparib vs placebo on HRQOL analyzed by change from baseline in TOI score (–3.1 vs –2.9, respectively, difference (O minus P) –0.2; 95% CI –2.4, 2.1; *P*=0.88) was found. There was a significant improvement for patients on maintenance olaparib in TWiST (13.5 vs 7.2 months, difference 6.3; 95% CI 2.9, 8.6; *P*<0.001) and QAPFS (mean 14.0 vs 7.3 months for O and P, respectively, difference 6.7; 95% CI 5.0, 8.5; *P*<0.0001).[48]

New patient-centric endpoints of the FACT-O

The overall impact of common ovarian cancer treatment related toxicities for patients who received treatment over a 12 month period following the start of randomised treatment was investigated to assess whether the duration of stability in physical functioning was longer for patients initially randomised to olaparib than for those initially randomised to placebo. There was no difference on average over a 12 month period between the treatment arms with respect to all patient-centric endpoints of the FACT-O (disease-related symptoms, common treated-related toxicities of cancer treatment, HRQoL and physical functioning). Over a 12 month period, the estimated average difference between the arms was less than 1 point for all 4 endpoints.

Euroquality of Life-5 dimensions, 5 level

The EQ-5D-5L, assessing impact of treatment and disease state on health state utility, showed that over time, a slight decrement in health state utility was observed across both treatment groups. No significant difference between the 2 treatment groups was found.

The mean Visual Analogue Scale score demonstrated a slight decline in how patients rated their health across both treatment groups over time, no significant difference between the 2 treatment groups was found. The observed decline did occur after the end of study treatment, suggesting disease progression may have played a role.

Table 9: Summary of Key Efficacy Outcomes in SOLO-2 and Study 19[2,4,6,45]

	SOLO-2 (tablet formulation, 300 mg bd)		STUDY 19 (capsule formulation, 400 mg bd)			
	DCO 19 September 2016 Full Analysis Set (n=295)		DCO 2012 BRCAm Subset (n=136)		DCO 2015 BRCAm Subset (n=136)	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
PFS						
Number of events: total number of patients (%)	107:196 (54.6%)	80:99 (80.8%)	26:74 (35%)	46:62 (74%)	NA	NA
Median PFS (months)	19.1	5.5	11.2	4.3	NA	NA
HR (95% CI)	0.30 (0.22-0.41)		0.18 (0.10-0.31)		NA	
P-value (2-sided)	p<0.0001		p<0.0001		NA	
PFS2						
Number of events: total number of patients (%)	70:196 (35.7%)	49:99 (49.5%)	NA	NA	NA	NA
Median PFS2 (months)	Not reached	18.4	NA	NA	NA	NA
HR (95% CI)	0.50 (0.34-0.72)		NA		NA	
P-value (2-sided)	p=0.0002		NA		NA	
OS						
Number of events: total number of patients (%)	45:196 (23.0%)	27:99 (27.3%)	37:74 (50%)	34:62 (55%)	47:74 (64%)	48:62 (77%)
Median OS (months)	Not reached	Not reached	34.9	31.9	34.9	30.2
HR (95% CI)	0.80 (0.50-1.31)		0.73 (0.45-1.17)		0.62 (0.41-0.94)	
P-value (2-sided)	p=0.4267		p=0.19175		p=0.02480	
TDT						
Number of events: total number of patients (%)	112:196 (57.1%)	86:99 (86.9%)	59:74 (80%)	59:62 (95%)	66:74 (89%)	61:62 (98%)
Median time (months)	19.4	5.6	11.0	4.6	11.0	4.6
HR (95% CI)	0.31 (0.23-0.42)		0.36 (0.24-0.53)		0.36 (0.25-0.52)	
P-value (2-sided)	p<0.0001 (nominal p-value)		p<0.00001		p<0.00001	
TFST						
Number of events: total number of patients (%)	92:196 (46.9%)	79:99 (79.8%)	46:74 (62%)	54:62 (87%)	53:74 (72%)	59:62 (95%)
Median time (months)	27.9	7.1	15.6	6.2	15.6	6.2
HR (95% CI)	0.28 (0.21-0.38)		0.33 (0.22-0.50)		0.32 (0.22-0.48)	
P-value (2-sided)	p<0.0001		p<0.00001		p<0.00001	
TSST						
Number of events: total number of patients (%)	68:196 (34.7%)	60:99 (60.6%)	42:74 (57%)	49:62 (79%)	52:74 (70%)	56:62 (90%)
Median time (months)	Not reached	18.2	23.8	15.2	22.0	15.3
HR (95% CI)	0.37 (0.26-0.53)		0.46 (0.30-0.70)		0.41 (0.28-0.62)	
P-value (2-sided)	p<0.0001		p=0.00013		p=0.00001	

Note: Nominal p-value means no adjustments were made for analyses within the BRCA subgroup in Study 19. Control of type I error for the exploratory endpoints was not defined and, as such, where p-values <0.05 are observed for these endpoints, we can say nominal significance was met. bd Twice daily; CI Confidence interval; CSR Clinical study report; DCO Data cut-off; HR Hazard ratio; OS Overall survival; PFS Progression free survival; PFS2 Time to second progression or death; TDT Time to discontinuation of treatment or death; TFST Time to first subsequent therapy or death; TSST Time to second subsequent therapy or death

Harms Outcomes[2,4]

The proportion of patients who experienced any AEs (all CTCAE grades) was similar between the olaparib and placebo groups, 98.5% and 94.9%, respectively (Please see Tables 10 and 11). Serious AEs were reported in 17.9% vs 8.1% of patients in the olaparib and placebo group, respectively. The incidence of any grade ≥3 AEs was 36.9% in the olaparib group and 18.2% in the placebo group. Anemia, identified by OCC as an AE of particular interest, was the most common grade ≥3 AE in the olaparib group (n=38, 19.5%), but the majority of cases were low grade. In approximately one-fifth of patients, AEs of anaemia led to temporary dose interruptions, and to dose reduction in approximately one-tenth of patients. In some instances grade 3 anemia was managed through blood transfusions. A higher percentage of patients in the olaparib group (17.9%; n=35) received blood and related products compared with the placebo group (1.0%, n=1). The highest proportion of patients requiring blood transfusions was during the period from 2 to 5 months on study.[47] Anaemia was reported as an SAE in a low proportion of patients and a low proportion of patients permanently discontinued study treatment as a result of anaemia AEs[4]. One case of AML that resulted in death and one case of myelodysplastic syndrome (MDS) were reported in the olaparib group during the study and 30-day follow-up period. No cases of MDS/AML were reported in the placebo group. Additional cases of AML (olaparib group, n=1; placebo group, n=1), MDS (placebo group, n=3) and a case of chronic myelomonocytic leukemia (CMML; olaparib group, n=1) were reported after the 30-day follow-up period, resulting in an overall incidence of AML/MDS/CMML of 2.1% in the olaparib group (n=4/195) and 4.0% in the placebo group (n=4/99).

Adverse events of grade 1-2 that occurred in at least 10% patients in either treatment group along with grade 3 or higher AEs are summarized in Table 10. The most common AEs that were reported by >30% patients were nausea, anaemia, fatigue/asthenia, vomiting, and diarrhoea in the olaparib arm. This compared to nausea, fatigue/asthenia and abdominal pain in the placebo arm. Events that were reported at a 5% greater frequency in the olaparib 300 mg tablet bd group compared with the placebo group included nausea, anaemia, fatigue/asthenia, vomiting, diarrhoea, dysgeusia, headache, decreased appetite, cough, dizziness, pyrexia, dyspnoea, neutropenia, blood creatinine increased, leukopenia, thrombocytopenia, neutrophil count decreased, cystitis, influenza like illness and platelet count decreased (data not shown). Abdominal pain was reported at a >5% greater frequency in the placebo group than the olaparib group.

A greater proportion of patients in the olaparib group experienced AEs leading to dose interruptions (45.1% vs 18.2%), dose reductions (25.1% vs 3.0%) and discontinued study treatment (10.8% vs 2.0%) (Table 10). The most common reason for dose reduction in the olaparib arm were anemia (12.8%), asthenia (3.1%) and fatigue (3.1%). The most common AEs leading to dose interruption in the olaparib arm were anemia (21%), vomiting (7.2%) and nausea (5.6%). Anemia (3.1%) and neutropenia (1.5%) were the most common AEs leading to discontinuation in the olaparib group.[47]

The median duration of the first AE event was longer in olaparib group than in the placebo group for nausea, fatigue/asthenia, anemia and neutropenia (Table 12).[49] In general, there was improvement in vomiting and nausea as treatment continued, though fatigue/asthenia and anemia could last for several months.[49]

The proportion of patients requiring supportive treatment for nausea (21% vs 9%) and anemia (17% vs 1%) was much greater in the olaparib group compared with the placebo group.

Table 10. Adverse events in any category - patient level (SAS)[4,47]

	Total number (%) of patients[a]	
	Olaparib 300 mg bd	**Placebo**
AE category	**(N=195)**	**(N=99)**
Any AE	192 (98.5)	94 (94.9)
Any AE of CTCAE Grade 3 or higher	72 (36.9)	18 (18.2)
Any AE with outcome = death	1 (0.5)	0
Any SAE (including events with outcome = death)	35 (17.9)	8 (8.1)
Any AE leading to discontinuation of olaparib/placebo	21 (10.8)	2 (2.0)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories. Multiple MeDRA PTs for a patient that are in the same AE category are counted multiple times in that AE category. Multiple PTs belonging to more than 1 AE category are counted multiple times in each of those AE categories.
Includes adverse events with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib/placebo.
AE adverse event; bd twice daily; CTCAE Common Terminology Criteria for Adverse Events version 4.0; MedDRA Medical Dictionary for Regulatory Activities; PT preferred term; SAE serious adverse event; SAS safety analysis set. Classified using MedDRA 19.0

Table 11. Adverse Events of Grade 1-2 Occurring in at least 10% of Patients in Either Treatment Group, together with the respective incidence of Grade ≥3 Adverse Events [2]

	Olaparib (n=195)		Placebo (n=99)	
Patients with any adverse event, n (%)	**Grade 1-2**	**Grade ≥3**	**Grade 1-2**	**Grade ≥3**
	120 (62)	71 (36)	76 (77)	18 (18)
Nausea	143 (73)	5 (3)	33 (33)	0
Fatigue/asthenia*	120 (62)	8 (4)	37 (37)	2 (2)
Anemia†	47 (24)	38 (20)	6 (6)	2 (2)
Vomiting	68 (35)	5 (3)	18 (18)	1 (1.0)
Diarrhea	62 (32)	2 (1)	20 (20)	0
Dysgeusia	52 (27)	0	7 (7)	0
Headache	48 (25)	1 (1)	13 (13)	0
Abdominal pain	42 (22)	5 (3)	28 (28)	3 (3)
Decreased appetite	43 (22)	0	11 (11)	0
Constipation	40 (21)	0	20 (20)	3 (3)
Neutropenia‡	28 (14)	10 (5)	2 (2)	4 (4)

*Includes patients with fatigue and patients with asthenia; †includes patients with anemia, hemoglobin decreased, hematocrit decreased and red blood cell count decreased; ‡includes patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutrophil count decreased, granulocytopenia and granulocyte count decreased

Table 12. Duration and Supportive Treatment of Adverse Events[49]

Adverse event	Median Duration of First Event* (Months)		Supportive Treatment (%)	
	Olaparib	Placebo	Olaparib (n=195)	Placebo (n=99)
Nausea	1.72	0.43	79 (41)	9 (9)
Vomiting	0.07	0.07	17 (9)	7 (7)
Fatigue/asthenia	5.78	2.04	7 (4)	1 (1)
Anemia	2.79	2.60	34 (17)	1 (1)
Neutropenia	0.95	0.69	5 (3)	2 (2)
*Only uses AEs with a resolution date, n<total sample size				

While only harm outcomes from the SOLO-2 study are reported in this section, it is worthwhile to point out that similar adverse effects were seen in patients in Study 19.

6.4 Ongoing Trials

[Table 13]: Ongoing trials of Olaparib as maintenance treatment for adult patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study NCT01844986 SOLO-1[50] Other Study ID numbers D0818C00001 Title: Olaparib Maintenance Monotherapy in Patients With BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer Following First Line Platinum Based Chemotherapy A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study Active, not recruiting, 15 countries N enrolled = 397 Patient Enrolment Dates: From Aug 2013 Recruitment complete Q1 2015 Primary analysis report Q2 2017 Data cut-off: Sept 13, 2017 Estimated completion date: March 29, 2023 Sponsor: AstraZeneca Collaborators: Gynecologic Oncology Group (GOG) Myriad Genetic Laboratories, Inc.	<u>Key Inclusion Criteria:</u> Newly diagnosed, histologically confirmed, high risk advanced (FIGO stage III - IV) BRCA mutated high grade serous or high grade endometrioid ovarian cancer, primary peritoneal cancer and / or fallopian-tube cancer who have completed first line platinum based chemotherapy Stage III patients must have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery. Documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious Patients who have completed first line platinum (e.g. carboplatin or cisplatin), containing therapy (intravenous or intraperitoneal) prior to randomisation: Patients must have, in the opinion of the investigator, clinical complete response or partial response and have no clinical evidence of disease progression on the post treatment scan or rising CA-125 level, following completion of this chemotherapy course. Patients must be randomized within 8 weeks of their last dose of chemotherapy <u>Key Exclusion Criteria:</u> BRCA1 and/or BRCA2 mutations that are considered to be non detrimental	Olaparib 300mg tablets bd Placebo tablets bd	<u>Primary:</u> PFS <u>Secondary:</u> OS HRQoL PFI Safety and tolerability TFST TSST Treatment discontinuation or death Time to earliest progression Time from randomisation to second progression

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	Patients with early stage, stable disease or progressive disease on the post-treatment scan or clinical evidence of progression at the end of the patient's first line chemotherapy treatment. Patients who have previously received chemotherapy for any abdominal or pelvic tumour Patients with synchronous primary endometrial cancer unless both of the following criteria are met: 1) stage <2 2) less than 60 years old at the time of diagnosis of endometrial cancer with stage IA or IB grade 1 or 2, or stage IA grade 3 endometrioid adenocarcinoma OR ≥ 60 years old at the time of diagnosis of endometrial cancer with Stage IA grade 1 or 2 endometrioid adenocarcinoma. Patients with serous or clear cell adenocarcinoma or carcinosarcoma of the endometrium are not eligible.		

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of Olaparib (Lynparza) monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy.

- What is the clinical effectiveness, safety and therapeutic equivalence of olaparib at 300 mg tablet PO BID (as in SOLO2) versus 400 mg capsule PO BID (as in Study 19)?

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

7.1 Comparative effectiveness, safety and therapeutic equivalence of tablets versus capsules

7.1.1 Objective

In December 2014, the capsule formulation of olaparib received EU and US approval.[7] However, to take the approved 400 mg BID capsule dose, patients are required to consume eight 50 mg large size capsules twice daily. In an attempt to improve dosing constraints of the capsule formulation, an alternative tablet formulation with improved bioavailability has been developed to facilitate olaparib administration to patients. Comparisons of the bioavailability of these two different oral formulations was investigated. PAG is seeking data demonstrating that dose using capsules is therapeutically equivalent to dose using tablets. PAG is also seeking bioequivalence data and safety of the two different formulations and doses.

7.1.2 Findings

Study 24[4,7]

Study 24 investigated the relative bioavailability of the tablet formulation of olaparib used in SOLO-2 and other ongoing Phase III trials compared to the currently approved capsule formulation. AstraZeneca's Clinical Summary Report explains that, "crystalline olaparib has low solubility across the physiological pH range relative to the desired dose so the development of dosage forms was directed towards solubility enhancing technologies". They further explain that "the tablet formulation has greater bioavailability due to improved solubility milligram to milligram compared to the capsule formulation enabling a lower 300 mg dose to achieve comparable clinical efficacy and similar tolerability to 400 mg capsules."

Trial

Study 24 was an open-label, multicentre, multistage, Phase I trial (Study D0810C00024-Study 24 [NCT00777582]) to compare the pharmacokinetics (PK), efficacy, and tolerability of different doses and schedules of the olaparib capsule and tablet formulations with a goal of determining an optimal tablet dosing strategy for Phase III studies of olaparib (See Table 13 for details). The study included two stages of sequentially enrolled cohorts: stage 1, pharmacokinetic properties of tablet and capsule formulations were compared in patients with advanced solid tumours; stage 2, tablet dose escalation with expansion cohorts at

doses/schedules of interest in patients with solid tumours and BRCAm breast/ovarian cancers.

Population
A total of 210 patients with metastatic or locally advanced non-resectable disease enrolled in the study and 196 received olaparib between 2008 and 2012. Females made up 87% of those enrolled. There were 51 patients enrolled in Stage 1 and 159 in Stage 2, which included 31 in the dose escalation phase. Patients in Group 8 had gBRCAm with ovarian, primary peritoneal or fallopian tube cancer and at least one measurable lesion.

The 18 patients participating in Stage 1 of the trial most commonly had ovarian, breast, and colorectal cancers and their ages ranged from 53.8 to 61.2. All patients had an ECOG performance status below 2. The median time on treatment was 87 days for patients in the PK Phase (PKP)/CSP (cohorts 1-3).

Patients in the dose-escalation and dose-expansion phase (Stage 2) had ovarian (n=114) or breast (n=27) cancer with the exception of five patients. There was a total of 62 gBRCAm patients with ovarian, primary peritoneal, or fallopian tube cancer that were randomized to receive the four alternative TAB schedules. gBRCAm was confirmed for all patients in groups 6 and 8.

Overall, there were 137 patients with serous (all grades) ovarian carcinoma, including primary peritoneal and fallopian tube adenocarcinoma, who received olaparib. Platinum sensitivity status was available for patients in groups 6 and 8, of which 40/100 patients (40%) had platinum-sensitive disease, assessed by the investigator, at study entry. The median number of prior lines of chemotherapy ranged from two to six across cohorts and groups.

Detailed Trial Characteristics

[Table 14]: Summary of Trial Characteristics of Study 24[4,7]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Supportive Data			
NCT00777582 Other Study ID numbers: D0810C00024 Study 24 Open-label, Phase I, randomized, 2 period cross over study Two stages of sequentially enrolled cohorts: Stage 1, pharmacokinetic properties of tablet and capsule formulations were compared in patients with advanced solid tumours;	<u>Key Inclusion Criteria:</u> • Adults (aged ≥ 18) and a life expectancy of ≥ 16 weeks • Histologically confirmed, malignant advanced solid tumour which was refractory to standard therapies (except group 8 patients who were not platinum refractory) or for which no suitable effective standard therapy existed. • ECOG PS 0-2 (0-1 for Group 8 only)	<u>Intervention:</u> Olaparib 300 mg bid tablet dose Olaparib 400 bid tablet dose Olaparib 400 mg bid capsule dose	<u>Primary:</u> Comparative bioavailability of the tablet and capsule formulations Safety and tolerability <u>Secondary:</u> Single dose PK data Comparison of steady-state exposures Efficacy based on change in tumour size

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Supportive Data			
Stage 2, tablet dose escalation with expansion cohorts at doses/schedules of interest in patients with solid tumours and *BRCAm* breast/ovarian cancers. 210 randomized ; 196 received olaparib Patient Enrolment Dates: 2008 to 2012 Estimated Study Completion Date: December 29, 2017 Funding: AstraZeneca	• Adequate bone marrow, renal, and hepatic function • Solid tumours originating from the ovary or breast with a confirmed genetic BRCA1/2 mutation (group 8 gBRCA ovarian [including primary peritoneal and fallopian tube] cancer patients only). • At least one lesion, not previously irradiated, that could be accurately measured as ≥10 mm in the longest diameter with spiral CT or as ≥20 mm with conventional techniques (conventional CT or MRI) and which was suitable for accurate repeated measurements (groups 1, 6, 7 and 8) <u>Key Exclusion Criteria:</u> • Received any chemotherapy, radiotherapy (except for palliative reasons), or any other anticancer therapy within 4 weeks from the last dose prior to study randomization • Considered a poor medical risk, symptomatic uncontrolled brain metastases or persistent toxicities (CTCAE grade 2 or greater) caused by previous cancer therapy (excluding alopecia) • Treatment with any investigational product during the previous 14 days • Received the following classes of inhibitors of CYP3A4 (azole antifungals, macrolide antibiotics, protease inhibitors) • Group 8 only: • Previous treatment with a PARP inhibitor • Myelodysplastic syndrome or acute myeloid leukemia • Patients who were platinum refractory		

Outcomes

Bioavailability Assessment
The capsule showed a slower rate of absorption (lower dosed normalized Cmax) at doses of up to 100 mg in vivo, but similar extent of absorption (similar dosed normalized AUC). At doses above 100 mg, the extent of absorption was higher for the tablet formulation.

Analyses based on geometric least squares mean (gLSmean), Cmax and AUC ratios and 90 % CIs from the patients in the study, determined that the tablet and capsule formulations cannot be considered bioequivalent. The relative bioavailability of tablet doses compared with capsules was higher based on Cmax ratios. Additional assessments of steady-state PK were conducted and determined olaparib tablet ≥ 300 mg matched or exceeded that of the olaparib 400 mg capsule.

A total of 65% of randomized patients in the expansion phase required dose reduction to 300 mg after dose escalation of up to 400 mg twice daily (tablet maximum tolerated dose based on haematological toxicity). An improvement in tolerability was observed with the olaparib 300 mg BD tablet formulation and was similar to that with capsules. The most common adverse events (AEs) leading to olaparib dose modification were nausea, fatigue and vomiting.

Objective Response Rate (ORR)
Objective response rate based on radiological assessment was 30% (16/53; 95% CI 18.3–44.3) across cohorts of gBRCAm carriers with serous ovarian carcinoma, although it appeared higher for patients receiving 300 mg tablets BD (5/13, 38%; 95% CI 13.9–68.4) and 400 mg tablets BD (5/12, 42%; 95 % CI 15.2–72.3). The ORR based on a RECIST and/or CA-125 was 40% (21/53, 95% CI 26.5–54.0).

Considering percentage change in tumour size, a similar degree of efficacy was seen after 8 and 16 weeks of treatment for both 300 and 400 mg tablets compared with 400 mg BD capsules. The study reported that the one-sided upper limit of the 80% CI was below the pre-specified criteria of 20 % compared with the original formulation (400 mg BD capsules) for both groups at 300 mg BD tablets (least squares mean [LSmean] change in tumour size at week 8: 1.8%, one-sided 80 % UCL 12.1) and 400 mg BD tablet (LSmean change in tumour size at week 8: −10.5%, one-sided 80% UCL 0), indicating similar efficacy. Antitumour activity data showed that 300 mg BD tablet was similar to the approved dose of 400 mg BD capsule for ovarian cancer patients

Safety and Tolerability
During TAB dose escalation, the 450 mg BID dose level was deemed non-tolerable; as such, the 400 mg BID TAB dose was defined as the MTD for additional expansion cohorts.

Nausea and vomiting were the most commonly reported AEs in the dose-expansion and dose-escalation phases (reported in 84% [nausea] and 80% [vomiting] of patients in groups 1 and 3–6); in these groups, 8 and 1 % of patients had a dose reduction because of nausea and vomiting, respectively. The incidence of G3–4 anaemia and thrombocytopenia was higher in the 400 mg BID group than the 300 mg BID group (30% vs 22% and 18% vs 0%, respectively).[7]

In 18 patients randomized to the approved 400 mg BID CAP regimen (group 6), anaemia was reported in 33% of patients, G1–2 nausea in 83% and vomiting in 28% of patients. Eight patients in the dose-expansion phase required permanent

discontinuation of olaparib because of an AE across dose levels .[7]There were seven deaths altogether; all were related to the disease under investigation. Three of these deaths had an intercurrent serious AE (one patient each for each of the following: pneumocystis carinii pneumonia; intraabdominal haemorrhage; small intestinal obstruction). The AE of pneumocystis carinii pneumonia was thought to be secondary to bone pancytopenia and was considered by the investigator as related to olaparib.[7]

When considering all patients who received 300 or 400 mg BID TAB (during dose-escalation and randomized expansion phases), 29% (22% in randomized expansion phase) and 61% (65 % in randomized expansion phase) patients required ≥1 dose reduction because of AEs (mainly due to gastrointestinal toxicities, fatigue, anaemia), respectively.[7]

The most common AEs observed in group 8 (intermittent dosing group) were nausea (82%) and vomiting (68%). Intermittent administration of 400 mg BID led to G3 vomiting in 18.8% of cases, while only one case was reported in each of the other dose schedules. Moreover, the 400 mg BID intermittent dose level had the most patients requiring dose reductions (37.5 %) because of AEs, compared with 6.7–18.8 % of patients in the other dose schedules.[7]

7.1.3 Summary

Study 24 demonstrated that patients' exposure following tablet doses ≥300 mg BID matched or exceeded that of the approved 400 mg BID capsule formulation (8×50 mg capsules BID). The 300 mg BID TAB dose was better tolerated than higher doses and it showed similar effectiveness in tumour shrinkage. As such, continuous dosing of olaparib tablets 300 mg BID (2 × 150 mg tablets BID) is recommended for olaparib Phase III clinical trials, thereby simplifying drug administration from 16 capsules to four tablets per day.[7]

Investigators did note some potential issues and limitations with the analysis that are worth discussing further [4]. For the change in tumour size analysis, a number of tumour size assessments were either missing or performed outside of the scheduled visit window. These were thereby imputed according to prespecified imputation rules. An increase in imputations over time, believed to be reflective of the number of patients withdrawing from the study, suggests change in tumour size comparisons for week 16 should be interpreted with caution.[4]

Also noteworthy was the higher frequency of early censoring in Group 8 at the time of study discontinuation than in Groups 1 and 6, which was explained by the shorter average duration of follow up for Group 8. Odds ratio estimates for objective response rate were not calculated in Group 8 due to the low number of responses per treatment comparison.[4]

PK parameters were produced using the dosing and sampling history provided to the pharmacokineticist based upon the state of the database at the time of that PK analysis being conducted. Discrepancies noted following the PK analysis were not accounted for in the reported PK parameters.[4]

8 COMPARISON WITH OTHER LITERATURE

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

9 ABOUT THIS DOCUMENT

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

pCODR 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 pCODR Disclosure of Information Guidelines. The manufacturer, 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 Initial Clinical Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Clinical Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Clinical Guidance Report will supersede this Initial Clinical Guidance Report.

The Genitourinary Clinical Guidance Panel is comprised of three clinicians. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See Appendix B for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2017, **Embase** 1974 to 2017 March 31, Ovid MEDLINE(R) **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

Line #	Searches	Results
1	(Lynparza* or Linparza* or Lyhnparza* or Olaparib* or AZD-2281 or AZD2281 or KU-59436 or KU59436 or KU-0059436 or KU0059436 or WOH1JD9AR8 or 76113-22-0 or 1021843-02-6 or 894104-70-2 or 937799-91-2).ti,ot,ab,rn,hw,nm,kf,kw.	3147
2	Genital Neoplasms, Female/ or exp Ovarian Neoplasms/ or Fallopian Tube Neoplasms/ or Peritoneal Neoplasms/	233826
3	(ovarian or ovary or ovaries or ovarial or ovarium or fallopian or uterine tube* or oviduct* or peritoneal or peritoneum or adnexa or adnexal).ti,ab,kf,kw.	746775
4	or/2-3	808583
5	1 and 4	1360
6	5 use ppez,cctr	307
7	*Olaparib/	630
8	(Lynparza* or Linparza* or Lyhnparza* or Olaparib* or AZD-2281 or AZD2281 or KU-59436 or KU59436 or KU-0059436 or KU0059436 or WOH1JD9AR8 or 76113-22-0 or 1021843-02-6 or 894104-70-2 or 937799-91-2).ti,ab,kw.	1761
9	or/7-8	1824
10	female genital tract tumor/ or female genital tract cancer/ or exp ovary tumor/ or exp peritoneum cancer/ or uterine tube tumor/ or uterine tube carcinoma/	143662

11	(ovarian or ovary or ovaries or ovarial or ovarium or fallopian or uterine tube* or oviduct* or peritoneal or peritoneum or adnexa or adnexal).ti,ab,kw.	741949
12	or/10-11	779869
13	9 and 12	785
14	13 use oemezd	512
15	6 or 14	819
16	limit 15 to english language	790
17	remove duplicates from 16	553

2. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#9	**Search #7 AND #8**	10
#8	**Search publisher[sb] OR 2017/03/30:2017/04/03[edat]**	526635
#7	**Search #5 AND #6**	231
#6	**Search Genital Neoplasms, Female[mh:noexp] OR Ovarian Neoplasms[mh] OR Fallopian Tube Neoplasms[mh] OR Peritoneal Neoplasms[mh] OR Ovarian[tiab] OR ovary[tiab] OR ovaries[tiab] OR fallopian[tiab] OR uterine tube*[tiab] OR oviduct*[tiab] OR peritoneal[tiab] OR peritoneum[tiab] OR adnexa[tiab] OR adnexal[tiab]**	350432
#5	**Search Lynparza*[tw] OR Linparza*[tw] OR Lyhnparza*[tw] OR Olaparib*[tw] OR AZD-2281[tiab] OR AZD2281[tiab] OR KU-59436[tiab] OR KU59436[tiab] OR KU-0059436[tiab] OR KU0059436[tiab] OR WOH1JD9AR8[rn] OR 76113-22-0[rn] OR 1021843-02-6[rn] OR 894104-70-2[rn] OR 937799-91-2[rn]**	572

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid

4. **Grey Literature search via:**

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

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

Search: ovarian OR ovary OR ovaries OR fallopian OR peritoneal OR peritoneum OR adnexa OR adnexal | Lynparza OR Linparza OR Lyhnparza OR Olaparib OR AZD-2281 OR AZD2281 OR KU-59436 OR KU59436 OR KU-0059436 OR KU0059436

Select international agencies including:

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

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

Search: Lynparza/olaparib

Conference abstracts:

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

European Society of Medical Oncology (ESMO)
http://www.esmo.org/

Search: Lynparza/olaparib; ovarian OR fallopian OR peritoneal OR peritoneum - last 5 years

APPENDIX B: LITERATURE SEARCH METHODS

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (March 2017) 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 concepts were Olaparib (Lynparza) and ovarian cancer.

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents, but not limited by publication year. The search is considered up to date as of August 2, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - 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 by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

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

Data Analysis

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

Writing of the Review Report

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

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

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