CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Olaparib (Lynparza) for Ovarian Cancer

September 29, 2016

DISCLAIMER

Not a Substitute for Professional Advice
This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability
pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

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 breast cancer 1 or 2 gene mutated (BRCA-m, germline or somatic) epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy.

The appropriate comparator for olaparib in this treatment setting is best-supportive care and close follow-up. The patient population under review by pCODR is 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 and is in line with the Health Canada approved indication.[1] A NOC/c has been issued for this indication under review, pending the results of trials to verify its clinical benefit.[1]

Olaparib (Lynparza) is a first-in-class, oral, potent inhibitor of poly (ADP-ribose) polymerase (PARP). Olaparib represents the first targeted medicine in ovarian cancer and is expected to be used as monotherapy for maintenance treatment in a genetically targeted group of patients, specifically those with platinum-sensitive relapsed BRCA-mutated ovarian cancer. The recommended dose for olaparib is 400mg (eight 50 mg capsules) taken orally twice daily, equivalent to a total daily dose of 800 mg.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One clinical trial was identified that met the eligibility criteria of this review and was selected for inclusion. 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 focussed on the subgroup of patients within Study 19 with

the mutated breast cancer 1 or 2 gene (BRCA-m, germline or somatic) epithelial ovarian, fallopian tube or primary peritoneal cancer. Among 265 enrolled patients (136 and 129 in the olaparib and placebo arms, respectively), 136/265 (51.3%) had the BRCA-m status (74 and 62 in the olaparib and placebo arms, respectively).

The primary outcome of the trial was progression free survival (PFS) with secondary outcomes including overall survival, objective response, patient reported outcomes and safety. Time to first subsequent therapy was an exploratory endpoint. Subgroups analysis in the BRCA-m population was pre-planned and exploratory for PFS, OS and other endpoint. However, the study was not powered to detect a statistically significant difference for any of these exploratory endpoints in the BRCA-m subgroup. Additionally, multiplicity testing was taken into account only for OS in the full analysis (ITT analysis) set but was not completed for any exploratory endpoint in the *BRCA*-m subgroup. Feedback was received from the submitter on the identification of PFS and OS as pre-planned exploratory analyses by the Methods team. While Study 19 was originally designed with the objective of having two co-primary endpoints (PFS in the overall and BRCA-m populations), the protocol was amended to make analysis of PFS in the BRCA-m population an exploratory analysis due to the absence of an assay to measure patients' BRCA-m status at the time of the primary analysis. Additionally, based on responses received from the submitter via the Checkpoint meeting, the Methods team confirmed that all subgroup analyses in the BRCA-m population were indeed prespecified exploratory analysis.

Results:

Primary Outcome: Progression free Survival (PFS)

BRCA-m Subgroup Analysis

BRCA-m patients with BRCA-m tumours, a 6.9 months prolongation of median PFS (11.2 compared to 4.3 months in the olaparib and placebo arms, respectively) was reported with a hazard ratio of 0.18 (95% CI: 0.1 to 0.31; p<0.0001). Additional analyses in the BRCA wild type population also demonstrated a statistically significant difference in favour of the olaparib maintenance treatment arm. However, the magnitude of difference was lower when compared to the BRCA-m - patient population (7.4 months vs. 5.5 months, with a hazard ratio of 0.54 (95% CI: 0.34 to 0.85; p=0.0075).

Secondary Outcomes: Overall Survival (OS)

BRCA-m Subgroup Analysis

At 52% maturity of data (71 deaths out of 136 patients), there was no statistically significant difference in OS between patients treated with olaparib and patients treated with placebo, 34.9 months versus 31.9 months, respectively. The hazard ratio was 0.73 (95% CI: 0.45 to 1.17; p=0.19). In an updated analysis at 70% maturity (95/136 events) of data in the BRCA-mutation population, OS was 34.9 months versus 30.2 months, in patients treated with olaparib versus placebo, respectively. This was a median improvement in OS that was 4.7 months longer for olaparib versus placebo, corresponding to a hazard ratio of 0.62 (95% CI: 0.41 to 0.94). It is notable that a threshold was not set to determine statistical significant for OS in the BRCA-m subgroup. Therefore the reported p-values are nominal.

In the BRCA-m subgroup, 23% of patients in the placebo arm received a subsequent PARP inhibitor compared to no patients in the olaparib group. This imbalance might have led to confounding of the overall survival results.[2] One publication[3] presented results in the BRCA-M subgroup of patients excluding all sites where at least one patient received post-progression treatment with a PARP inhibitor. Given the small sample size of the main trial and the use pre-planned exploratory endpoints to determine efficacy in the BRCA-m subgroup, the CGP agreed that any additional analysis further removing patients from the

cohort would be considerably uncertain. Therefore this analysis was not considered further in this review.

Table 1. Select efficacy outcomes for Study 19[4,5]

	Study 19[4]		Study 19[5]	
	ITT Population		BRCA-m	
	Olaparib	Placebo	Olaparib	Placebo
Primary Outcome				
Median PFS, months Primary Analysis (June 2010)	8.4	4.8	11.2	4.3
HR	0.35 (95% CI 0.25-0.49) p<0.001)		0.18 (95% CI 0.1-0.31) p<0.0001	
Number of PFS event at analysis	154/265 (58%)		72/136 (53%)	
	60 (44.1%)	94 (72.9%)	26 (35%)	46 (74%)
Select Secondary Outcomes				
Median OS, months Interim Analysis (November 2012)	29.8	27.8	34.9	31.9
HR	0.88 (95% CI 0.64-1.21) p=0.44		0.73 (95% CI 0.45-1.17) p=0.19	
Number of OS events at analysis	154/265 (58%)		71/136 (52%)	
	77 (57%)	77 (60%)	37 (50%)	34 (55%)
Updated Median OS, months (September 2015)	29.8	27.8	34.9	30.2
HR	0.73 (95% CI 0.55-0.96) p=0.02483 nominal p-value		0.62 (95% CI 0.41-0.94) p=0.02480 nominal p-value	
Number of OS events at analysis	203		95	
	94 (69.1%)	109 (84.5%)	47 (63.5%)	48 (77.4%)
ORR	12%	4%	16%	5%
Odds ratio	3.36% (95% CI 0.75-23.72) p=0.12		Not available[‡]	

Notes:
Primary Data Analysis: June 30, 2010
First Interim Analysis: October 31, 2011
Second Interim Analysis: November 26, 2012
Updated Analysis: September 30, 2015
[‡]Statistical analysis not possible due to too few events
NR: not reported; **OS**: overall survival; **PFS**: progression free survival; **ORR:** objective response rate; **HR:** hazard ratio; **BRCA:** breast cancer gene; **ITT:** intention to treat; BRCA-m: breast cancer 1 gene mutation (germline and somatic)

Adverse Events and Safety:

In the BRCAm subgroup, all grade AE's between the olaparib and placebo groups, were 97% and 94%, respectively. However, grade ≥3 AEs were 38% compared to 18% in the olaparib and placebo BRCAm subgroup, respectively. Please see table 9 in section 6 of the systematic review for further details.

Results for dose interruptions and reductions were available for the overall ITT population. A greater proportion of patients in the olaparib arm experienced dose interruptions (36% vs. 21%) and dose reductions (42% vs. 22%). It is notable however that the median actual treatment was longer in the olaparib compared to placebo groups for both the ITT population (258.5days and

135.5 days, respectively) and BRCAm population (328.5days and 138.5days, respectively).[7] The most common cause for dose interruption or reductions was vomiting, nausea and fatigue. Generally, the tolerability profile was similar between the ITT and BRCA-m positive populations.

Treatment-related deaths

As of the January 31 2014 safety cut-off date, one patient in the olaparib treatment arm (in the subgroup of patients with BRCA-m) was reported to have died as a result of treatment. This patient died due to thrombocytopenia and a haemorrhagic stroke, which the investigator considered related to study treatment. A second death was also reported in the olaparib treatment arm among patients without a BRCA-m status, which was considered to be related to ovarian cancer, with a secondary cause of death being Myelodysplastic syndrome (MDS) which was diagnosed after the 30-day follow-up period.[6]

Patient Reported Outcomes[6]

Symptoms and Health-related quality of life was assessed in Study 19 at regular intervals using three validated instruments: 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. Although not reported, the Leddermann et al 2014 noted that time to worsening of PRO's and HRQoL was the same between treatment groups.

Please see table 11 in section 6 of the systematic review for further details on health-related quality of life.

Important Limitations

- The sample size calculation, conducted only in the overall population for PFS, allowed for a type 1 error rate of 20%. Though the result reported in the overall and subgroup analyses for PFS demonstrated statistical significance (statistical significance was only declared if $p<0.025$ as outlined in the study protocol), 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 (eg. OS) in the ITT analysis nor the exploratory endpoints in the subgroup analysis of patients with the BRCA-m (eg. PFS, OS) were powered to detect a statistically significant difference. Therefore all interpretation of testing for significance within these analysis should be done with caution.
- Adjustments were made for multiple testing for OS in the ITT analysis. OS was not significant at any interim analysis based on this analysis plan. Therefore interpretation of testing for significance within the OS results of the ITT population should be done with caution. No adjustments were made for multiple testing within any of the exploratory endpoints in the BRCA-m subgroup.
- Overall, the trial design (type 1 error rate of 20% which allowed for a recruitment of a small sample size in the overall population), the small sample size in the subgroup of patients with the BRCA-m and multiple testing lead to an increase in Type 1 error rate which create considerable uncertainty in the internal validity of the study. Therefore

interpretation of testing for significance within the subgroup analysis should be done with caution.

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's perspective, there are significant psycho-social impacts, including fear, depression, worry and anxiety for patients diagnosed with ovarian cancer. Because early symptoms can be non-specific and because there is no screening test, ovarian cancer is usually detected in its later stages, resulting in a grim prognosis.

According to OCC, surgery and chemotherapy, particularly platinum agents have been the mainstays of treatment for ovarian cancer. Notwithstanding some challenges with current treatments, most respondents who were surveyed reported that their current treatments were able to manage their ovarian cancer. Respondents indicated they were deeply affected by fatigue, hair loss, bowel problems and blood problems from their treatments. OCC found that a side effect that was rated as having no effect by most respondents was the impact on their fertility. OCC surmised this may be because many of the respondents would have been peri-menopausal or menopausal.

OCC reported that the most important reasons for respondents who are considering taking olaparib were that it could increase the length of time before recurrence and that they can take the treatment at home. These respondents anticipate the benefits of taking olaparib could prolong life and improve quality of life. Most of these respondents would be willing to tolerate most side effects if olaparib were to improve overall daily functioning or prognosis. However, these respondents noted that blood disorders or blood cancer and inflammation of lungs were those side effects that they were least willing to tolerate. Respondents who have experience with olaparib indicated the top three issues that olaparib managed or managed better than previous treatments were prolonged time until recurrence, shrunk tumour size and prolonged survival. The key side effects that these respondents experienced were tiredness/weakness, nausea, taste changes, diarrhea, blood disorder or blood cancer, headaches, blood problems (e.g. anemia), pain under the ribs, dizziness, infections and sore mouth. The majority of respondents believed the benefits of olaparib outweighed the risks.

Please see Section 3 for more details.

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

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 Section 4 for more details.

Registered Clinician Input

The clinicians providing input have identified that olaparib is an oral drug with fewer toxicities than intravenous chemotherapy and provides a maintenance treatment option for women with BRCA positive, platinum sensitive ovarian cancer after first-line platinum based chemotherapy.

Please see Section 5 for more details.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did identified one relevant literature providing supporting information for this review.

Study 41,[7] was a phase II, prospective, open-label randomized study evaluating the benefit of olaparib in combination with paclitaxel and carboplatin administered as induction followed by olaparib administered as maintenance versus paclitaxel and carboplatin alone, followed by no further therapy, in patients with platinum-sensitive relapsed ovarian cancer who had received no more than 3 previous platinum-containing regimens. The Clinical Guidance Panel agreed that study 41 contained relevant information to the current review and a brief summary of the study design and results was provided.

Please see Section 8 for more details.

1.2.3 Factors Related to Generalizability of the Evidence

[Table 2]: Assessment of generalizability of evidence for olaparib as maintenance treatment for 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. 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).

Domain	actor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	ECOG PS	In Study 19, inclusion criteria was for patients with an ECOG ≤2 and life expectancy ≥16 weeks < 2% of patients in each arm who had an ECOG PS of 2 or unknown performance status.	Do trial results apply to patients with an ECOG PS ≥2? If so, why?	If ECOG PS is ≥2, on account of recent chemotherapy and treatment related fatigue or other toxicities, then the patient may still be considered eligible to switch to olaparib. If the ECOG PS is ≥2 due to advancing disease then the patient would not be eligible for olaparib
	Line of Therapy	Study 19 required patients wo have completed at least 2 previous courses of platinum-containing therapy 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 trial 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?	1) Results do not apply to patients after first-line treatment with platinum-based therapy. This is the subject of ongoing phase III trials. 2) Any patient with BRCA mutation and response to 2nd or later like of platinum therapy is eligible. There is no specification of the number of cycles of platinum required to switch to olaparib, only that evidence of benefit be observed (either by CA125 response or objective measurement of the tumour).
	BRCA status	The submitted funding request is limited to patients with BRCA mutated (germline or somatic) ovarian cancer. Study 19 also includes patients without a BRCA mutation (57 and 61 in olaparib and placebo arms, resp.)	Do the trial results apply to the ITT population?	While the ITT population included patients with and without BRCA mutations, all subsequent analyses have demonstrated that a BRCA mutation is a predictive biomarker of greatest treatment benefit. Studies are ongoing to find other predictive markers of treatment benefit in non-BRCA patients. Until further data are available, olaparib use is not generalized to non-BRCA patients.
Intervention	Administration of intervention	In Study 19, the recommended dose of olaparib was eight 50 mg capsules taken twice daily (total of 16 capsules), equivalent to a total daily dose of 800 mg	Given the high pill burden, do trial results apply to patients who may take less capsules due to low treatment compliance?	Non-compliant patients should not have their treatment discontinued for this reason, but should be assisted in finding ways to achieve optimal doses as determined by their oncologist. Up to 25% of patients on trial experience treatment interruption or dose modification, therefore it can be anticipated that not all patients will be treated at full doses.

1.2.4 Interpretation

Burden of the Disease

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 (2/3) 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 live years.

Need

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 the only molecular subgroup that can be consistently and reliably identified through molecular testing,

Currently, maintenance therapy is not standardly used following platinum based chemotherapy for recurrent, platinum-sensitive ovarian cancer. However, previous trials have shown benefits in PFS of maintenance treatment with anti-VEGF therapy (i.e. bevacizumab) and tyrosine kinase inhibitors (e.g. cediranib) but this strategy is not widely adopted.[9-11] PARP inhibitors, including olaparib, have activity in the BRCA mutation positive patients, a finding that is consistent with the know mechanism of action of these agents (see section 2.1). When combined with chemotherapy, olaparib leads to significant myelosuppression,[12] however, as a single agent myelosuppression is less pronounced. Given its oral administration, absence of toxicities such as alopecia and neuropathy, it is a logical agent to consider for "maintenance" treatment to maintain disease control following a response to platinum-based chemotherapy.

Effectiveness

At this time, olaparib efficacy data are limited to early phase trials. Study 19, is a randomized phase II trial[4] that enrolled 265 patients with recurrent platinum sensitive disease following a response to platinum based therapy. Response was defined by partial or complete response using RECIST criteria (version1.0),[13] or by the GCIG definition of CA-125 response.[14] Participants were then randomized, in a 1:1 ratio, to maintenance placebo or maintenance olaparib (400 mg PO BID). Double blinding was applied, and stratification by interval between disease progression and the penultimate platinum based therapy (6-12 months versus >12 months), the objective response to their most recent regimen (complete versus partial) and their ancestry (Jewish versus non-Jewish). Treatment could continue until objective progression, or significant, unmanageable toxicity.

At first reporting, Study 19 met its primary endpoint objective and demonstrated an improvement in the PFS of patients treated with maintenance olaparib. In the ITT population the PFS on the olaparib arm was 8.4 months versus 4.8 months for those on placebo (HR 0.35; 95% CI: 0.25 – 0.49 and p<0.00001). The CGP views this magnitude of improvement in PFS as meaningful since the overall value of retreatment with chemotherapy diminishes with every line (less effective, shorter duration of benefit) and as patients become more ill it is often less well tolerated.

Primary and secondary analysis of outcomes within the BRCA mutation (germline and somatic) subgroup have also been reported. BRCA mutated cancers were anticipated to

benefit most from PARP inhibitors on the basis of the mechanism of action of these agents (see section 2.1). Therefore, a pre-planned analysis of BRCA mutation carries enrolled in Study 19 was scientifically justified.

After a median of 37.3 months of follow up, with 52% data maturity, PFS in the BRCA mutation subgroup was improved from 4.3 months in the placebo group, to 11.2 months in the olaparib group [HR=0.18 (95% CI 0.1-0.13) p<0.001].OS in the BRCA mutation subgroup reached a median of 34.9 months in the olaparib group, versus 31.9 months in the placebo group ([HR 0.73 (95% CI 0.45-1.17) p=0.19).[2] An update of those outcomes, with 70% data maturity demonstrated that BRCA mutated cancers gain a survival advantage of 4.7 months (34.9 months versus 30.2 months) [HR=0.62 (95% C 0.41-0.94, nominal p=0.02480)] while in the ITT population OS did not improve significantly following olaparib maintenance [HR=0.73 (95% CI 0.55-0.96, nominal p= 0.02483)]. The nominal statistical analysis is not statistically significant as it did not reach the required p-value when correcting for multiple time point analyses (this was the 3rd time point examined). The trial design did not include a statistical plan for OS analysis of the BRCA mutated subgroup.

Therefore, the reported benefit from olaparib observed in the BRCA mutated cancers is consistent with the *a priori* hypotheses of drug effect mainly in the BRCA mutated patient group. The demonstrated magnitude of benefit on the PFS from olaparib in the BRCA mutated subgroup is considered clinically meaningful.

Study 19 included 3 clinically validated instruments to assess patient reported outcomes: [FOSI, Total Functional assessment of Cancer Therapy – Ovarian (FACT-O), and Trial Outcome Index]. The data provided by these quality of life tools suggest no change in the physical and functional well-being of patients on the olaparib maintenance arm as compared to those on the placebo arm, irrespective of BRCA status.

The results of a smaller open-label, randomized phase II trial, Study 41[15] support, but cannot be considered to validate, the findings of Study 19, although the design of the trial differs and the study enrolled relatively few BRCA mutation carriers. Study 41 was a trial of patients with recurrent, platinum sensitive ovarian/fallopian tube/primary peritoneal cancer randomized to treatment with chemotherapy with or without concurrent olaparib (for 6 cycles) followed by maintenance olaparib in the investigational arm. Patients randomized to the concurrent therapy arm had olaparib at a dose of 200 mg PO BID for 10 days out of each 21 day cycle, and they had carboplatin at an AUC 4 (standard being AUC 6) and paclitaxel a 175 mg/m2 repeated on a 21 day schedule for 6 cycles. Those on the chemotherapy alone arm had carboplatin at an AUC of 6 and paclitaxel at 175 mg/m2 every 21 days for 6 cycles. At the completion of 6 cycles of chemotherapy, patients on the olaparib arm remained on maintenance olaparib at 400 mg PO BID until disease progression. The control group went on to post chemotherapy observation.

One hundred and seventy three patients were enrolled onto Study 41. Study 41 demonstrated that during the phase of concurrent chemotherapy and olaparib, the rate of disease progression was no different than for chemotherapy alone, with perfectly overlapping PFS curves from months 1-6 on the Kaplan-Meier analysis curves. However, at the start of maintenance treatment, a divergence of the PFS curves is observed, and the study primary end-point of PFS was prolonged from 9.6 months in the conventional arm to 12.2 months in the investigational/olaparib arm [HR 0.51 (95% CI 0.34-0.770 p=0.0012]. Only 41 patients with known BRCA mutations were enrolled onto Study 41, and they too experienced improved median PFS [median PFS was not reached at the time of data analysis for the olaparib treated patients, and was 9.7months in the chemotherapy alone arm, HR 0.21 (95% CI 0.08-0.55); p=0.0015]. OS in the overall study population and in the BRCA positive subgroups were not statistically different between the two arms of the study.

Limitations of the Evidence

Study 19, being a randomized phase II, is a relatively small trial. The statistical design uses a one-sided type 1 error of 20%, meaning the risk of a false-positive result is high. The clinical standard, as seen in phase III trials, typically accepts no greater than 5% risk of a type 1 error, and includes a two-sided analysis. The statistical analysis was adjusted for multiplicity of testing only for OS in the ITT analysis. There was no statistical plan for examining OS in the BRCA subgroup. While the subgroup analysis of BRCA mutation carriers was pre-planned, the analysis is based on relatively small patient numbers. Conventionally, subgroup analyses are used for hypothesis generation and require future validation in larger studies. While the results of Study 41 are supportive, they are not considered sufficient to validate Study 19 based on differences in the study design, smaller study size, and enrollment of few BRCA mutation carriers. Thus far, confirmatory phase 3 trials of the benefits of maintenance olaparib (as demonstrated in Study 19) have not been reported, although a phase 3 trial in patients with BRCA mutated, relapsed, platinum-sensitive ovarian/fallopian tube/peritoneal cancers is underway with an estimated primary completion date of September 2016 (SOLO2 trial: NCT01874353).

Safety

Low grade toxicities were common on the olaparib arm of Study 19, and in all adverse events were more common in to olaparib arm (at least 10% greater incidence than the placebo arm). Among patients on olaparib, 35% experienced at least one grade 3 or greater toxicity, with fatigue, anemia and gastro-intestinal symptoms (nausea, vomiting and diarrhea) being the most common. There were 2 patient deaths attributed to olaparib, one from thrombocytopenia and hemorrhagic stroke, and another from progressive ovarian cancer in conjunction with a possible drug induced myelodysplasic syndrome. In the placebo arm, 20.3% of patients experienced at least one grade 3 or greater adverse event. Most toxicities were manageable with simple treatment interruption and dose reductions. MDS in both the placebo (n=1) and the treatment groups (n=1) has been reported, and one case of leukemia in the treatment group has also been reported. While very serious, the risk of MDS and leukemia is very low and at this time cannot be attributed solely to olaparib in this population of pretreated with chemotherapy.

Other consideration

The CGP noted input from Registered Clinicians that stated olaparib is indicated for patients in first relapse after first line platinum based chemotherapy. The CGP clarified that the funding request and basis of the current review was for maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated ovarian cancer who are in response (complete response or partial response) to platinum-based chemotherapy. Essentially 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 then have experienced a relapse, and received an additional course of platinum-based chemotherapy (e.g. 2nd 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. As to the use of olaparib in patients after first relapse, the results of Study 19 cannot be generalized into this population.[44] The efficacy of maintenance olaparib in patients after first line therapy is the subject of ongoing phase III trials.

Following the posting of the Initial Recommendation, feedback was received addressing the following:

- As related to the statistical design of the trial, the CGP re-iterated that the design was sufficient to demonstrate a very good signal for efficacy with olaparib. The results however require confirmatory data through a phase 3 RCT. As outlined by the Methods discussion, the statistical significance achieved in the overall population is limited by the increased chance of detecting a false positive as the trial had a randomized phase 2 design with all associated design limitations (e.g., type 1 error rate of 20%).
- The CGP discussed the impact of delayed access of treatment to patients and considered the body of evidence available on olaparib. The CGP agreed that currently the consensus among gynecologic oncologists is to have access to this class of drugs for use in their patients. The biologic rationale does support that PARP inhibitors are very active in this population. Recent press release of a phase 3 trial using another PARP inhibitor suggests a benefit in this population however this data has not been submitted or reviewed by pCODR and the CGP is limited in using this press release as supportive information. Without the context of other trials which have reported positive results in this patient population, the results of Study 19 on their own are vulnerable to being a false positive based on the randomized phase 2 statistical plan, and the subgroup analysis. The CGP noted that there are numerous examples of strongly positive phase 2 trials in oncology that had failed to be confirmed in phase 3 confirmatory trials so it is in the opinion of the CGP that one cannot skip the SOLO 2 results and decide based on Study 19. It is notable that the FDA has not approved Olaparib for this indication and is awaiting further data at this time.
- The CGP discussed the timeline for the availability of the SOLO 2 trial and noted that the trial has now stopped accrual. Typically, initial reports should be made available within 6-12 months of the end of accrual. The CGP do agree with the assessment on the delayed timeline for the availability of data. A timeline of about 2 years from the data maturation from SOLO 2 is reasonable but the CGP is unable to provide more details.
- The CGP discussed the importance of PFS and QoL as an outcome in this patient population. At this time, recurrent ovarian cancer is still considered an incurable disease. As such patient's quality of life is the main consideration to select therapy. It had been well established that in a recurrent setting, stable or partial response to treatment can improve patients' QoL over progressive disease. It would therefore be important clinically to maximize PFS to maintain QoL. Therefore PFS is important if it is achieved with a low toxicity agent that prevents patients from being on other, more toxic treatments and keeps their disease symptoms to a minimum. The CGP noted data from Study 19 demonstrating that 15% and 13% of patients being progression free over 4 years and 5 years, respectively to be unprecedented and meaningful in this population. It will be important to note that the patient population under consideration is the best prognostic subgroup of all recurrent patients (platinum sensitive, responded to second line platinum therapy, BRCA positive) and not all patients with recurrences as commented on in the feedbacks. The benefits of Olaparib must be evaluated with this in mind.
- OS is clearly still the gold standard, but many trials cannot achieve this often because cross over occurs (for example, many patients enter serial clinical trials, and can gain access to PARP inhibitors in the future, or patients enrol in drug access programs, as is currently happening in Canada). The 2010 GCIC consensus regarding PFS is based on correlation with QoL/ symptom improvement. The consensus inflated that the correlation between PFS and OS was very poor although it would be ideal in a

recurrent setting however certainly, PFS with good QoL scores/lack of disease symptoms, is a desired endpoint. The consensus statement from GCIC was not specific to maintenance treatment, but the CGP do think that it pertains to maintenance treatment nonetheless.

1.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net clinical benefit to maintenance olaparib therapy in the treatment of recurrent, platinum-sensitive high grade ovarian/fallopian tube/peritoneal carcinoma, defined by the presence of a germline or somatic BRCA mutation. This conclusion is based on the results of a pre-planned subgroup analysis of BRCA mutation carriers enrolled in Study 19, a randomized, controlled, blinded phase 2 trial of 265 patients, 51% of whom had either a germline or somatic BRCA mutation. This trial demonstrated a clinically significant benefit in the primary endpoint, PFS for olaparib used in BRCA mutation carriers, as compared with placebo. PFS at interim analysis (53% data maturity) was improved from 4.3 months to 11.2 months [HR 0.18(95% CI 0.1-0.310); p<0.0001]. At last analysis (70% data maturity), patients with BRCA mutation had a median OS of 34.9 months with olaparib therapy compared to 30.2 months on the placebo arm [HR=0.62 (95% C 0.41-0.94); p=0.02480, a nominal value which did not meet criteria for statistical significance], a clinically meaningful improvement of 4.7 months.

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

- The observed benefit in this molecular subgroup of patients is consistent with the known mechanism of action of olaparib (a PARP inhibitor). These results of the trial are generalizable to patients who are sensitive to platinum based therapy in the second or later lines of therapy.
- The results of Study 19 are not generalizable to patients following first-line therapy, those with disease progression during platinum based therapy for disease recurrence, or patients who do not have a germline or somatic BRCA-mutation.
- Adverse event were more commonly observed with olaparib than with placebo, toxicities were manageable
- Patient reported outcomes did not suggest any deterioration of QoL while on olaparib as maintenance treatment.
- Study 19 was a small study, the pre-planned analysis of the BRCA population is based on small patient numbers, the statistical design of the study combined with the multiple time point analyses increase the possibility of a false positive result. Confirmatory data is required to validate these results.
- Although the inclusion criteria of Study 19 was limited to patients who have an ECOG ≤2, the CGP agreed that a decline in ECOG PS (>2) on account of recent chemotherapy and treatment related fatigue or other toxicities, should not preclude patients from eligibility to receive olaparib. Patients with a decline in PS due to advancing disease should however not be eligible for olaparib.

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 form of all gynecologic malignancies with a high case fatality ratio due to frequent advance stage at diagnosis. According to the 2015 Canadian Cancer Statistics,[8] Canadian women have an estimated lifetime risk of 1.4% to develop the disease. 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 for metastatic disease includes a combination of aggressive tumour debulking surgery to minimize amount of residual disease[16-18] and platinum/taxane combination chemotherapy.[19-21] Expected response rate to this combination therapy is in the range of 75% to 85%. Unfortunately, most patients will subsequently recur after finishing primary treatment requiring additional therapy for further disease control. At time of recurrence, patients are commonly classified as being 'platinum sensitive' if time from the last platinum chemotherapy is at least 6 months or more due to an expected higher response rate to further platinum based chemotherapy.[22,23] The majority of patients will have some degree of platinum sensitivity at time of first recurrence.

Serous epithelial ovarian cancer is the most commonly encountered histology in advanced ovarian cancers. BRCA-m 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[24,25] 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.[18] 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.[26,27,27] 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 and 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.

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 and secondary cytoreductive surgery.[28,29] 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[30,31] can have an expected response rate of around 50% - 60%.

Due to the high-expected recurrence rate in advanced cases (stage III and IV), maintenance strategies had been studied in an effort to delay / prevent recurrences. Prolonged uses of alkylating agents, platinum agents, and paclitaxel had not been shown to significantly increased overall survival but at a cost of increased toxicities.[32-35] Maintenance therapy after response to cytotoxic chemotherapy is not currently in standard clinical practice. In the past where maintenance taxanes were studied in this population (e.g., the SWOG trial), PFS was positive but not OS. The biggest issue with the taxane maintenance study was the toxicity – alopecia and neuropathy (e.g., impaired QoL).The improvement in median PFS was 8 months (improvement from 14 to 22 months) but at the cost of 9 months on treatment with a toxic therapy and no hint of OS improvement. The study was stopped early due to the impact on PFS and OS is not interpretable. The current standard of care is "watch and wait" after response is observed following a fixed number of cycles of platinum based regimen until further disease progression occurs. Eventually, all patients with recurrent disease will develop resistance to platinum drugs with increasingly shortened progression free interval with each subsequent line of therapy.[36] 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 3 clinical trials with very encouraging preliminary results after first line chemotherapy as maintenance and in the recurrence settings.[37]

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.[3] 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.

In a recent Cochrane review,[38] Olaparib was also noted to improve the progression-free survival when used as maintenance treatment in women with platinum-sensitive disease compared with placebo (hazard ratio (HR) 0.42, 95% confidence interval (CI) 0.29 to 0.60; 426 participants ; two studies), but did not improve overall survival (OS) (HR 1.05, 95% CI 0.79 to 1.39; 426 participants; two studies). Olaparib was associated with more severe adverse events (G3/4) during the maintenance phase compared with controls (risk ratio (RR) 1.74, 95% CI 1.22 to 2.49; 385 participants, two studies; moderate quality evidence).

Olaparib had been specifically studied in a maintenance setting in a double blind, placebo-controlled, multicentre, phase II international study (Study 19).[4] In this study, patients with platinum-sensitive relapsed, high-grade serous ovarian cancer who had received two or more platinum-based regimens and had had a partial or complete response to their most recent platinum-based regimen only were enrolled. Patients were randomly assigned to receive Olaparib, at a dose of 400 mg twice daily, or placebo. The primary end point was progression-free survival according to the Response Evaluation Criteria in Solid Tumors guidelines. Patients were to continue assigned treatment until objective disease progression. The primary endpoint was progression-free survival (PFS) according to RECIST guidelines. BRCA status was not known at study entry for all patients, but was determined blinded post-study for approximately 95% of women (in a pre-planned retrospective analysis).

Study 19 showed Olaparib resulted in a significantly longer PFS (the primary endpoint) than placebo: 8.4 vs. 4.8 months, with a hazard ratio of 0.35 (95% CI 0.25-0.49). In the BRCA mutated (BRCAm) subgroup, the median PFS was 11.2 months with Olaparib compared with 4.3 months with placebo (HR=0.18; 95% CI 0.10-0.31). The median PFS gain in non-BRCAm patients was 1.9 months (7.4 vs. 5.5 months). An OS analysis was conducted in the BRCAm population at 52% maturity (71 deaths out of 136). The median OS was 3 months longer for Olaparib compared with placebo (34.9 vs. 31.9 months), HR 0.73 (95% CI 0.45-1.17; p=0.19). In the overall population, the median OS was similar in the two groups (29.8 mos for Olaparib and 27.8 mos for placebo). It should be noted that a total of 23% of placebo treated BRCAm patients went on to receive PARP inhibitors following completion of the study which probably had confounded the OS results. An exploratory analysis of OS with

PARPi crossover use excluded was conducted and a statistically significant improvement in OS in favour of Olaparib was observed: 34.9 months for Olaparib vs. 26.6 months for placebo, HR 0.52 (95% CI 0.28- 0.97; p=0.039). An updated analysis of OS at 70% maturity in the BRCAm subgroup demonstrated a 4.7 month improvement in OS with Olaparib vs. placebo: 34.9 months vs. 30.2 months, HR = 0.62 (95% CI 0.41, 0.94).

Symptoms and QOL were assessed using three validated instruments: FOSI, Total FACT-O, and Trial Outcome Index (TOI). Olaparib had consistently greater improvement than placebo on all 3 instruments, and for both the overall and BRCAm subpopulations. However, these differences in QoL were not statistically different from placebo. In term of toxicities, more patients in the Olaparib arm had grade 3 or higher AEs (40%) compared with the placebo arm (22%) in the overall population, with similar findings in the BRCAm population (38% vs. 18%).The most common grade 3 or higher AEs reported on Olaparib were fatigue (7.4%) and anaemia (5.1%).

Further updated pre planned subgroup analysis of Study 19 focussing only on BRCA mutated patients with platinum sensitive relapsed serous ovarian cancer was also published.[2] In the main study, 136 patients were assigned to Olaparib and 129 to placebo. BRCA status was known for 131 (96%) patients in the Olaparib group versus 123 (95%) in the placebo group, of whom 74 (56%) versus 62 (50%) had a deleterious or suspected deleterious germline or tumour BRCA-m. Of patients with a BRCA-m, median PFS was significantly longer in the Olaparib group than in the placebo group (11·2 months [95% CI 8·3-not calculable] vs. 4·3 months [3·0-5·4]; HR 0·18 [0·10-0·31]; p<0·0001); similar findings were noted for patients with wild-type BRCA, although the difference between groups was lower (7·4 months [5·5-10·3] vs. 5·5 months [3·7-5·6]; HR 0·54 [0·34-0·85]; p=0·0075). At the second interim analysis of overall survival (58% maturity), overall survival did not significantly differ between the groups (HR 0·88 [95% CI 0·64-1·21]; p=0·44); similar findings were noted for patients with mutated BRCA (HR 0·73 [0·45-1·17]; p=0·19) and wild-type BRCA (HR 0·99 [0·63-1·55]; p=0·96). The most common grade 3 or worse adverse events in the Olaparib group were fatigue (in ten [7%] patients in the Olaparib group vs. four [3%] in the placebo group) and anaemia (seven [5%] vs. one [<1%]). Serious adverse events were reported in 25 (18%) patients who received Olaparib and 11 (9%) who received placebo.

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 subsequent platinum-based chemotherapy (second line or beyond) for disease recurrence. Olaparib will be used in a maintenance setting as monotherapy until further disease progression or intolerable toxicities.

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. Utilization of Olaparib should be limited to patients with proven BRCA 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.

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[15,39] 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.[40,41]

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Ovarian Cancer Canada (OCC), provided input for olaparib (Lynparza) as monotherapy 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.

OCC conducted an anonymous online survey in English and French, and promoted through the organization's database, website, social media sites and partners to those living with ovarian cancer and their caregivers. Specifically, the survey was targeted to those who were 1) 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 after six months of diagnosis and; 4) tested positive for a BRCA gene mutation and; 5) may or may not have taken olaparaib as a treatment for their recurrent ovarian cancer.

There were a total of 40 respondents, of which 29 were people living with ovarian cancer and 11 were caregivers. Respondents living with ovarian cancer included those diagnosed with epithelial ovarian cancer (n=24), primary peritoneal cancer (n=4) and one respondent (n=1) did not know the type of ovarian cancer. Of the 29 respondents diagnosed with ovarian cancer, the majority of respondents (n=25 or 86%) had been diagnosed between 2010-2015 and four respondents (14%) were diagnosed between 2000-2010. The majority of the women had a BRCA 1 gene mutation (n=24), eleven (n=11) had a BRCA 2 gene mutation and the remainder (n=5) did not know the type of mutation. Respondents living with ovarian cancer were women who ranged in age from 32–75 years; a little more than half of the respondents were between the ages of 60-75 and the remainder were between the ages of 32-59. A total of 10 respondents indicated that they or those they were caring for had used olaparib as a treatment for ovarian cancer.

Of the total 40 respondents: 39 were from Canada and one (1) was from the United States. There were no respondents from Alberta, Manitoba, New Brunswick, Prince Edward Island, Nova Scotia, Newfoundland or the Northwest Territories, Nunavut or the Yukon.

From a patient's perspective, there are significant psycho-social impacts, including fear, depression, worry and anxiety for patients diagnosed with ovarian cancer. Because early symptoms can be non-specific and because there is no screening test, ovarian cancer is usually detected in its later stages, resulting in a grim prognosis.

According to OCC, surgery and chemotherapy, particularly platinum agents have been the mainstays of treatment for ovarian cancer. Notwithstanding some challenges with current treatments, most respondents who were surveyed reported that their current treatments were able to manage their ovarian cancer. Respondents indicated they were deeply affected by fatigue, hair loss, bowel problems and blood problems from their treatments. OCC found that a side effect that was rated as having no effect by most respondents was the impact on their fertility. OCC surmised this may be because many of the respondents would have been peri-menopausal or menopausal.

OCC reported that the most important reasons for respondents who are considering taking olaparib were that it could increase the length of time before recurrence and that they can take the treatment at home. These respondents anticipate the benefits of taking olaparib could prolong life and improve quality of life. Most of these respondents would be willing to tolerate most side effects if olaparib were to improve overall daily functioning or prognosis. However, these respondents noted that blood disorders or blood cancer and inflammation of lungs were those side effects that they were least willing to tolerate. Respondents who have experience with olaparib

indicated the top three issues that olaparib managed or managed better than previous treatments were prolonged time until recurrence, shrunk tumour size and prolonged survival. The key side effects that these respondents experienced were tiredness/weakness, nausea, taste changes, diarrhea, blood disorder or blood cancer, headaches, blood problems (e.g. anemia), pain under the ribs, dizziness, infections and sore mouth. The majority of respondents believed the benefits of olaparib outweighed the risks.

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, without modification.

Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with ovarian cancer

According to OCC, the impact of ovarian cancer is enormous for those diagnosed with this disease and their caregivers. The majority of patients are diagnosed in late stage and the majority will have one if not multiple recurrences of this disease.

Respondents to the survey were asked to describe overall how their life has been affected by their diagnosis with ovarian cancer. OCC submits that the respondents' lives were affected profoundly by ovarian cancer. In particular, they described significant psycho-social impacts, including fear, depression, worry and anxiety. Other areas that were negatively impacted included their sleep, work life, physical activity and well-being.

Respondents were asked "*On a scale from 1 (no effect) to 5 (extremely negative), please rate how ovarian cancer has impacted the following issues in your life*." Of the 27 respondents who responded to the question, the following five areas that were found to have most negatively impact respondents (being rated 4 or 5 on the scale) were:

- Sleep (n=15)
- Sexual relationship (n=15)
- Work life (n=14)
- Physical activity (n=14)
- Well-being (n=10)

To help illustrate some these psycho-social impacts, OCC have collated the key responses below:

- "*I thought I would be back to work after a few months, but it is 5 years and I have not been able to return to work*."
- "*…have been out of work since so we are living on one income. It has destroyed us financially…worrying about finances all the time affects my quality of life in a big way*."
- "*Have financial concerns, aggravation dealing with disability insurer. In permanent state of anxiety, with profound sleep disturbance*."
- "*Live with a continual level of uncertainty about the future…constant fear of not being present*."
- "*We have not taken a real holiday in 4 years. Life is centered on trying to keep on top of the physical impact of my disease, which unfortunately has resulted in 3 recurrences. I have been on some form of chemo for 3.5 yrs continuously…*"

- "*Chronic anxiety affecting work, ability to withstand stress, fear of recurrence became paralyzing…*"
- "*Le coût des médicaments a une incidence sur mes revenus, mon état de santé représente une baisse de mes capacités, et dû a l,opération, les stations debout ne me sont plus permises, alors je ne travaille plus depuis 2013 et la baisse de mes revenus est extrême*." "*Le stress constant d'avoir une récidive, les effets secondaires de la chimio causant des troubles cognitifs légers…*"

3.1.2 Patients' Experiences with Current Therapy for Ovarian Cancer

OCC stated that respondents' reported that their current treatments included chemotherapy and surgery. Respondents were asked: "*Please rate the extent to which you agree or disagree with the following statement: 'My current (or past) treatments were able to manage my ovarian cancer.'*" Of the 35 respondents (including caregivers and those living with the disease) who responded to this question, 24 respondents had indicated they agreed or strongly agreed. Notwithstanding the above, respondents also commented on the hardship experienced by patients with regards to their current therapies. These comments are highlighted below:

- "*Each course of treatment halted the progression for a period, but another recurrence then evolved (3x). The last treatment on a research trial was brutal for my body and effectively did not manage the cancer*."
- "*The cancer came back in 6 mos after second chemo…*"
- "*After chemo and surgery I got 18 months before the cancer reoccurred. I had 6 more treatments of chemo and got 8 months before I had another reoccurrence. I just finished another 6 rounds of chemo*."
- "*Was not able to contain the tumour and the side effects were awful*."
- "*Les traitements ont contrôlés en partie la propagation. Cependant les effets secondaires ont été plus difficiles lors de la deuxième série de traitement*."

Respondents reported that the ovarian cancer treatments negatively affected those diagnosed with ovarian cancer. In particular, those diagnosed with ovarian cancer indicated they were deeply affected by fatigue, hair loss, bowel problems and blood problems from their treatments. 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. Of the 35 respondents who responded to this question, the areas that respondents (patients and caregivers) rated as 4 (very negative) or 5 (extremely negative) are noted below:

- Fatigue (n=28)
- Hair loss (n=21)
- Bowel problems (n=19)
- Blood problems (n=19)
- Nausea/vomiting (n=16)
- Aching joints (n=13)
- Neuropathy (n=11)
- Skin irritations (n=8)
- Loss of fertility (n=7)
- Ascites (n=6)

A majority of respondents (approximately 80%) rated fatigue as having a large effect or extremely large effect on their quality of life. Below were key comments from respondents:

- "*Fatigue due to treatments. Required blood transfusions, and platelet transfusion*."

- "*…ongoing chemo after a 3rd recurrence…has put me into a depression of sorts which I've never been. I'm definitely more tired and I used to be extremely active and after 3.5 years I'm just getting back into it*."
- "*Having low energy, body aches and pains and fatigue are difficult to deal with as I like to stay active and busy*.

Another key area that respondents reported having an impact was in regards to their bowels. Specifically, respondents noted the following:

- "*Diarrhea; muscle aching; constipation; bowel blockage one time causing obstruction, second time tending to an obstruction which hasn't yet occurred*."
- "*Severe stomach discomfort while on treatments*."
- "*I have had 5 recurrences. I have an ostomy due to the cancer spreading in 2008. This last time I ended up with kidney drains, but thankfully they have been taken out - they were torture!*"
- "*She now has a stoma and must deal with it now that it has herniated*."

OCC found that a side effect that was rated as having no effect by most respondents (approximately 77%) was the impact on their fertility. OCC surmised this may be because many of the respondents would have been peri-menopausal or menopausal.

Below were additional reported responses to help illustrate some of the side-effects experienced by respondents in regards to their current therapies:

- "*No appetite, no energy, difficulty eating and being mobile*."
- "*Memory…recall issues ….often mid-sentence unable to recall word or what I was talking about or what I was going to do*."
- "*Apparition de douleur thoracique aigue après chaque traitement*."
- "*The operation did control the growth for a while but once it came back, it really spread. Ascites, nausea, vomiting, pain, loss of appetite, loss of hair, loss of strength… are just some side effects during this process and they haven't stopped*."
- "*My sense of smell became so acute I could smell down to the essence of everything. I no longer wanted to eat, but forced myself to eat what I could, knowing I had to feed my body*."
- "*Treatments were very harsh and also included debulking procedure mid-way through treatment. Which almost killed her*."

Respondents were asked, "*Would you have been willing to tolerate additional side effects if the benefits of the treatment were considered to be short term (e.g. months vs. years of improvement)?*" Out of 35 respondents (including patients and caregivers), 21 answered yes, two (2) answered no and 12 were uncertain. OCC highlighted comments from those diagnosed with ovarian cancer, which included:

- "*As long as I can still walk, talk, eat and there is quality to my life I can tolerate a lot*."
- "*I could not tolerate severe nausea, bone pain or severe fatigue*."
- "*If I thought it could cure me or substantially delay recurrence, I would put up with considerable inconvenience*."
- "*I can take a lot, but can't deal with constant vomiting*."

In addition to the above, caregiver respondents provided comments that their family or friend would be willing to tolerate side effects. Their comments are noted below:

- "*If it helps to improve her state, side effects come with it*."

- "*It is an important option when one wants to delay return to traditional chemo which is so destructive to the body and which ultimately can result in a non-sensitive status…*"

Four (4) out of five (5) caregivers also indicated that olaparib should be made available in Canada, one respondent indicated "maybe".

Respondents were asked how significant specific barriers (e.g., financial, travel and treatment not available) were in accessing their treatment. Of the 21 respondents who responded to this question, the following barriers were rated as "significant" and "extremely significant" included: travel issues (n=9); financial issues (n=6); treatment not available (n=6). Below were reported responses to help illustrate some of the challenges and hardships experienced by the respondents:

- "*We have no clinical trials available in Saskatchewan. I am not financially able to travel to and stay in another city…*"
- "*I am on a fixed low monthly income. Without help from family, my situation would be dire*."

3.1.3 Impact of Ovarian Cancer and Current Therapy on Caregivers

According to OCC, responses were received from 11 caregivers: spouses/partners (n=4), mothers (n=4), other family member or friend (n=3). Three (3) caregivers have been providing care for less than two years and eight (8) caregivers have been providing care for three years or more. Almost three quarters (n=8) of the caregivers provided 1-6 hours of care a day and three (n=3) provided care between 6-12 hours per day.

Respondents reported the areas that were most impacted for caregivers were the following: sexual relationships, physical activity, family/friend relationships and sleep. Specifically, respondents were asked: "*On a scale from 1 (no effect) to 5 (extremely negative), please rate how caregiving has impacted the following issues in your life.*" Of the ten (10) who responded to the question, the following six areas were found to have most negatively impact respondents (rated 4 or 5 on the scale) were:

- Sexual relationship (n=4)
- Physical activity (n=4)
- Family/friend relationships (n=4)
- Sleep pattern (n=4)
- Ability to care for yourself (n=3)
- Work life (n=3)

Below were reported responses from caregiver respondents to help illustrate some of the impacts on their day-to-day activity and/or quality of life:

- "*…Once she came to live with us, it was difficult as I was also caring for two very young grandchildren … The treatments and drugs prescribed afterwards left my sister with lots of other problems other than the cancer…*"
- "*Our plans to retire…were put on hold…and going on holidays…out of the question. It took four years ... have been several re-occurrences of the cancer…when needed, I am at her side 24/7 and the rest of family life takes a back seat*."
- "*Have to reorganize work, personal, and exercise schedules around care. Not able to leave her home alone for extended periods of time*."

- "*It's very upsetting to watch my wife suffer from pain and anxiety.*"
- "*Moins de temps pour moi et pour ma propre famille. Fatigue, difficulté à se concentrer, insomnia*."

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Ovarian Cancer

Patient Expectations for Olaparib

In terms of patient expectations for olaparib, of the 25 respondents who responded to this question and who have not been treated with olaparib, 16 respondents considered taking this new therapy, and four caregivers were unsure if it had been considered as a treatment option.

Of the 16 respondents who considered taking olaparib, the most important reasons for considering this therapy were:

- it could prolong time until recurrence (n=14) and
- you can take the treatment at home (n=9).

Of the 16 respondents who responded to the question on potential risks with using olaparib, two respondents (n=2) did not see any risks with taking olaparib; six respondents (n=6) were not sure about potential risks, and eight respondents (n=8) considered side effects and quality of life to be risks. OCC identified that olaparib does not cause hair loss, but this was not deemed to be a particularly attractive factor.

Of the 19 respondents who responded, 11 respondents believe the benefits of olaparib outweighed the risks; seven (7) respondents were not sure; and one (1) respondent thought the benefits did not outweigh the risks. The 19 respondents anticipates the benefits of taking olaparib included: increasing the length of time before recurrence (n=10); prolonging life (n=6); improved quality of life (n=3).

Respondents were asked: "*If you were to take Olaparib, how important is it to you that it be able to address the following issues*?" 22 respondents who responded to this question rated the following as being very important:

- Expect the drug to prolong their survival (n=22)
- Prolong time until recurrence (n=22)
- Improve their quality of life (n=20)
- Reduce visits to the cancer centre (n=16)

According to OCC, of the 22 respondents, a little over half (n=12) indicated they (or their family/friend) would be willing to take olaparib if there was only a little to some (score of 2 or 3 out of 5) improvement in their ovarian cancer.

Over half of the respondents would be willing to tolerate most side effects if olaparib were to improve overall daily functioning or prognosis. Those side effects rated most tolerable were:

- Tiredness (n=20)
- Nausea (n=16)
- Taste changes (n=14)

- Blood problems (n=13)
- Bruising and bleeding easily (n=13)
- Dizziness (n=13)
- Headaches (n=13)
- Pain under the ribs (n=13)

Respondents noted that blood disorders or blood cancer (n=5) and inflammation of lungs (n=7) were those side effects that they were least willing to tolerate. Below were the reported reasons given for willingness to tolerate side effects with using olaparib:

- "*They can be managed*."
- "*Prolong my life*."
- "*I would be willing to try the drug, but if any of the side effects were severe I would cease to take the drug*."
- "*These seem easily manageable*."
- "*I would find it difficult to tolerate all of the above side effects indefinitely*."
- "*Pour éviter une récidive*."
- "*Si tout ca n'est que temporaire et me permet de guérir, je suis prête à me batter*."

Patient Experiences with Olaparib

OCC reported that 10 respondents had direct experience with olaparib as a treatment for ovarian cancer. Of these respondents, three (3) were caregivers. Respondents indicated the top three issues that olaparib managed or managed better than previous treatments were:

1. prolonged recurrence;
2. shrunk tumour size; and
3. prolonged survival.

The key side effects that the 10 respondents experienced were:

- Tiredness/weakness (n=6)
- Nausea (n=5)
- Taste changes (n=4)
- Diarrhea (n=3)
- Blood disorder or blood cancer (n=3)
- Blood problems (e.g. anemia) (n=3)
- Headaches (n=2)
- Pain under the ribs (n=2)
- Dizziness (n=1)
- Infections (n=1)
- Sore mouth (n=1)
- Bruising/bleeding easily (n= 0)
- Inflammation of the lungs (n=0)
- None = 1

Unacceptable side effects mentioned by four (4) respondents include: tiredness, hair loss, nausea, bowel issues and blood disorders.

Of the seven (7) respondents who responded to this question, five (5) respondents agreed or strongly agreed that olaparib had improved their quality of life compared to previous treatments used. It was rated as neither positive nor negative by two respondents (2).

When asked about the impact of olaparib on their quality of life, both patients and caregiver respondents noted the following:

- "*Dosage scheduling was difficult; but I was willing to tolerate this as long as I knew that there was prolongation of tumor reduction*."
- "*Able to look more into a future. Able to travel. No infusions All improve quality of life*."
- "*Taking pills is so much easier than chemo treatments downtown. The symptoms from olaparib are very manageable. My quality of life and state of mind is better*."
- "*Improved her mental state believing she was on the drug combatting her cancer and prolonging/stopping recurrence*."
- "*L'effet positive est qu'il était une nouvelle source d'espoir. Le negative est que nous ne savions pas à quel point les effets secondaires étaient dus à Olaparib ou à la recrudescence du cancer, étant donné la recherche à l'aveugle*."

3.3 Additional Information

OCC submits that the low numbers of respondents to this survey is not indicative of a lack of interest of women living with ovarian cancer to provide feedback on a new treatment. The low numbers are likely due to the restrictive criteria, as approximately 20% of the high grade serous ovarian cancer is due to 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

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.

Study 19 is a phase 2, placebo-controlled trial. At the time of the PAG input, there was no overall survival data. This is a barrier to implementation. PAG is seeking information on the long term benefits and safety of maintenance therapy from a phase 3 trial.

4.2 Factors Related to Patient Population

Olaparib would fill a gap in therapy. However, given the large number of patients with platinum sensitive disease, PAG indicated that a phase 3 trial would be feasible to conduct.

PAG noted that olaparib would be additional therapy as it is maintenance therapy and does not replace chemotherapy. Patients who relapsed on olaparib maintenance therapy may be treated with additional intravenous chemotherapy upon progression.

PAG has concerns for indication creep given the ongoing trials for use in first-line in combination with chemotherapy and published abstracts on maintenance therapy after first-line chemotherapy. PAG noted that the FDA approval is for patients with advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Understanding that these indications are out of the scope of this review, PAG is seeking information form the manufacturer on if and when a submission for these other treatment settings would be made.

In the absence of overall survival data, PAG is seeking information on the quality of life gains compared with the gains in progression free survival.

4.3 Factors Related to Dosing

The one capsule strength allows for easy dose adjustment by adjusting the number of capsules per dose. This is an enabler to implementation.

PAG has noted that the dose requires eight capsules twice a day for a total of sixteen capsules per day. This is a huge pill burden for these patients. In addition, a large number of pills would be dispensed and there is the potential for wastage if the patient has to discontinue treatment.

4.4 Factors Related to Implementation Costs

There will be costs associated the BRCA testing, specifically in provinces where the testing is not currently available, as resources would be required for genetic counselling. 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. 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 genetic testing and counselling resources.

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

PAG noted that there are trials, SOLO1 and SOLO2, with olaparib tablets at a different dose and with a lower pill burden. PAG is seeking information on if and when the tablet formulation becomes available in Canada.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided on olaparib for ovarian cancer:

1. Dr. Walter H. Gotlieb, jointly with seven physicians, on behalf of Gynecologic Oncology Canada (GOC)
2. Dr. Sandeep Sehdev

The clinicians providing input have identified that olaparib is an oral drug with fewer toxicities than intravenous chemotherapy and provides a maintenance treatment option for women with BRCA positive, platinum sensitive ovarian cancer after first-line platinum based chemotherapy.

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

5.1 Current Treatment(s) for this Ovarian Cancer

According to the GOC, standard therapy at the time of first relapse would be with a combination of carboplatin plus one of 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.

Dr. Sehdev indicated that after platinum based chemotherapy, there currently is no maintenance therapy given. It was also noted that trials have previously shown benefits of continuing the initial chemotherapy, in terms of progression free survival, but not for quality of life or overall survival and cumulative toxicities usually limit the utility of those approaches.

5.2 Eligible Patient Population

The clinicians providing input reported that ovarian cancer is not a very common cancer in general oncology practice and germline BRCA mutant patients are a small minority of patients with ovarian cancer. They estimated that the potential numbers of patients per year over the next five years across Canada would probably number about 1000. They believe that the number of patients eligible for olaparib will be small but if testing for de novo tumoral mutations becomes available, the number may be slightly higher if that additional population becomes identifiable.

The clinicians providing input noted that the question regarding prevalent population does not apply as the indication being presented to pCODR is for first relapse, platinum sensitive maintenance therapy. They identified a population of BRCA positive patients who have received three or greater lines of therapy where PARP inhibitors will be very useful and noted that olaparib confers a targeted therapy with a specific biomarker for a clearly defined population of patients.

5.3 Identify Key Benefits and Harms with Olaparib

The clinicians providing input believe that the benefits of well tolerated oral therapy are clear – the delay of symptomatic relapse is clinically meaningful since patients suffer tremendously with the symptoms of this disease, which include bowel obstructions (never eating again in many cases), abdominal pain, nausea and vomiting, and distension requiring weekly needle drainage of large amount of abdominal fluid. The symptoms often lead to emergency department visits and hospital admissions, often of lengthy durations.

The delay in the need for subsequent chemotherapy is also meaningful since the overall value of retreatment with chemotherapy diminishes with every line (less effective, shorter duration of benefit) and as patients become more ill, it is often much less well tolerated with respect to the well known serious toxicities it can cause.

The clinicians providing input stated that PARP inhibitors have a superior toxicity profile compared to chemotherapy. Fatigue, anaemia and nausea are the predominant side-effects, which are easily managed by dose interruption alones but if they are not, then dose reduction usually resolves the problem. These adverse effects are such that sophisticated, subspecialist assessment is not required. Patients report here that their quality-of-life is better on PARP inhibitors than any standard cytotoxic treatments.

The GOC noted one 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. Given the incurability of relapsed ovarian cancer, the clinicians providing input noted that 1% chance of myelodysplastic syndrome becomes an acceptable risk in this patient population.

5.4 Advantages of Olaparib Over Current Treatments

The clinicians providing input indicated that olaparib is an oral drug that prolongs the chemotherapy free interval with a low and manageable toxicity profile, maintaining a high quality-of-life for a group of patients where there is no currently accepted routine maintenance treatment.

5.5 Sequencing and Priority of Treatments with Olaparib

The GOC identified that olaparib would be used as maintenance therapy, after first-line platinum based chemotherapy and the intent is not to replace pre-existing therapies but to be an additional line of therapy. Dr. Sehdev indicated olaparib might replace “ongoing” maintenance chemotherapy in some patients.

5.6 Companion Diagnostic Testing

The clinicians providing input indicated that BRCA testing is essential as the treatment is indicated for treatment for patients with BRCA-ms either in the germline or somatic.

5.7 Additional Information

No additional information provided.

6 SYSTEMATIC REVIEW

6.1 Objectives

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) epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy.

Note: Supplemental Questions most relevant to the PCODR review and to the Provincial Advisory Group have not been identified as of yet while developing the review protocol.

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 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs or non RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of olaparib should be included.	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	Best Supportive Care and close follow-up	• OS • PFS • ORR • HRQoL • AEs • SAEs • WDAE • Myelodysplastic syndrome (MDS) • Leukemia • Time to subsequent therapy • Rate of treatment discontinuation
[Abbreviations] **OS**= overall survival; **PFS**= progression-free survival; **ORR**= overall response rate; **HRQoL**= health-related quality of life; **RCT=**randomized controlled trial; **SAE**=serious adverse events; **AE**=adverse events; **WDAE**=withdrawals due to adverse events				

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

6.2.2 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 in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (February 2016) 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 7 July 2016.

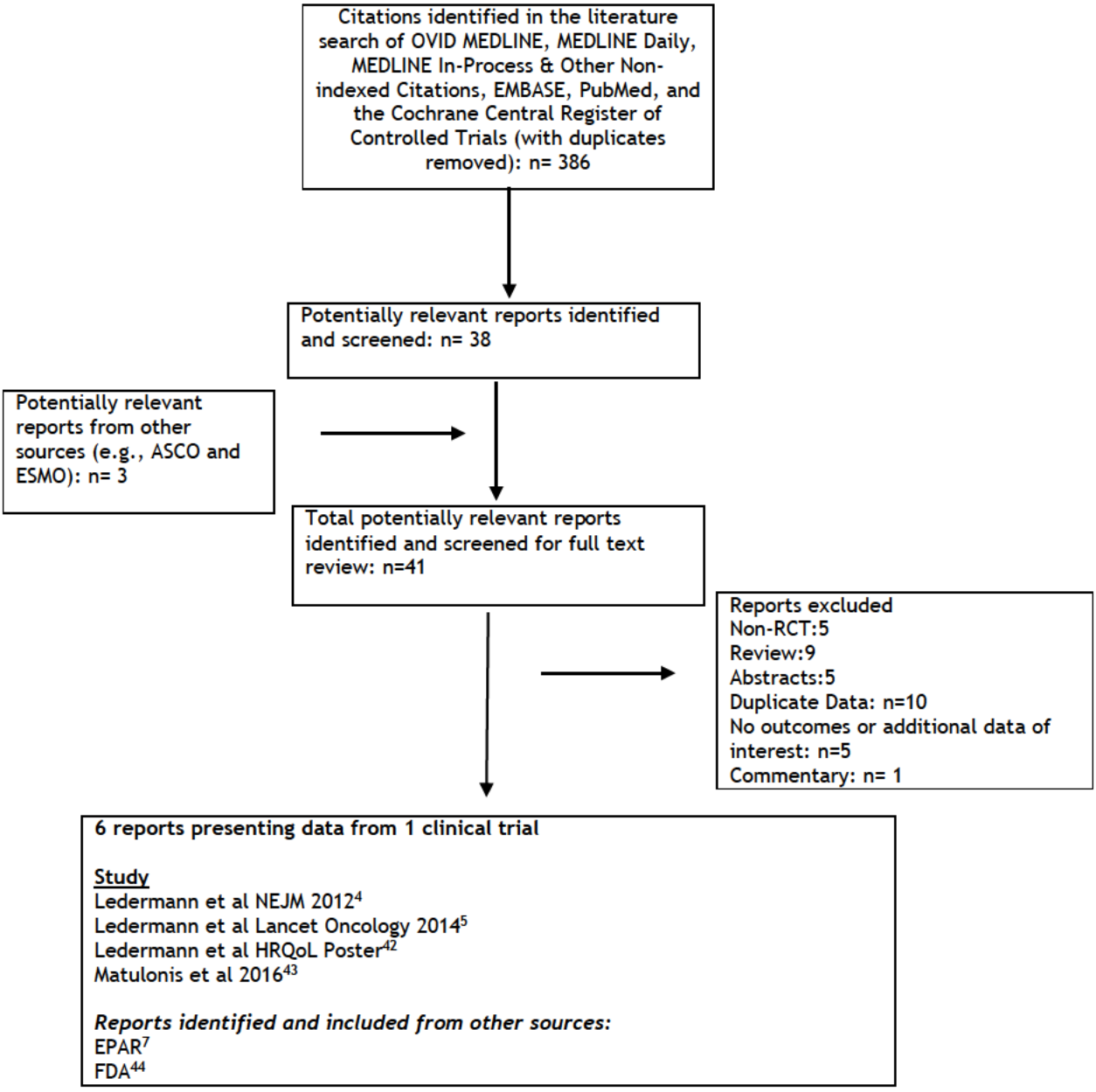
Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. 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.

6.3 Results

6.3.1 Literature Search Results

Of the 41 potentially relevant reports identified, 2 studies were included in the pCODR systematic review[4,5] and 36 studies were excluded. Reasons for exclusion are provided in the diagram below.

QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to Study 19 will also be obtained through requests to the Submitter by pCODR[6]

6.3.2 Summary of Included Studies[4,7]

One clinical trial was identified that met the eligibility criteria of this review and was selected for inclusion (Please see Table 4). Study 19 was a randomized phase II study conducted in patients with platinum-sensitive relapsed (PSR) high-grade serous ovarian cancer, regardless of BRCA-mutation status.

Further information was also available from EPAR and FDA reports, information that comes from the trial noted above but that is not found in the primary publication.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Studies[4,5,7,44]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT00753545 Other Study ID numbers: D0810C00019 Study 19 Randomized, double-blind, phase II study Enrollment: 265 Start date: August 2008 Primary Completion date: June 2010 (final data collection date for primary outcome measures) Study Sponsor: AstraZeneca	**Key Inclusion Criteria:** • Adults (aged ≥18) • Female patients with histologically diagnosed recurrent ovarian or fallopian tube cancer or primary peritoneal cancer with high 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. BRCA1/2 mutation status testing was not required **Key Exclusion Criteria:** • Previous treatment with PARP inhibitors including AZD2281 • 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).	**Intervention:** Olaparib (capsule formation) orally at 400 mg bd continually throughout a 28 day cycle (Eight 50 mg olaparib capsules) **Comparator:** Matching placebo capsules	**Primary:** PFS **Secondary:** OS 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 **Exploratory:** 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 PSR ovarian cancer[7,44]

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
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= Interactive voice response system											

Two co-primary analysis were planned based on an ITT analysis for PFS and a second based on the BRCA-m status.

- For the ITT analysis, assuming that the true hazard ratio for progression or death with olaparib versus placebo was 0.75 (corresponding to a 33% increase in the median duration of progression- free survival, from 9 to 12 months after randomization) and that the overall type 1 error was 20% (one-sided test), the analysis would have 80% power to show a significant difference in favor of olaparib. Notably, in the accompanying NEJM supplemental appendix and files provided through feedback from the submitter citing the clinical study report, the authors indicate there was approximately 80% power to demonstrate a promising difference in favor of olaparib (*P*<0.2, 1-sided) and statistical significance is not referred to using this sample size calculation.
- For the BRCA mutation positive analysis, if the true HR was equal to 0.62 (corresponding to a 61% increase in the median PFS from 9–14 months) and the overall type I error rate was 20% (1-sided), there was approximately 80% power to demonstrate a promising difference in favor of olaparib (P<0.2, 1-sided) in the HRD group, when 50 events were expected to occur. An observed HR ≤0.79 was required to achieve this level of significance.

Multiplicity testing was performed for OS in the ITT analysis only. See table 8 for details and corresponding p-values observed in the trial at multiple analysis. Multiplicity testing was not conducted for any other outcome in either analysis set (ITT of BRCA-m subgroup)

a) Trials[4,7]

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.

Investigation sites for Study 19 were globally distributed across 16 countries including Australia, Belgium, Czech Republic, Estonia, France, Germany, Israel, Canada, Netherlands, Poland, Romania, Russia, Spain, Ukraine, UK, and the USA.

Platinum sensitivity was defined as disease progression greater than 6 months after completion of a patient's penultimate platinum regimen prior to enrolling into this study. In addition, the last chemotherapy course must have consisted of a minimum of 4 treatment cycles. It was noted across both treatment arms of olaparib and placebo that the majority of patients received 6 or more cycles of platinum immediately prior to randomization.

Patients with stable disease (SD) following platinum-based chemotherapy were not included in Study 19.

Crossover to olaparib from the placebo treatment arm was not permitted within the study design. However, patients were able to access other PARP inhibitors outside of the study and PARP inhibitor use was documented. One publication[3] was identified where additional analysis was performed that excluded all patients from sites where at least one patient received post-progression treatment with a PARP inhibitor. However, due to inherent limitations associated with this post-hoc analysis, the Clinical Guidance Panel did not explore this further.

b) Populations[4,6,7]

Patients in Study 19 were stratified according to the interval between disease progression and the completion of their penultimate platinum-based regimen (6 to 12 months versus greater than 12 months), objective response to their most recent regimen (complete versus partial response) and their ancestry (Jewish versus non-Jewish).

BRCA 1 and BRCA 2 mutation status was not a requirement for enrollment and was not known a study entry for all patients. However, BRCA-m status was determined in the blinded post-study period for the majority of patients, which was part of the a priori planned analysis. Hence, BRCA-m status was known for approximately 95% of women.[45]

Somatic BRCA-m was determined using the FoundationOne in Study 19. Based on a minimum sample requirement of ≥40µm tissue with minimum 20% tumour cell content, the FoundationOne assay has a >99% sensitivity and specificity for base substitutions. The latest version of the test simultaneously sequences all coding exons of 315 cancer-related genes (including BRCA1 and BRCA2) to a typical medium depth of coverage of greater than 500X. The assay detects all classes of genomic alterations, including base substitutions, insertions and deletions (indels), copy number alterations (CNAs) and rearrangements using routine formalin fixed paraffin embedded (FFPE) tissue samples.[6]

In order to positively assign a variant call to a sample, the detected variant must be present in >5% of sequences analyzed, i.e. there must be a 5% allelic frequency for the variant sequence. Provided this cut-off is met the sample is reported as positive for the variant identified.

The BRCA-m positive population was a pre-planned subgroup analysis and a pre-specified exploratory analysis of all efficacy endpoints, including PFS, TFST, TSST, OS and QoL, was completed according to BRCA status.[5] In addition, predictive and prognostic factors for PFS were explored with the use of preplanned subgroup analyses, including status with respect to BRCA 1/2 germline mutation, age, Jewish or non-Jewish ancestry, response status at baseline, and time to progression from the start of the penultimate platinum-based regimen.

Baseline characteristics of enrolled patients 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.

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. Please see Table 6 below for further details.

Table 6. Select Baseline Characteristics in Study 19[7]

	ITT Population		BRCA-m	
	Olaparib, n=136	Placebo, n=129	Olaparib, n=74	Placebo, n=62
Median age (range)	58 (21-89)	59 (33-84)	57.5 (38-89)	55 (33-84)
Ancestry, n (%)				
Non-Jewish	116 (85.3%)	112 (86.8%)	60 (81%)	48 (77%)
Jewish	20 (14.7%)	17 (13.2%)	14 (19%)	14 (23%)
ECOG PS				
0	110 (80.9%)	95 (73.6%)	62 (84%)	45 (73%)
1	23 (16.9%)	30 (23.3%)	11 (15%)	15 (24%)
Time to progression with penultimate platinum-based regimen, n (%)				
>6–12 months	53 (39.0%)	54 (41.9%)	28 (38%)	26 (42%)
>12 months	83 (61.0%)	75 (58.1%)	46 (62%)	36 (58%)
Objective response to most recent platinum-based regimen, n (%)				
Complete	57 (41.9%)	63 (48.8%)	36 (49%)	34 (55%)
Partial	79 (58.1%)	66 (51.2%)	38 (51%)	28 (45%)
BRCA-germline-mutation status, n (%)				
BRCA 1 or BRCA 2 mutation	31 (22.8%)	28 (21.7%)	100%	100%
Negative	18 (13.2%)	20 (15.5%)	N/A	N/A
Unknown	87 (64.0%)	81 (62.8%)	N/A	N/A

Notes: ECOG PS: Eastern Cooperative Oncology Group Performance Status; **BRCA1 or 2**: breast cancer gene 1 or 2; **ITT**: intention to treat

c) Interventions[4]

Patients in Study 19 were randomly assigned using an interactive voice response system (IVRS) in a 1:1 ratio 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. Treatment was blinded with the use of unique identifiers generated during randomization. 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.[4]

d) Patient Disposition

A total of 326 patients were enrolled into Study 19, all of whom provided informed consent. Of those who enrolled, 61 patients were not randomized as they failed the screening criteria. A total of 136 patients were randomized into the olaparib treatment

arm at 400 mg bd and 129 patients were randomized into the placebo arm. One of the patients randomized to the placebo arm voluntarily withdrew consent and completely withdrew from the study without receiving treatment, leaving a total of 128 patients randomized to the placebo arm.

Olaparib treatment arm

Of the total 136 patients randomized, 23 patients had ongoing treatment and 113 patients discontinued treatment due to AEs (n=6), worsening of condition (n=87), severe protocol non-compliance (n=2), lost to follow-up (n=1), subject withdrawal (n=11), and other reasons not specified (n=6). A total of 77 patients discontinued from the study due to death, 5 were lost to follow-up and 8 due to subject decision. At the 26 November 2012 data cut-off, 46 patients were ongoing in the study.

Placebo arm

A total of 128 patients were treated in the placebo arm, 3 had ongoing treatment and 125 discontinued treatment due to AEs (n=2), worsening of condition (n=110), severe protocol non-compliance (n=1), lost to follow-up (n=0), subject withdrawal (n=8), and other reasons not specified (n=4). A total of 87 patients discontinued from the study due to death (n=77), lost to follow-up (n=5) and subject decision (n=5). At the 26 November 2012 data cut-off, 41 patients were ongoing in the study.

Table 7. Summary of patients disposition for patients with BRCA-m[7]

	Number (%) of patients		
	Olaparib (n=74)	**Placebo (n=62)**	**Total (n=136)**
Patients randomized	74 (100.0)	62 (100.0)	136 (100.0)
Patients who received treatment	74 (100.0)	62 (100.0)	136 (100.0)
Patients ongoing study treatment at data cut-off †	15 (20.3)	3 (4.8)	18 (13.2)
Patients who discontinued initial study treatment †	59 (79.7)	59 (95.2)	118 (86.8)
Adverse event	5 (6.8)	0	5 (3.7)
Condition under investigation worsened	42 (56.8)	52 (83.9)	94 (69.1)
Severe non-compliance to CSP	0	1 (1.6)	1 (0.7)
Voluntary discontinuation by patient	9 (12.2)	4 (6.5)	13 (9.6)
Other	3 (4.1)	2 (3.2)	5 (3.7)
Patients ongoing in study	30 (40.5)	22 (35.5)	52 (38.2)
Patients who terminated study	44 (59.5)	40 (64.5)	84 (61.8)
Death	37 (50.0)	34 (54.8)	71 (52.2)
Patient lost to follow-up	1 (1.4)	4 (6.5)	5 (3.7)
Voluntary discontinuation of patient	6 (8.1)	2 (3.2)	8 (5.9)

Notes: † Percentages are calculated from the number of patients who received treatment
One patient withdrew from the study prior to database lick, but at the time, the necessary CRF pages were unavailable, therefore this patient incorrectly appears as ongoing.
CSP= Clinical Study Protocol
Data cut-off: 26 November 2012

Limitations/Sources of Bias

Sample Size of the Study[7,46]

- 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 (eg. OS) in the ITT analysis nor the exploratory endpoints in the subgroup analysis of patients with the BRCA-m (eg. PFS, OS) were powered to detect a statistically significant difference. Therefore all interpretation of testing for significance within these analysis should be done with caution.

  Following the posting of the initial recommendation, feedback was received from the submitter further clarifying the statistical design of Study 19.

  - The submitter acknowledged that Study 19 was designed to assess whether there was sufficient promise to warrant a phase III study. The Methods Team noted that the design of the study, which had a type 1 error rate of 20% (one-sided),[4,7] is reasonable in such a scenario where the objective is hypothesis generating. Therefore it is not uncommon to have a high type 1 error rate in trials where the intent of the study is to determine whether or not there is a promising outcome which requires verification in a confirmatory phase III RCT.
  - The pCODR Methods team acknowledges that the study protocol specifies that statistical significance for PFS was concluded based on a p-value of <0.025 (2.5%), 1-sided in the overall population. The results of the trial met and exceeded this criteria (with a HR of 0.35 for PFS in the ITT population 95% CI: 0.25 to 0.49, p<0.00001), which indicate that the treatment effect measured in this sample was large. This does not however negate the limitation of the study design. By using a type 1 error rate of 20%, a smaller sample size was required for the study, while also allowing for a greater chance of detecting a false positive result. The investigators were willing to accept the increased risk of a false positive result (i.e., higher Type I error) as the objective of this randomized phase II trial was to determine whether olaparib had sufficient promise to conduct a confirmatory phase III randomized controlled trial. This increased risk of a false positive result needs to be considered with the results demonstrated in the trial, both for the overall trial population and the BRCA-mutated subgroup. It is possible that the HR and statistical significance observed in this small cohort of patients may represent a sample of outliers in the population and not represent the treatment effect expected in the full population. Additional to this, it is possible that the observed treatment effect may be a false positive result or that the true treatment effect may be smaller than what was reported in this study. Therefore, a more stringent trial design (e.g., typically using an alpha level of 0.05 or a type 1 error rate of 5%) is required to confirm the results as is being done in the confirmatory phase 3 RCT, SOLO 2.
  - Overall, the statistical significance reached for PFS within this cohort of patients indicates that there is likely a true treatment effect with the use of olaparib in terms of PFS. However, the current data are not sufficient to comment on the magnitude of effect. The results for OS are not as promising as the p-value in the overall population (0.0248) was not as impressive and therefore it is unclear whether any OS benefit is to be expected in the confirmatory phase 3 trial. Therefore, the Methods Team concluded that, due to the limitations described above, the results of Study 19 need to be interpreted with caution.

- The BRCA-m population subgroup was identified retrospectively based on convenience samples. Therefore, randomization that was executed in the ITT population may not hold for this subgroup of patients.
    - A Cox proportional hazards model was however used to adjust the PFS and OS data for baseline covariates that were considered to be important prognostic factors. These included ethnic descent (Jewish *vs* non-Jewish), time to progression on penultimate platinum therapy (6–12 months *vs* >12 months), and response to platinum therapy before randomisation (complete response *vs* partial response).
- No adjustments were made for multiplicity introduced by analysing multiple secondary endpoints (excluding OS) or analyses within the BRCA subgroups. Therefore, p-values in these analyses are uninterpretable. Multiple testing can also increase the false positive rate inadvertently leading to a possibility of an increase in the probability of making a Type 1 error.
- The sample size in the BRCA-m subgroup is small. Consequently, the estimate of magnitude of treatment effect is likely to be unstable

Patient Characteristics

- 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.
- A low number of patients were enrolled in the trial (ITT: 136 and 129; BRCA-m positive: 74 and 62 in the olaparib and placebo arms, respectively). Therefore, differences of greater than 5% across treatment arms may have an impact on the results. Notably, 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. There were more patients having an ECOG performance status of 1 in the olaparib arm and more patients having an ECOG PS of 2 in the placebo arm. If patients with a lower ECOG PS have better outcomes (i.e. if ECOG PS is a prognostic factor and/or predictive factor), then this imbalance has the potential to bias results in favour of the olaparib treatment arm.
- There was also a greater than 5% difference observed in the proportion of patients who had a CR or PR to their most recent platinum-based regimen. In the ITT population, there were more patients in the placebo arm who had a complete response while more patients in the olaparib arm had a partial response to their last platinum-based regimen. In addition, for the BRCA-m positive subgroup, there were more patients in the olaparib arm who had a partial response while more patients in the placebo arm had a complete response to their last platinum-based regimen. This can also bias results in favour of the placebo arm.

Protocol Deviations[7,44]

- There was a total of 52.8% patients (57.4% in the olaparib arm and 48.1% in the placebo arm) who were defined as having "important" deviations in the study that could have potentially influenced the efficacy assessment

- These deviations included 79 patients (29.8%) who were mis-stratified in the interactive voice response system (IVRS) by study sites, with a larger proportion of patients in the olaparib group compared to the placebo group (35.3% olaparib versus 24.0% placebo)Following a request to clarify these protocol deviations, the submitter indicated through the Checkpoint meeting that as the primary statistical analysis of the treatment effect is adjusted for the covariate factors based on source-data-verified CRF data, the larger proportion of patients in the olaparib group compared with the placebo group being mis-stratified is not considered to unduly affect the efficacy results.
- Other than IVRS mis-stratifications, 34% of all randomized patients had other 'important' deviations (33.8% olaparib vs 34.1% placebo). The submitter noted that a minority were considered to have the potential to impact the overall efficacy conclusions.
    - A small proportion of patients had the RECIST baseline scan >28 days before first dose (3.7% olaparib vs 6.2% placebo). However, in the majority of cases (11/13) the scan was performed within 4 days of the permitted window, and this is considered unlikely to influence interpretation of the results.
    - A sensitivity analysis (HR 0.39) indicated that the PFS outcome is likely not biased by differential scan times between groups despite a larger proportion of patients in the olaparib group with RECIST scans performed outside the protocol scheduled window on ≥2 occasions compared with the placebo group (16.2 % olaparib vs 10.1% placebo).
    - A greater proportion of placebo patients had disease progression determined by the investigator by methods not considered acceptable by RECIST criteria (2.9% olaparib vs 7.0% placebo) and thus these patients were censored at their previous evaluable RECIST assessment. Any potential bias resulting from this would favour the placebo group as, had protocolled methods been used, this is likely to have led to a differential number of additional events in the placebo group. Despite this potential bias, the PFS results based on blinded independent central review showed consistent results with the investigator-assessed results.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Primary Outcome

Progression-free survival (PFS)[7]

Progression free survival in Study 19 was defined as the time from randomization (on completion of chemotherapy) until an objective assessment of disease progression according to RECIST guidelines or death (from any cause in the absence of progression of disease). Progression-free survival was assessed with the use of computed tomographic scans obtained every 12 weeks and was calculated on the basis of measurements of target and non-target lesions and assessment for new lesions that were recorded by the investigators.

A blinded independent central review of tumor scans was performed retrospectively. Two co-primary analyses were planned based on an ITT analysis for PFS and a second based on the BRCA-m status. For the ITT analysis, assuming that the true hazard ratio for progression or death with olaparib versus placebo was 0.75 (corresponding to a 33% increase in the median duration of progression- free survival, from 9 to 12 months after randomization) and that the overall type 1 error was 20% (one-sided test), the analysis would have 80% power to show a significant difference in favor of olaparib (one-sided $p < 0.20$). Although the *BRCA-m* status was a pre-specified

exploratory subgroup, the study was not powered by this subgroup of patients nor any other analysis in the ITT set or the subgroup of patients with BRCA-m status.[6]

PFS - BRCA-m Subgroup Analysis

In patients with BRCA-mutated tumours, a 6.9 months prolongation of median PFS (11.2 compared to 4.3 months for olaparib compared to placebo, respectively) was reported with a hazard ratio of 0.18 (95% CI: 0.1 to 0.31; p=0.0001).

Following the receipt of feedback on the Initial recommendations, the submitter discussed that a long duration of PFS was observed in a proportion of patients receiving olaparib maintenance therapy. These data were reported in the most recent data cut-off from September 2015 (third analysis).[6] The Methods team acknowledges that event driven outcomes can demonstrate a group of long-term survivors as well as a group of patients that perform poorly on the treatment and have short survival, while the median PFS is considered to be the best representation of the outcome expected in patients. Although the long term PFS distribution for patients in the placebo group was not provided, the submitter reported that after a median follow-up of 5.9 years, 11% and 1% of patients in the olaparib and placebo groups, respectively were still receiving treatment.

Long Term Treatment Exposure after a median follow up of 5.9 years [5]						
	≥1 years	≥2 years	≥3 years	≥4 years	≥5 years	≥6 years
ITT	40%	24%	18%	15%	13%	5%
BRCA-m	46%	28%	22%	16%	15%	5%

PFS - ITT Analysis:
In the overall analysis, Study 19 met its primary objective with a demonstrated statistically significant improvement in PFS for olaparib maintenance monotherapy at 400 mg bd compared to placebo in the overall population. The hazard ratio was 0.35 with a 95% CI: 0.25 to 0.49 and p<0.00001. The PFS gain of 3.6 months (median of 4.8 and 8.4 months) was observed in the overall population.

Secondary Outcomes

Overall Survival (OS) - BRCA-m Subgroup Analysis[4-7]

At 52% maturity of data (71 deaths out of 136 patients), there was no statistically significant difference in OS demonstrated between patients treated with olaparib and patients treated with placebo, 34.9 months versus 31.9 months, respectively. The hazard ratio was 0.73 (95% CI: 0.45 to 1.17; p=0.19).

In the most recent OS analysis at 70% maturity of data in the BRCA-mutation population, the OS demonstrated between patients treated with olaparib and patients treated with placebo was 34.9 months versus 30.2 months, respectively. This was a median improvement in OS that was 4.7 months longer for olaparib versus placebo, corresponding to a hazard ratio of 0.62 (95% CI: 0.41 to 0.94, nominal p=0.02480).

In the BRCA-m subgroup, 23% of patients in the placebo arm received a subsequent PARP inhibitor compared to no patients in the olaparib group. This imbalance might have led to confounding of the overall survival results (Ref- Ledermann et al Lancet Oncol 2014). One publication (Ref- Matulonis et al 2016) presented results in the BRCA-M subgroup of patients excluding all sites

where at least one patient received post-progression treatment with a PARP inhibitor. Given the small sample size of the main trial and the use pre-planned exploratory endpoints to determine efficacy in the BRCA-m subgroup, the CGP agreed that any additional analysis further removing patients from the cohort would be considerably uncertain. Therefore this analysis was not considered further in this review.

Overall Survival - ITT Analysis:
Overall Survival was defined as the time from randomization to the date of death. An interim analysis of overall survival was performed after 101 deaths had been recorded. Statistical significance for OS, in favor of olaparib, was declared in the overall population if, at the first OS analysis, P<0.0125 (1-sided). The corresponding level of significance at the second OS analysis was calculated at the time of analysis. The overall type I error rate for OS was controlled at the 2.5% level (1-sided). Multiplicity adjustment for overall survival in the full analysis set was pre-specified in the clinical study protocol. The testing strategy states that statistical significance, for overall survival, in favour of olaparib, will be declared in the overall study population if the observed p-value is <0.001 (2-sided) at the firs interim analysis, <0.03 (2-sided) at the second analysis with each subsequent analysis testing at half of the remaining alpha, unless it is the final analysis where all the remaining alpha will be spent. This allows the overall alpha to be controlled at 5% (2-sided).[6]

The most recent data cut-off from September 2015 is the third analysis and the 2-sided p-values required are listed in the table below.[6]

Table 8. OS analysis and observed p-value

OS Analysis	Maturity in Full Analysis Set (FAS)	Alpha after the analysis	Test Value	Observed p-value full analysis set
June 2010	7%	0.05	N/A	No analysis
October 2011	38%	0.049	<0.001	0.75
November 2012	58%	0.019	<0.03	0.44
September 2015	77%	0.0095	<0.0095	0.02483
Final (2016)	~80%	0	<0.0095	

Although the 2015 p-value meets nominal significance, the full analysis set p-value is insufficient to claim statistical significance. Without statistical significance in the full analysis set, the result in the BRCAm group cannot be considered statistically significant.

As part of the September 2015 updated OS analysis, a restricted mean analysis was done for the OS results.[6] This methodology is used in instances where the proportion hazard assumption may not hold (or is violated). The proportional hazards assumption dictates that the survival curves for two groups must have hazard functions that are proportional over time or have constant relative hazard. Restricted mean analysis can be used as an alternative where the proportional hazards assumption is violated.[48] It is employed by measuring the average survival from time 0 to a specified time point and estimated using the area under the curve up to that point. Although details were not provided on the rationale for why a restricted mean analysis was performed, the submitter noted in the ASCO presentation that statistical tests did not provide sufficient evidence to dismiss the proportional hazards assumption for OS. A restricted mean analysis was performed to compare mean survival (Ref-ASCO presentation for OS update). It is in the opinion of the Methods team that the alternative analysis may have been performed as an exploratory analysis and not because the proportion hazard assumption was violated. Using this approach OS was 44.3 months vs 36.9 months in the olaparib and placebo groups among patients with the BRCAm status, respectively translating into a 7.4 month difference. In the ITT population, OS was 40.1 months vs 34.9 months in the olaparib and placebo groups, respectively.[6]

Table 9. Study Design and select efficacy outcomes in Study 19[4-7]

	Study 19[4]		Study 19[5]	
	ITT Population		BRCA-m	
	Olaparib	Placebo	Olaparib	Placebo
Randomized	136	129	74	62
Efficacy analysis set	136	129	74	62
Safety analysis set	136	128	74	62
Primary Outcome				
Median PFS, months Primary Analysis (June 2010)	8.4	4.8	11.2	4.3
HR	0.35 (95% CI 0.25-0.49) p<0.001)		0.18 (95% CI 0.1-0.31) p<0.0001	
Number of PFS event at analysis	154/265 (58%)		72/136 (53%)	
	60 (44.1%)	94 (72.9%)	26 (35%)	46 (74%)
Select Secondary Outcomes				
Median OS, months Interim Analysis (November 2012)	29.8	27.8	34.9	31.9
HR	0.88 (95% CI 0.64-1.21) p=0.44		0.73 (95% CI 0.45-1.17) p=0.19	
Number of OS events at analysis	154/265 (58%)		71/136 (52%)	
	77 (57%)	77 (60%)	37 (50%)	34 (55%)
Updated Median OS, months (September 2015)	29.8	27.8	34.9	30.2
HR	0.73 (95% CI 0.55-0.96) p=0.02483* nominal p-value		0.62 (95% CI 0.41-0.94) p=0.02480* nominal p-value	
Number of OS events at analysis	203		95	
	94 (69.1%)	109 (84.5%)	47 (63.5%)	48 (77.4%)
ORR	12%	4%	16%	5%
Odds ratio	3.36% (95% CI 0.75-23.72) p=0.12		Not available*	
Updated ORR (Sept 2015)	12%	4%	16%	5%
Odds ratio	3.36 (95%CI 0.75-23.72) p=0.12		Not available‡	

Notes:
Primary Data Analysis: June 30, 2010
First Interim Analysis: October 31, 2011
Second Interim Analysis: November 26, 2012
Updated Analysis: September 30, 2015
‡Statistical analysis not possible due to too few events
NR: not reported; **OS**: overall survival; **PFS**: progression free survival; **ORR:** objective response rate; **HR:** hazard ratio; **BRCA:** breast cancer gene; **ITT:** intention to treat; BRCA-m: breast cancer 1 gene mutation (germline and somatic)

Figure 1. Kaplan-Meier survival curves for PFS in patients with gBRCA-m in Study 19[44]

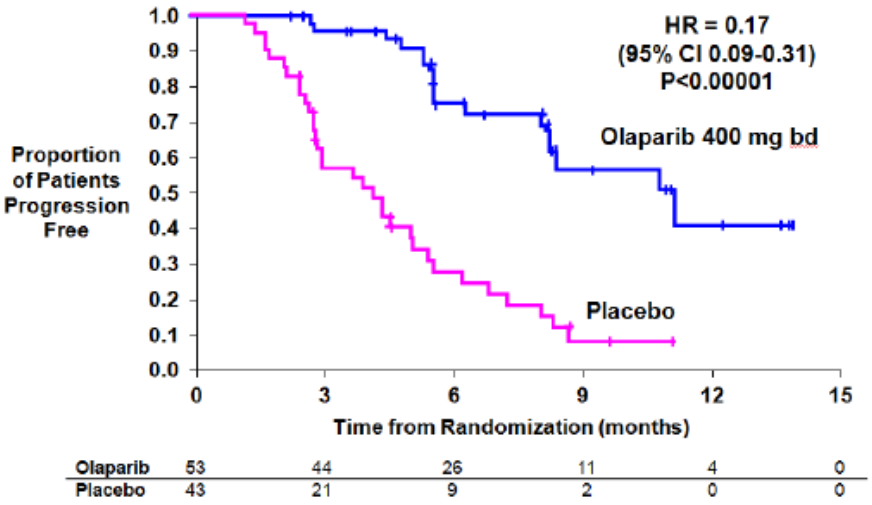
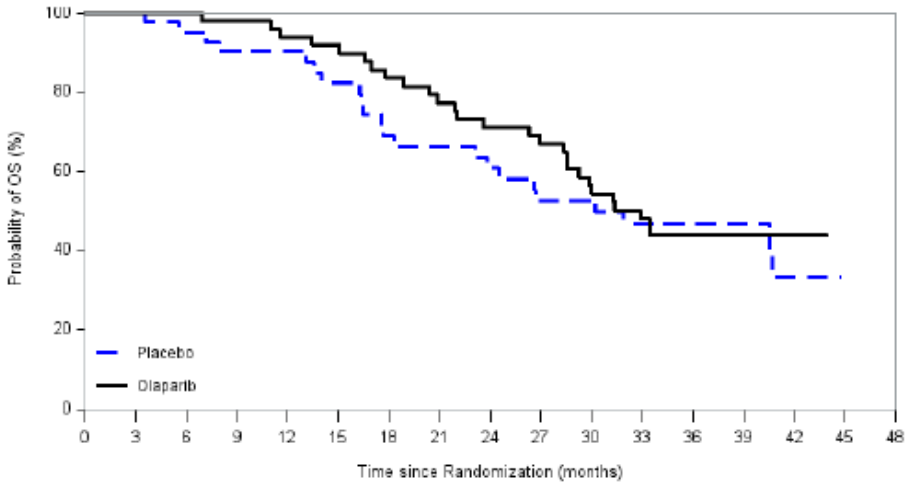


Figure 2: Kaplan-Meier survival curves for Overall Survival in patients with BRCA-m based on a November 2012 analysis*.[44]



* Updated OS data were reported as reported in Table 9 with 70% maturity (September 2015).

Time to first subsequent therapy (TFST)[5,7]

In study 19, TFST was defined as the time from randomization to the start date of the first cancer therapy received following discontinuation of olaparib/placebo or death.

In the overall population, the median TFST was demonstrated to be significantly longer in the olaparib group than in the placebo group. The TFST was also longer in both the mutated BRCA and the wild-type BRCA subgroups.[2] Please see table 8 below for further details.

Table 10. Analysis of time to first subsequent therapy or death in the overall population and BRCA-m subgroups[5]				
Time to first subsequent therapy or death (TFST)	Events/total Patients	Median time, months (range)	Hazard Ratio	95% CI & p-value
ALL PATIENTS (n=264)	Olaparib: 95/136 (70%)	13.4 (11.3-15.7)	0.40	0.30 to 0.52 p<0.0001
	Placebo: 118/128 (92%)	6.7 (5.7-8.2)		
Patients with BRCA-m (n=136)	Olaparib: 46/74 (62%)	15.6 (12.3-28.2)	0.33	0.22 to 0.50 p<0.0001
	Placebo: 54/62 (87%)	6.2 (5.3-9.2)		
*Patients with wild-type BRCA** (n=118)	Olaparib: 45/57 (79%)	12.9 (7.8-15.3)	0.45	0.30 to 0.67 p<0.0001
	Placebo: 59/61 (97%)	6.9 (5.7-9.3)		
Notes: *Wild type BRCA includes patients with no known BRCA-m and those with a BRCA-m of unknown significance.				

Adverse Events and Safety:

In the BRCAm subgroup, all grade AE's between the olaparib and placebo groups, were 97% and 94%, respectively. However, grade ≥3 AEs were 38% compared to 18% in the olaparib and placebo BRCAm subgroup, respectively. Please see table 9 in section 6 of the systematic review for further details.

Results for dose interruptions and reductions were available for the overall ITT population. A greater proportion of patients in the olaparib arm experienced dose interruptions (36% vs. 21%) and dose reductions (42% vs. 22%). It is notable however that the median actual treatment was longer in the olaparib compared to placebo groups for both the ITT population (258.5days and 135.5 days, respectively) and BRCAm population (328.5days and 138.5days, respectively).[7] The most common cause for dose interruption or reductions was vomiting, nausea and fatigue. Generally, the tolerability profile was similar between the ITT and BRCA-m positive populations.

Generally, the tolerability profile was similar between the ITT and BRCA-m positive populations. Serious adverse events were reported in 25/136 (18%) vs. 11/128 (9%) of patients in the olaparib and placebo groups, respectively. The most common SAE was intestinal obstruction occurring in 2 (1%) and 3 (2%) of patients in the olaparib and placebo groups, respectively. Grade 3 or higher AE's were higher in the olaparib vs. placebo groups at 40% and 22% respectively. Occurrence of all grades AE's were similar between the olaparib and placebo groups, 97% and 93%, respectively.

Myelodysplastic Syndrome (MDS)[6]

As of July 31, 2013, 2 cases of myelodysplastic syndrome (MDS) have been reported. One in the olaparib arm among patients without a BRCA mutation and one in the subgroup of patients with the BRCA-m status randomised to the placebo group. Since that data cut-off, one case of AML has been reported in the olaparib BRCA-*m* group.

Treatment-related deaths

As of the January 31 2014 safety cut-off date, one patient in the olaparib treatment arm (in the subgroup of patients with BRCA-m) was reported to have died as a result of treatment. This patient died due to thrombocytopenia and a haemorrhagic stroke, which the investigator considered related to study treatment. A second death was also reported in the olaparib treatment arm among patients without a BRCA-m status, which was considered to be related to ovarian cancer, with a secondary cause of death being Myelodysplastic syndrome (MDS) which was diagnosed after the 30-day follow-up period.[6]

In the overall ITT population, there were 7/136 and patients and 6/128 deaths classified as 'other' reported in the olaparib and placebo groups, respectively. Among these 4/74 and 4/62 deaths in the olaparib and placebo groups, respectively were in the subgroup of patients with the BRCA-m status. These 'other' deaths were reported outside of the 30-day follow-up period; many months after olaparib treatment had been discontinued and after patients had received subsequent anti-cancer therapy. In the Olaparib group, the 'other' causes of death were due to unknown causes (n=3), euthanasia, septic shock, cerebrovascular disorder and cerebral haemorrhage. In the placebo group, the 'other' causes of death were due to acute renal failure, pulmonary embolism, unknown causes (n=2), cardiopulmonary failure and septic shock. Please see table 12 for further details.[6]

Table 11. All grades adverse events occurring in ≥10% of patients overall and grade ≥3 events occurring in ≥3% of patients in either treatment group for Study 19[5]

	Overall Patient Population				Patients with BRCA-m			
	All grades		Grade ≥3		All grades		Grade ≥3	
	Olaparib (n=136)	Placebo (n=128)	Olaparib (n=136)	Placebo (n=128)	Olaparib (n=74)	Placebo (n=62)	Olaparib (n=74)	Placebo (n=62)
Patients with any AE	132 (97%)	119 (93%)	55 (40%)	28 (22%)	72 (97%)	58 (94%)	28 (38%)	11 (18%)
Nausea	96 (71%)	46 (36%)	3 (2%)	0	54 (73%)	20 (32%)	1 (1%)	0
Fatigue	71 (52%)	50 (39%)	10 (7%)*	4 (3%)	40 (54%)	23 (37%)	5 (7%)	1 (2%)
Vomiting	46 (34%)	18 (14%)	3 (2%)	1 (<1%)	27 (36%)	5 (8%)	2 (3%)	0
Diarrhea	37 (27%)	31 (24%)	3 (2%)	3 (2%)	22 (30%)	12 (19%)	2 (3%)	1 (2%)
Abdominal Pain	34 (25%)	34 (27%)	3 (2%)	4 (3%)*	17 (23%)	18 (29%)	0	2 (3%)
Anemia	29 (21%)	7 (5%)	7 (5%)*	1 (<1%)	19 (26%)	3 (5%)	4 (5%)	1 (2%)
Headache	28 (21%)	16 (13%)	0	1 (<1%)	13 (18%)	10 (16%)	0	1 (2%)
Constipation	28 (21%)	14 (11%)	0	0	14 (19%)	7 (11%)	0	0
Decreased Appetite	28 (21%)	17 (13%)	0	0	14 (19%)	6 (10%)	0	0

	Overall Patient Population				Patients with BRCA-m			
	All grades		Grade ≥3		All grades		Grade ≥3	
	Olaparib (n=136)	Placebo (n=128)	Olaparib (n=136)	Placebo (n=128)	Olaparib (n=74)	Placebo (n=62)	Olaparib (n=74)	Placebo (n=62)
Dyspepsia	24 (18%)	11 (9%)	0	0	13 (18%)	4 (6%)	0	0
Cough	24 (18%)	13 (10%)	0	0	11 (15%)	7 (11%)	0	0
Upper Abdominal Pain	24 (18%)	10 (8%)	0	1 (<1%)	14 (19%)	4 (6%)	0	0
Arthralgia	23 (17%)	18 (14%)	1 (<1%)	0	11 (15%)	10 (16%)	1 (1%)	0
Back Pain	22 (16%)	14 (11%)	3 (2%)	0	14 (19%)	9 (15%)	2 (3%)	0
Dysgeusia	22 (16%)	8 (6%)	0	0	14 (19%)	4 (6%)	0	0
Nasopharyngitis	20 (15%)	14 (11%)	0	0	10 (14%)	4 (6%)	0	0
Asthenia	19 (14%)	12 (9%)	1 (<1%)	0	12 (16%)	8 (13%)	1 (1%)	0
Dizziness	18 (13%)	9 (7%)	0	0	11 (15%)	3 (5%)	0	0
Abdominal distension	17 (13%)	11 (9%)	0	0	9 (12%)	6 (10%)	0	0
Neutropenia	7 (5%)	5 (4%)	5 (4%)	1 (<1%)	5 (7%)	3 (5%)	3 (4%)*	1 (2%)

Notes: AE = adverse event
*Includes one patient with grade 4 AE.

Table 12. Number (%) of patients who died in Study 19 (Safety Analysis Set)[6]

Category	All patients		*BRCAm*	
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=74	Placebo N=62
Total number of deaths	86 (63.2)	93 (72.7)	42 (56.8)	41 (66.1)
Death related to disease under investigation only	77 (56.6)	87 (68.0)	37 (50.0)	37 (59.7)
AE with outcome = death only	1 (0.7)	0	1 (1.4)	0
Death related to disease and an AE with outcome = death	1 (0.7)	0	0	0
Other deaths[a]	7 (5.1)	6 (4.7)	4 (5.4)	4 (6.5)

Notes: **AE=** Adverse event; **bd=**Twice daily; **BRCAm=**Breast cancer susceptibility gene-mutated; **DCO=** Data cut-off; **N =**Total number of patients.
[a]Patients who died and are not captured in the earlier categories.
Numbers above include events that occurred during treatment, in the 30-day follow-up period, or post follow-up.

Patient Reported Outcomes[6,42]

Symptoms and Health-related quality of life was assessed in Study 19 at regular intervals using three validated instruments: FOSI, Total Functional Assessment of Cancer Therapy – Ovarian (FACT-O) and Trial Outcome Index (TOI). The TOI is derived from the physical and functional wellbeing and ovarian cancer subscales of the FACT-O questionnaire (Ref- Ledermann et al, Study

19 HRQoL poster) and measures the impact of treatment side effects and feeling ill. The TOI captures a patient's ability to lead a normal fulfilling life. The TOI subscales, FOSI and total FACT-O analyses compared the proportion of patients with best responses of 'improved', 'no change', and 'worsened' between the two treatment arms.

The Compliance rates in both treatment groups at baseline were high at approximately 85%. Across all time points studied for TOI, FOSI and FACT-O, compliance was approximately 80% in each treatment group. Notably, the compliance rates fell after 6 months in the placebo group.

Although there was a numerically higher proportion of patients who reported improvements in TOI, FOSI, and total FACT-O following treatment with olaparib versus placebo, there was no statistically significant differences observed in the overall population.

Improvement rates and worsening rates were calculated using pre-determined values for a minimum important difference (MID) relevant to each endpoint [MID's were defined as a change from baseline of 9 (FACT-O), 7 (TOI) or 3 (FOSI)]. Time to worsening was determined from the date of randomization until the date when the MID worsening criteria had been reached without a response of 'improved' or 'no change' within 21 days.

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. Although not reported, the Leddermann et al 2014 noted that time to worsening of PRO's and HRQoL was the same between treatment groups.

Please see Table 13 below.

Nausea, vomiting and Fatigue

Based on the FACT-O scale, patients treated with Olaparib experienced more nausea during the first few months of treatment compared to the placebo arm. However, over time the differences between the treatment groups were observed to be minimal.

Table 13. HRQoL best response in Study 19 for the overall population and by BRCA status[4,6,42]

	Overall Population		BRCAm		BRCAwt	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
TOI, n (%)	n=115	n=111	n=64	n=53	n=49	n=54
Improved*	23 (20.0)	20 (18.0)	16 (25.0)	10 (18.9)	7 (14.3)	10 (18.5)
No change[n]	72 (62.6)	67 (60.4)	38 (59.4)	30 (56.6)	32 (65.3)	36(66.7)
Worsened†	16 (13.9)	20 (18.0)	7 (10.9)	10 (18.9)	9 (18.4)	8 (14.8)
Non-evaluable	4 (3.5)	4 (3.6)	3 (4.7)	3 (5.7)	1 (2.0)	0
FOSI, n (%)	n=117	n=115	n=66	n=56	n=49	n=55
Improved*	20 (17.1)	17 (14.8)	14 (21.2)	9 (16.1)	6 (12.2)	8 (14.5)
No change[n]	74 (63.2)	74 (64.3)	39 (59.1)	36 (64.3)	33 (67.3)	36 (65.5)
Worsened†	20 (17.1)	21 (18.3)	11 (16.7)	9 (16.1)	9 (18.4)	11 (20.0)

	Overall Population		BRCAm		BRCAwt	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
Non-evaluable	3 (2.6)	3 (2.6)	2 (3.0)	2 (3.6)	1 (2.0)	0
FACT-O, n (%)	n=114	n=111	n=63	n=53	n=49	n=54
Improved*	24 (21.1)	21 (18.9)	17 (27.0)	11 (20.8)	7 (14.3)	10 (18.5)
No change[n]	68 (59.6)	63 (56.8)	35 (55.6)	26 (49.1)	31 (63.3)	36 (66.7)
Worsened†	20 (17.5)	24 (21.6)	10 (15.9)	14 (26.4)	10 (20.4)	8 (14.8)
Non-evaluable	2 (1.8)	3 (2.7)	1 (1.6)	2 (3.8)	1 (2.0)	0

Notes:
*Best response of improved defined as two visit responses of 'improved' a minimum of 21 days apart without an intervening visit response of 'worsened'. Improved was defined as an increase from baseline of 9 (FACT-O), 7 (TOI) or 3 (FOSI); an odds ratio >1 indicates a greater chance of improvement with olaparib.
[n]Defined as two visit responses of 'no change' or a response of 'no change' and a response of 'improved', a minimum of 21 days apart without an intervening visit response of 'worsened'. No change is defined as a change from baseline of greater than -7 (TOI), -3 (FOSI), -9 (FACT-O), but less than +7 (TOI), +3 (FOSI), +9 (FACT-O).
†Defined as a visit of 'worsened' without a response of 'improved' or 'no change' within 21 days. Worsened is defined as a change from baseline of less than or equal to -7 (TOI), -3 (FOSI), -9 (FACT-O).

6.4 Ongoing Trials

Table 14: Ongoing trials of Olaparib as maintenance treatment for 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[47]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT01874353 Other Study ID numbers: D0816C00002 SOLO 2 Phase III Randomized Double-blind, Placebo-controlled, multicentre study Estimated enrollment: 297 Estimated Primary Completion date: September 2016 (final data collection date for primary outcome measure) Estimated Completion date: April 2021 Study Sponsor: AstraZeneca Collaborators: • European Network of Gynaecological Oncology Trial Groups (ENGOT)	<u>Key Inclusion Criteria:</u> Patients must be ≥ 18 years of age. Female patients with histologically diagnosed relapsed high grade serous ovarian cancer (including primary peritoneal and / or fallopian tube cancer) or high grade endometrioid cancer. Documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Patients who have received at least 2 previous lines of platinum containing therapy prior to randomisation For the penultimate chemotherapy course prior to enrolment on the study: • Patient defined as platinum sensitive after this treatment (disease progression greater than 6 months after completion of their last dose of platinum chemotherapy) <u>Key Exclusion Criteria:</u> Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). BRCA 1 and/or BRCA2 mutations that are considered to be non- detrimental	<u>Intervention:</u> Olaparib 300 mg tablets *Note:* The capsule and tablet formation are not bioequivalent. The 300 mg bd tablets were designed to match the 400 mg bd capsule dose (in Study 19) in terms of efficacy and tolerability. The 300 mg bd tablet dose was selected as the dose/schedule for phase III based on the efficacy and safety data from Study 24 (dose ranging study in patients with advanced gBRCA mutated ovarian cancer) <u>Comparator:</u> Placebo tablets	<u>Primary:</u> PFS <u>Secondary:</u> OS Time to earliest progression Time from randomization to second progression TSST TDT Change from baseline in HRQoL Safety and Tolerability AEs

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
• Myriad Genetic Laboratories, Inc.	Patients who have had drainage of their ascites during the final 2 cycles of their last chemotherapy regimen prior to enrolment on the study.		
NCT02292020 SOLO 3 Phase III, Open-label randomized, controlled, multi-centre study Estimated Enrollment: 411 Estimated Primary Completion date: December 2017 Estimated Completion date: December 2019 Study Sponsor: AstraZeneca Collaborators: Myriad Genetic Laboratories, Inc.	<u>Key Inclusion Criteria:</u> • Patients must be ≥ 18 years of age • Patients with histologically diagnosed relapsed high grade serous ovarian cancer (including primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer • Documented germline mutation in Breast Cancer susceptibility genes: BRCA1 and/or BRCA2 that is predicted to be deleterious or suspected deleterious • At least one lesion that can be accurately assessed at baseline by CT/MRI and is suitable for repeated assessment. • Patients must have received at least 2 prior platinum based lines of chemotherapy - Patients must be partially platinum sensitive or platinum sensitive • Patients must be suitable to start treatment with single agent chemotherapy based on physician's choice • Patients must have normal organ and bone marrow function measured within 28 days of randomisation, • ECOG PS 0-2 • Patients must have a life expectancy ≥ 16 weeks • Formalin fixed, paraffin embedded tumour sample from the primary or recurrent cancer must be available for central testing <u>Key Exclusion Criteria:</u> • BRCA 1 and/or BRCA2 mutations that are considered to be non detrimental	<u>Intervention:</u> 300 mg olaparib tablets taken orally twice daily <u>Comparator:</u> Single agent chemotherapy based on physician's choice of weekly paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine.	<u>Primary:</u> PFS by blinded independent central review using RECIST data <u>Secondary:</u> OS Time to earliest progression Time from randomization to second progression Time to deterioration of HRQoL as assessed by TOI and FACT-O TFST TSST TDT Safety and tolerability

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Exposure to any investigational product within 30 days or 5 half-lives (whichever is longer) prior to randomisation • Any previous treatment with a PARP inhibitor, including olaparib. • Patients who have platinum resistant or refractory disease • Patients receiving any systemic chemotherapy within 3 weeks prior to first dose of study treatment • Previous single agent exposure to the selected chemotherapy regimen for randomisation. - Prior malignancy in the last 5 years, unless curatively treated and recurrence free (few exceptions apply)		
Abbreviations: OS= overall survival; **PFS** = progression free survival; **TSST**= time to second subsequent therapy; **TDT**= time to treatment discontinuation or death; **HRQoL**= health-related quality of life; **BRCA 1/2**= breast cancer susceptibility gene 1/2; **AEs**= adverse events			

7 SUPPLEMENTAL QUESTIONS

No supplemental question considered to be relevant to the review was identified.

8 COMPARISON WITH OTHER LITERATURE

One phase II trial, Study 41,[7] which did not meet the protocol's inclusion criteria, was identified as relevant to this review. The Clinical Guidance Panel agreed that study 41 contained relevant information to the current review and a brief summary of the study design and results was provided below.

Study 41 was a phase II, prospective, open-label randomized study evaluating the benefit of olaparib in combination with paclitaxel and carboplatin administered as induction followed by olaparib administered as maintenance versus paclitaxel and carboplatin alone, followed by no further therapy, in patients with platinum-sensitive relapsed ovarian cancer who had received no more than 3 previous platinum-containing regimens. Patients were enrolled at 43 sites in 12 countries including Australia, Belgium, Canada, Czech Republic, Germany, Italy, Japan, the Netherlands, Panama, Spain, UK and the USA.

A total of 173 patients were enrolled into the study, of which 162 were eligible and were randomly assigned to the two treatment groups. 81 patients were assigned to the olaparib plus chemotherapy group and 81 to the chemotherapy alone group. Of these randomized patients, 156 were treated in the combination phase (81 in the olaparib plus chemotherapy group and 75 in the chemotherapy alone group) and 121 patients continued to the maintenance or no further therapy (66 in the olaparib plus chemotherapy and 55 in the chemotherapy alone group).

Of the 162 randomized patients, 41 (25%) had a BRCA-m, with 59 patients identified as wildtype and 7 with a variant of unknown significance, 41% of patients were non-mutated and information was unavailable on BRCA-m status for 55(34%) patients.

The primary endpoint of Study 41 was PFS by blinded independent central review. Secondary endpoints included OS, percentage change in tumour size, ORR, CA-125 and/or RECIST response, CA-125 response rate, safety and tolerability.

[Table 15]: Select quality characteristics of Study 41[7]

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
Study 41	Arm A: Olaparib/ paclitaxel/ carboplatin + maintenance olaparib Arm B: paclitaxel/ carboplatin + No maintenance	PFS blinded independent central review	150 patients to provide 70 events (at 47% maturity) for the primary analysis. With the assumption of a HR of 0·6, with a one-sided type I error rate of 10%, the analysis would have 80% power to show a significant difference between groups	162 patients; 81 patients randomized to each group	Randomization via IVRS	Unknown	Double-blind	Yes	Yes	No	Yes

Table 16. Key efficacy outcomes for Study 41[7]								
	Full Analysis Set		**BRCA mutated**		**BRCA wild type/VUS**		**BRCA status missing**	
	O/C4/P	C6/P	O/C4/P	C6/P	O/C4/P	C6/P	O/C4/P	C6/P
PFS (Data cut-off October 10 2011) FAS								
# of events: total # of patients (%)	47:81 (58%)	55:81 (68%)	7:20 (35%)	16:21 (76%)	24:34 (71%)	24:32 (75%)	16:27 (59%)	15:28 (54%)
Median PFS (months)	12.2	9.6	Not reached	9.7	NR	NR	NR	NR
HR (95% CI) p-value	0.51 (0.34-0.77) p=0.0012		0.21 (0.08-0.55) p=0.0015		0.77 (0.41-1.44) p=0.4129		0.64 (0.27-1.52) p=0.3095	
TFST (Data cut-off November 26 2012) **-** FAS								
# of events: total # of patients (%)	59:81 (73%)	57:81 (70%)	9:20 (45%)	16:21 (76%)	28:34 (82%)	23:32 (72%)	22:27 (82%)	18:28 (64%)
Median time (months)	14.8	11.3	Not reached	11.3	NR	NR	NR	NR
HR (95% CI) p-value (2-sided)	0.63 (0.44-0.92) p=0.0160		0.13 (0.04-0.33) P<0.0001		0.85 (0.49-1.50) P=0.5725		0.83 (0.42-1.65) P=0.5909	
TSST (Data cut-off November 26 2012) - FAS								
# of events: total # of patients (%)	50:81 (62%)	44:81 (54%)	8:20 (40%)	13:21 (62%)	22:34 (65%)	16:32 (50%)	20:27 (74%)	15:28 (54%)
Median time (months)	21.3	25.1	Not reached	18.1	NR	NR	NR	NR
HR (95% CI) p-value (2-sided)	0.94 (0.62-1.41) p=0.7571		0.35 (0.13-0.88) p=0.0258		1.28 (0.66-2.52) p=0.4641		1.52 (0.75-3.16) p=0.2502	
Interim OS at 38% maturity (Data cut-off November 26 2012) - FAS								
# of events: total # of patients (%)	37:81 (46%)	24:81 (30%)	-	-	-	-	-	-
Median OS (months)	Not reached	Not reached	-	-	-	-	-	-
HR (95% CI) p-value (2-sided)	1.38 (0.83-2.29) p=0.2113		-		-		-	
Final OS at 62% maturity (Data cut-off January 31 2014) - FAS								
# of events: total # of patients (%)	54:81 (67%)	47:81 (58%)	10:20 (50%)	10:21 (48%)	22:34 (65%)	19:32 (59%)	22:27 (81%)	18:28 (64%)
Median OS (months)	33.8	37.6	Not reached	39.2	33.7	36.7	28.8	27.1
HR (95% CI) p-value (2-sided)	1.17 (0.79-1.73) p=0.4379		1.28 (0.39-4.18) P=0.6861		1.23 (0.65-2.33) p=0.5285		1.17 (0.57-2.37) p=0.6699	
Notes: **O/C4/P=** Olaparib in combination with carboplatin AUC4 & paclitaxel; **C6/P=** Carboplatin AUC6/paclitaxel; **VUS=** variants of unknown significance; **TFST=** time to first subsequent therapy; **TSST=** time to second subsequent therapy; **FAS=** full analysis set								

Figure 3. PFS (independent central review) in BRCA*m* patients in Study 41[44]

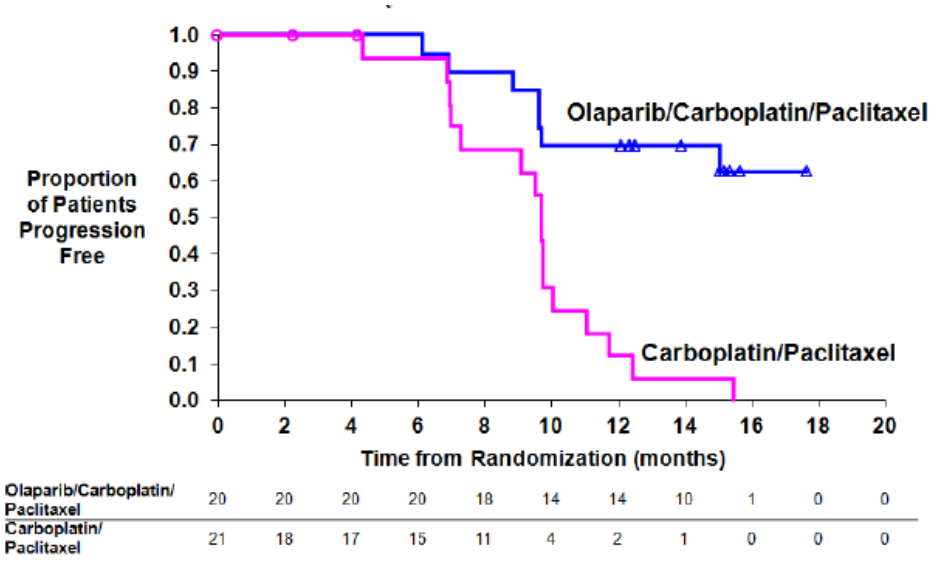
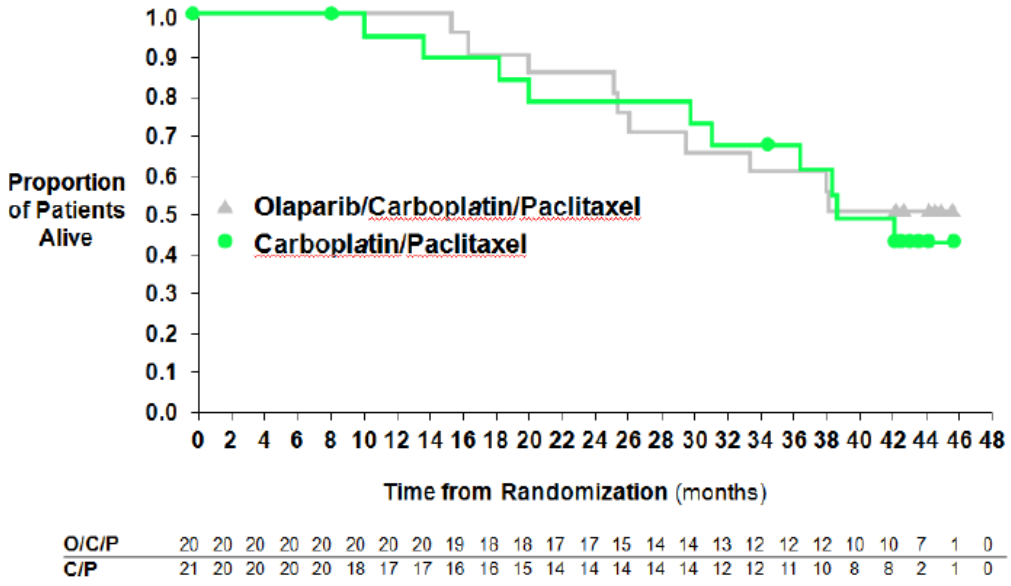


Figure 4. Overall Survival in BRCA*m* patients in Study 41[44]



OCP= olaparib/carboplatin/paclitaxel (olaparib arm)
C/P=carboplatin/paclitaxel (control arm).

Key Limitations:

Trial Design

- Study 41 was an open-label study in which the treatment arm to which patients were randomized was known. This trial design may have affected subsequent therapies patients received and may have introduced bias through unblinding.

- Early censoring of patients in Study 41 was defined as any patient who was censored for OS prior to the data cut-off, including patients who withdrew consent or were lost to follow-up. There was an imbalance in the number of patients who were censored early in the olaparib arm (1.2%) than in the control arm (9.9%). This difference could potentially introduce bias in favour of the control C6/P arm for overall survival as more death events could have been missed through early censoring of patients with a relatively poor prognosis.

Sample Size of the Study[44]

- The primary efficacy analyses of Trial 41 were based on the ITT population and not the BRCA subgroup. The sample size in the BRCA-m subgroup is small (n=41). Consequently, the estimate of magnitude of treatment effect is likely to be unstable.
- The sample size calculation was conducted only in the overall population for PFS. None of the secondary outcomes in the ITT analysis nor the exploratory endpoints in the subgroup analysis of patients with the BRCA-m (eg. PFS, OS) were powered to detect a statistically significant difference. Given that the sample size for the BRCA-m population was small (n=41 total), the results should be considered as exploratory and hypothesis generating.
- Although the BRCA-m population subgroup was a pre-planned exploratory analysis, randomization was not stratified based on status and may not hold for this subgroup of patients.
- It is unclear whether adjustments were made for multiplicity introduced by analysing multiple secondary endpoints or analyses within the BRCA subgroups. Multiple testing can increase the false positive rate inadvertently leading to a possibility of an increase in the probability of making a Type 1 error.

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 (Lynparza) 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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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

The Genitourinary Clinical Guidance Panel is comprised of three oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR 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 section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** February 2016, **Embase** 1974 to 2016 April 08, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches
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.
2	Genital Neoplasms, Female/ or exp Ovarian Neoplasms/ or Fallopian Tube Neoplasms/ or Peritoneal Neoplasms/
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.
4	2 or 3
5	1 and 4
6	5 use pmez,cctr
7	*Olaparib/
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.
9	7 or 8
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/
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.
12	10 or 11
13	9 and 12
14	13 use oemezd
15	6 or 14
16	limit 15 to english language
17	remove duplicates from 16

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Add to builder	Query
#5	Add	Search **(#3 AND #4)**
#4	Add	Search **publisher[sb]**
#3	Add	Search **(#1 AND #2)**

Search	Add to builder	Query
#2	Add	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]**
#1	Add	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])**

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 terms: 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 terms: Lynparza OR Olaparib

Conference abstracts:

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

European Society for Medical Oncology
http://www.esmo.org/

Search terms: Lynparza OR olaparib | ovarian OR fallopian OR peritoneal OR peritoneum
last 5 years

REFERENCES

1. PrLynparza™ olaparib capsules 50 mg [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2016 Apr 27.

2. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol. 2014 Jul;15(8):852-61.

3. Matulonis UA, Penson RT, Domchek SM, Kaufman B, Shapira-Frommer R, Audeh MW, et al. Olaparib monotherapy in patients with advanced relapsed ovarian cancer and a germline BRCA1/2 mutation: a multistudy analysis of response rates and safety. Ann Oncol. 2016 Jun;27(6):1013-9.

4. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012 Apr 12;366(15):1382-92.

5. Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin GJS, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (SOC) and a BRCA mutation (BRCAm) [abstract]. J Clin Oncol [Internet]. 2013 [cited 2016 Apr 27];31(15 Suppl 1). Available from: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/5505?sid=0c31ee1e-4a1e-4f0a-9047-ebee4cc12ee7

6. pan-Canadian Oncology Drug Review checkpoint meeting: olaparib (Lynparza). AstraZeneca response to pCODR request for additional information. Mississauga (ON): AstraZeneca Canada Inc.; 2016 May.

7. Committee for Medical Products for Human Use (CHMP) assessment report: Lynparza [Internet]. London: European Medicines Agency; 2014. [cited 2016 Jul 12]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003726/WC500180154.pdf

8. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2015 [Internet]. Toronto: Canadian Cancer Society; 2015. [cited 2016 Jul 12]. Available from: https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2015-EN.pdf

9. Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012 Jun 10;30(17):2039-45.

10. Ledermann JA, Embleton AC, Raja F, Perren TJ, Jayson GC, Rustin GJ, et al. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016 Mar 12;387(10023):1066-74.

11. Basen-Engquist K, Huang HQ, Herzog TJ, Armstrong DK, Sabbatini P, Walker JL, et al. Randomized phase III trial of carboplatin/paclitaxel alone (CP) or in combination with bevacizumab followed by bevacizumab (CPB) and secondary cytoreduction surgery in platinum-sensitive recurrent ovarian cancer: GOG0213, an NRG Oncology/GOG Study-Analysis of patient reported outcomes (PRO) on chemotherapy randomization [abstract]. J Clin Oncol [Internet]. 2015 [cited 2016 Jul 11];33(suppl):abstr 5525. Available from: http://meetinglibrary.asco.org/content/153528-156

12. Rajan A, Carter CA, Kelly RJ, Gutierrez M, Kummar S, Szabo E, et al. A phase I combination study of olaparib with cisplatin and gemcitabine in adults with solid tumors. Clin Cancer Res. 2012 Apr 15;18(8):2344-51.

13. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

14. Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011 Feb;21(2):419-23.

15. Oza AM, Cibula D, Benzaquen AO, Poole C, Mathijssen RH, Sonke GS, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol. 2015 Jan;16(1):87-97.

16. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol. 2002 Mar 1;20(5):1248-59.

17. Chi DS, Eisenhauer EL, Lang J, Huh J, Haddad L, Abu-Rustum NR, et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? Gynecol Oncol. 2006 Nov;103(2):559-64.

18. Chang SJ, Hodeib M, Chang J, Bristow RE. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis. Gynecol Oncol. 2013 Sep;130(3):493-8.

19. McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med. 1996 Jan 4;334(1):1-6.

20. Vasey PA, Jayson GC, Gordon A, Gabra H, Coleman R, Atkinson R, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. J Natl Cancer Inst. 2004 Nov 17;96(22):1682-91.

21. Aabo K, Adams M, Adnitt P, Alberts DS, Athanazziou A, Barley V, et al. Chemotherapy in advanced ovarian cancer: four systematic meta-analyses of individual patient data from 37 randomized trials. Advanced Ovarian Cancer Trialists' Group. Br J Cancer. 1998 Dec;78(11):1479-87.

22. Thigpen JT, Blessing JA, Ball H, Hummel SJ, Barrett RJ. Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group study. J Clin Oncol. 1994 Sep;12(9):1748-53.

23. Friedlander M, Trimble E, Tinker A, Alberts D, Avall-Lundqvist E, Brady M, et al. Clinical trials in recurrent ovarian cancer. Int J Gynecol Cancer. 2011 May;21(4):771-5.

24. Mafficini A, Simbolo M, Parisi A, Rusev B, Luchini C, Cataldo I, et al. BRCA somatic and germline mutation detection in paraffin embedded ovarian cancers by next-generation sequencing. Oncotarget. 2016 Jan 12;7(2):1076-83.

25. De Picciotto N, Cacheux W, Roth A, Chappuis PO, Labidi-Galy SI. Ovarian cancer: Status of homologous recombination pathway as a predictor of drug response. Crit Rev Oncol Hematol. 2016 May;101:50-9.

26. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. Cancer Discov. 2015 Nov;5(11):1137-54.

27. Scott CL, Swisher EM, Kaufmann SH. Poly (ADP-ribose) polymerase inhibitors: recent advances and future development. J Clin Oncol. 2015 Apr 20;33(12):1397-406.

28. Pfisterer J, Ledermann JA. Management of platinum-sensitive recurrent ovarian cancer. Semin Oncol. 2006 Apr;33(2 Suppl 6):S12-S16.

29. Chi DS, McCaughty K, Diaz JP, Huh J, Schwabenbauer S, Hummer AJ, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. Cancer. 2006 May 1;106(9):1933-9.

30. Pfisterer J, Plante M, Vergote I, Du Bois A, Hirte H, Lacave AJ, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol. 2006 Oct 10;24(29):4699-707.

31. Parmar MK, Ledermann JA, Colombo N, Du Bois A, Delaloye JF, Kristensen GB, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet. 2003 Jun 21;361(9375):2099-106.

32. Lambert HE, Rustin GJ, Gregory WM, Nelstrop AE. A randomized trial of five versus eight courses of cisplatin or carboplatin in advanced epithelial ovarian carcinoma. A North Thames Ovary Group Study. Ann Oncol. 1997 Apr;8(4):327-33.

33. Bertelsen K, Jakobsen A, Stroyer J, Nielsen K, Sandberg E, Andersen JE, et al. A prospective randomized comparison of 6 and 12 cycles of cyclophosphamide, adriamycin, and cisplatin in advanced epithelial ovarian cancer: a Danish Ovarian Study Group trial (DACOVA). Gynecol Oncol. 1993 Apr;49(1):30-6.

34. Hakes TB, Chalas E, Hoskins WJ, Jones WB, Markman M, Rubin SC, et al. Randomized prospective trial of 5 versus 10 cycles of cyclophosphamide, doxorubicin, and cisplatin in advanced ovarian carcinoma. Gynecol Oncol. 1992 Jun;45(3):284-9.

35. Markman M, Liu PY, Wilczynski S, Monk B, Copeland LJ, Alvarez RD, et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. J Clin Oncol. 2003 Jul 1;21(13):2460-5.

36. Eng KH, Hanlon BM, Bradley WH, Szender JB. Prognostic factors modifying the treatment-free interval in recurrent ovarian cancer. Gynecol Oncol. 2015 Nov;139(2):228-35.

37. Korkmaz T, Seber S, Basaran G. Review of the current role of targeted therapies as maintenance therapies in first and second line treatment of epithelial ovarian cancer; In the light of completed trials. Crit Rev Oncol Hematol. 2016 Feb;98:180-8.

38. Wiggans AJ, Cass GK, Bryant A, Lawrie TA, Morrison J. Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer. Cochrane Database Syst Rev. 2015;(5):CD007929.

39. Lee JM, Hays JL, Annunziata CM, Noonan AM, Minasian L, Zujewski JA, et al. Phase I/Ib study of olaparib and carboplatin in BRCA1 or BRCA2 mutation-associated breast or ovarian cancer with biomarker analyses. J Natl Cancer Inst. 2014 Jun;106(6):dju089.

40. Liu JF, Barry WT, Birrer M, Lee JM, Buckanovich RJ, Fleming GF, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol. 2014 Oct;15(11):1207-14.

41. Higuchi T, Flies DB, Marjon NA, Mantia-Smaldone G, Ronner L, Gimotty PA, et al. CTLA-4 Blockade Synergizes Therapeutically with PARP Inhibition in BRCA1-Deficient Ovarian Cancer. Cancer Immunol Res. 2015 Nov;3(11):1257-68.

42. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Health-related quality of life (HRQoL) during olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (PSR SOC) and a *BRCA* mutation (*BRCA*m). 885PD. Poster presented at: ESMO Congress. 2014; Madrid, Spain 26-30 September. Presented at ESMO, Madrid, Spain, 26-30 September 2014.

43. Matulonis U, Friedlander M, Du Bois A, Gourley C, Vergote I, Rustin GJS, et al. Frequency, severity and timing of common adverse events (AEs) with maintenance olaparib in patients (pts) with platinumsensitive relapsed serous ovarian cancer (PSR SOC) [abstract]. J Clin Oncol [Internet]. 2015 [cited 2016 Apr 27];33(15 Suppl 1). Available from: http://meeting.ascopubs.org/cgi/content/abstract/33/15_suppl/5550?sid=b334f352-8a72-4b64-ad3c-69dc6954d00f

44. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. FDA briefing document: Oncologic Drugs Advisory Committee meeting. NDA 206162; Olaparib (Lynparza®); AstraZeneca [Internet]. Rockville (MD): FDA; 2014 Jun 25. [cited 2016 Jul 7]. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM402207.pdf

45. Clinical summary report. In: pan-Canadian Oncology Drug Review manufacturer submission: Lynparza™ (olaparib), 50 mg capsules. Company: AstraZeneca Canada Inc. Mississauga (ON): AstraZeneca Canada Inc.; 2016 Mar 31. Page 23.

46. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s). In: Lynparza (olaparib) Capsule. Company: AstraZeneca Pharmaceuticals LP. Application No.: 206162. Approval Date: 12/19/2014 [Internet]. Rockville (MD): FDA; 2014 Dec 19 [cited 2016 Apr 4]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000TOC.cfm

47. ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - Available from: https://clinicaltrials.gov/

48. Royston P. and Parmar KB. M. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMC Medical Research Methodology201313:152