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Guideline 4-3 Version 4 IN REVIEW

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Therapy for Recurrent Epithelial Ovarian Cancer

J. Francis, N. Coakley, L. Elit, E.B. Kennedy, H. Mackay, and the Gynecologic Cancer Disease Site Group

An assessment conducted in November 2025 placed Guideline 4-3 Version 4 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 4-3 Version 4 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/37871

Section 1:	**Guideline Recommendations**
Section 2:	**Recommendations and Key Evidence**
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PUBLICATIONS RELATED TO THIS REPORT

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Systemic Therapy for Recurrent Epithelial Ovarian Cancer

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

To recommend systemic therapy options for women with recurrent epithelial ovarian cancer including fallopian tube and primary peritoneal cancers.

TARGET POPULATION

The target population comprises women with recurrent epithelial ovarian cancer who have previously received platinum-based chemotherapy. Specific subgroups of interest are identified based on response to therapy.

INTENDED USERS

The intended users of this guideline are gynecologic oncologists or medical oncologists in the province of Ontario.

BACKGROUND INFORMATION

This guideline was based on an updated systematic review of the 2011 evidence base [1]. New evidence has led to new recommendations in some areas.

RECOMMENDATIONS

Recommendations 1, 2, and 3 are endorsements of those found in the 2011 version of this guideline; the original recommendations continue to be valid and have not changed.

Recommendations 4 and 5 are new in this current version of the guideline.

Recommendation 1
Systemic therapy for recurrent ovarian cancer is not curative. As such, it is recognized that, to determine the optimal therapy, each patient needs to be assessed individually in terms of recurrence, sensitivity to platinum, toxicity, ease of administration, and patient preference.

Recommendation 2
All patients should be offered the opportunity to participate in clinical trials, if appropriate.

Recommendation 3

Chemotherapy for patients with platinum-sensitive recurrent ovarian cancer:
• If the option to participate in a clinical trial is not available, combination platinum-based chemotherapy should be considered, providing that there are no contra-indications. The decision regarding which combination to use should be based on toxicity experienced with primary therapy, patient preference, and other factors. Recommended combinations are:
  ○ carboplatin and paclitaxel
  ○ carboplatin and gemcitabine
  ○ carboplatin and pegylated liposomal doxorubicin

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- If combination platinum-based chemotherapy is contraindicated, then a single platinum agent should be considered. Carboplatin has demonstrated efficacy across trials and has a manageable toxicity profile.
- If a single platinum agent is not being considered (e.g., because of toxicity or allergy), then monotherapy with paclitaxel, topotecan, or pegylated liposomal doxorubicin is a reasonable treatment option.

Recommendation 4

For patients with platinum-sensitive recurrent ovarian cancer:

- Women with platinum-sensitive recurrent ovarian cancer should be offered chemotherapy with biologics after a discussion concerning the safety profile

Targeted agents:

- Bevacizumab combined with combination chemotherapy and as maintenance therapy can be considered.
- Cediranib administered during the chemotherapy and maintenance therapy can be considered.
- PolyADP-ribose polymerase (PARP) inhibitors are recommended for patients with known *BRCA* 1 or 2 mutation (somatic and germline) as maintenance treatment post platinum-based chemotherapy for recurrent disease.
- Niraparib can be considered for patients who are *BRCA* wild-type as maintenance post-platinum-based chemotherapy for recurrent disease.

Qualifying Statements for Recommendation 4

- With the increase in evidence supporting the use of PARP inhibitors in patients with homologous recombination deficiency mutations, consideration should be given to testing the *BRCA* status of all women with ovarian cancer at initial diagnosis.
- PARP inhibitors have demonstrated an increase in progression-free survival in patients with *BRCA* mutations without a significant improvement in overall survival
- Women with wild-type *BRCA* also showed a minor improvement in progression-free survival

Recommendation 5

For patients with platinum-refractory or platinum-resistant recurrent ovarian cancer:

- Lower levels of response to treatment are expected for this group; therefore, the goals of treatment should be to improve patient's quality of life by extending the symptom-free interval, reducing symptom intensity, increasing progression-free interval, or if possible, prolonging life.
- Monotherapy with a non-platinum agent should be considered since there does not appear to be an advantage in the use of non-platinum-containing combination chemotherapy in this group of patients. Single-agent paclitaxel, topotecan, pegylated liposomal doxorubicin, and gemcitabine have demonstrated activity in this patient population and are reasonable treatment options.
- There is no evidence to support or refute the use of more than one line of chemotherapy in patients with platinum-refractory or platinum-resistant recurrences. There are many treatment options that have shown modest response rates but their benefit over best supportive care has not been studied in clinical trials.

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- Bevacizumab combined with chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan) can be considered for women who meet the eligibility criteria of the Avastin Use in Platinum-Resistant Ovarian Cancer (AURELIA) phase III randomized controlled trial: confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer that had progressed within six months of completing ≥4 cycles of platinum-based therapy, age ≥18 years, Eastern Cooperative Oncology Group performance status ≤2, and adequate liver, renal, and bone marrow function. Ineligible patients include those who have received >2 prior anticancer regimens or who had refractory disease, patients with a history of bowel obstruction (including subocclusive disease) related to underlying disease, a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess, or evidence of rectosigmoid involvement by pelvic examination, bowel involvement on computed tomography, or clinical symptoms of bowel obstruction.

Qualifying Statements for Recommendation 5

- At the time of the writing of this guideline there are numerous targeted agents in addition to vascular endothelial growth factor inhibitors, programmed death-1 and programmed death ligand-1 inhibitors, as well as other immunotherapies that are under investigation and that show promise in early trials. It is likely that one or some of these will become part of the lexicon of treatment protocols in the near future, either independently or in combination with conventional chemotherapy.

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Systemic Therapy for Recurrent Epithelial Ovarian Cancer

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To recommend systemic therapy options for women with recurrent epithelial ovarian cancer (EOC) including fallopian tube and primary peritoneal cancers.

TARGET POPULATION

The target population comprises women with recurrent EOC who have previously received platinum-based chemotherapy. Specific subgroups of interest in the target population are identified based on their response to therapy.

INTENDED USERS

The intended users of this guideline are gynecologic oncologists or medical oncologists in the province of Ontario.

BACKGROUND INFORMATION

This guideline was based on an updated systematic review to the 2011 evidence base [1]. New evidence has led to new recommendations in some areas.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendations 1, 2, and 3 are endorsements of those found in the 2011 version of this guideline; the original recommendations continue to be valid and have not changed.

Recommendations 4 and 5 are new in this current version of the guideline.

Recommendation 1
Systemic therapy for recurrent ovarian cancer is not curative. As such, it is recognized that, to determine the optimal therapy, each patient needs to be assessed individually in terms of recurrence, sensitivity to platinum, toxicity, ease of administration, and patient preference.

Recommendation 2
All patients should be offered the opportunity to participate in clinical trials, if appropriate.

Recommendation 3

<u>Chemotherapy for patients with platinum-sensitive recurrent ovarian cancer:</u>
• If the option to participate in a clinical trial is not available, combination platinum-based chemotherapy should be considered, providing that there are no contra-indications. The decision regarding which combination to use should be based on toxicity experienced with primary therapy, patient preference, and other factors. Recommended combinations are:
  ○ carboplatin and paclitaxel (C–P)
  ○ carboplatin and gemcitabine
  ○ carboplatin and pegylated liposomal doxorubicin (C-PLD)
• If combination platinum-based chemotherapy is contraindicated, then a single platinum agent should be considered. Carboplatin has demonstrated efficacy across trials and has a manageable toxicity profile.

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- If a single platinum agent is not being considered (e.g., because of toxicity or allergy), then monotherapy with paclitaxel, topotecan, or pegylated liposomal doxorubicin is a reasonable treatment option.

Key Evidence for Recommendation 3

- A 976-patient study, CALYPSO [2], compared C-P with C-PLD and found an improvement in progression-free survival (PFS) with the C-PLD combination (11.4 vs. 9.3 months; p=0.005), a more favourable toxicity profile, no difference in overall survival (OS) (although significantly more patients crossed over to the C-PLD arm), and a superior crossover treatment rate in the C-P arm. Global quality of life (QOL) scores did not differ between groups [3].
- A 672-patient study, OVA-301 [4], compared PLD with trabectedin-PLD, and found a statistically significantly improved PFS with the combination (7.3 vs. 5.8 months; p=0.019). Despite this finding, which implies the viability of the combination as a treatment option, the trabectedin-PLD combination is not recommended at this time, based on the finding of no differences in QOL [5] or OS [6], the lack of clinical significance of a six-week PFS difference, the lack of comparison with the Gynecologic Cancer InterGroup standard taxane and platinum agent [7], and the elevated rate of adverse events such as raised liver enzymes, non-fatal congestive heart failure, and neutropenia in the combination group.
- A study by Sehouli et al. [8] of topotecan versus topotecan combined with other agents did not find a benefit with the combination therapy in a population of mainly platinum-sensitive women; thus, topotecan combination therapy is not recommended.
- Two smaller trials that compared PLD with gemcitabine showed no difference in PFS. A small significant difference in OS was found in one trial (56 weeks for PLD vs. 51 weeks for gemcitabine; p=0.048) [9]. The adverse events profiles differ for these two agents; therefore, gemcitabine can be considered another option in this patient population, considering patient preference and previous toxicity [9,10].

Recommendation 4

<u>For patients with platinum-sensitive recurrent ovarian cancer:</u>

- Women with platinum-sensitive recurrent ovarian cancer should be offered chemotherapy with biologics after a discussion concerning the safety profile

Targeted agents:

- Bevacizumab combined with combination chemotherapy and as maintenance therapy can be considered.
- Cediranib administered during the chemotherapy and maintenance therapy can be considered.
- PolyADP-ribose polymerase (PARP) inhibitors are recommended for patients with known *BRCA* 1 or 2 mutation (somatic and germline) as maintenance treatment post platinum-based chemotherapy for recurrent disease.
- Niraparib can be considered for patients who are *BRCA* wild-type as maintenance post-platinum-based chemotherapy for recurrent disease.

Qualifying Statements for Recommendation 4

- With the increase in evidence supporting the use of PARP inhibitors in patients with homologous recombination deficiency (HRD) mutations, consideration should be given to testing the *BRCA* status of all women with ovarian cancer at initial diagnosis.

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- PARP inhibitors have demonstrated an increase in PFS in patients with *BRCA* mutations without a significant improvement in OS.
- Women with wild-type *BRCA* also showed a minor improvement in PFS.

Key Evidence for Recommendation 4

- It was shown that in the platinum-sensitive population of the OCEANS phase III randomized controlled trial (RCT), PFS for bevacizumab with gemcitabine and carboplatin (BEV+CT) was superior compared with carboplatin with gemcitabine plus placebo (CT) (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.39 to 0.61). Median PFS of 12.4 months in the BEV+CT arm versus 8.4 months in the CT arm [11].
- It was shown that in the platinum-sensitive population of the moderate quality ICON6 phase III RCT, PFS for Arm C with cediranib was superior compared with the reference Arm A of platinum-based therapy plus placebo (HR, 0.56; 95% CI, 0.44 to 0.72). Median PFS was 11.0 months in the experimental arm versus 8.7 months in the non-experimental arm [12].
- Niraparib significantly prolonged PFS in platinum-sensitive patients when compared with a placebo, in patients with no germline *BRCA* mutations (HR, 0.45; 95% CI, 0.34 to 0.61; p<0.001) [13].

Interpretation of Evidence for Recommendation 4

- The above listed recommendations are conditional in nature (i.e., "can be considered") considering the trade-off between the benefits (i.e., PFS) weighed against the harms (i.e., adverse effects).
- Based on moderate quality of evidence in the OCEANS trial [11,14], statistically significantly increased risks for BEV+CT vs. CT were shown for the following adverse events:
  - Serious adverse events (grade 3 to 5): relative risks [RR], 1.53; 95% CI, 1.11 to 2.09
  - Grade ≥3 hypertension: RR, 21.22; 95% CI, 5.21 to 86.51
  - Grade ≥3 proteinuria: RR, 12.73; 95% CI, 3.06 to 52.96
  - Notably, very wide confidence intervals were shown for both grade ≥3 hypertension and proteinuria due to few events in the CT arm (<5 events).
- In the ICON6 trial [12], statistically significantly increased risks during the chemotherapy phase for Arms B+C of platinum-based chemotherapy plus cediranib vs. the reference Arm A of platinum-based chemotherapy plus placebo were shown for the following adverse events:
  - Grade ≥3 fatigue: RR, 2.11; 95% CI, 1.07 to 4.11
  - Grade 3 to 4 diarrhea: RR, 5.94; 95% CI, 1.45 to 24.34
  - Grade 3 to 5 hypertension: RR, 3.32; 95% CI, 1.21 to 9.10
  - Notably, very wide confidence intervals were shown for grade 3 to 5 diarrhea due to few events in the CT arm (<5 events).

Recommendation 5

<u>For patients with platinum-refractory or platinum-resistant recurrent ovarian cancer:</u>

- Lower levels of response to treatment are expected for this group; therefore, the goals of treatment should be to improve patient's QOL by extending the symptom-free interval, reducing symptom intensity, increasing PFS, or if possible, prolonging life.
- Monotherapy with a non-platinum agent should be considered since there does not appear to be an advantage in the use of non-platinum-containing combination chemotherapy in this group of patients. Single-agent paclitaxel, topotecan, PLD, and

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gemcitabine have demonstrated activity in this patient population and are reasonable treatment options.

- There is no evidence to support or refute the use of more than one line of chemotherapy in patients with platinum-refractory or platinum-resistant recurrences. There are many treatment options that have shown modest response rates but their benefit over best supportive care has not been studied in clinical trials.
- Bevacizumab combined with chemotherapy (PLD, weekly paclitaxel, or topotecan) can be considered for women who meet the eligibility criteria of the Avastin Use in Platinum-Resistant Ovarian Cancer (AURELIA) phase III RCT; confirmed epithelial ovarian, fallopian tube, or primary peritoneal cancer that had progressed within six months of completing ≥4 cycles of platinum-based therapy, age ≥18 years, Eastern Cooperative Oncology Group performance status ≤2, and adequate liver, renal, and bone marrow function. Ineligible patients include those who have received >2 prior anticancer regimens or who had refractory disease, patients with a history of bowel obstruction (including subocclusive disease) related to underlying disease, a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess, or evidence of rectosigmoid involvement by pelvic examination, bowel involvement on computed tomography, or clinical symptoms of bowel obstruction.

Qualifying Statements for Recommendation 5

- At the time of the writing of this guideline there are numerous targeted agents in addition to vascular endothelial growth factor (VEGF) inhibitors, programmed death-1 (PD1) and programmed death ligand-1 inhibitors (PDL1), as well as other immunotherapies that are under investigation and that show promise in early trials. It is likely that one or some of these will become part of the lexicon of treatment protocols in the near future, either independently or in combination with conventional chemotherapy.

Key Evidence for Recommendation 5

- Based on moderate quality of evidence, in the AURELIA phase III RCT, in women with platinum-resistant recurrent ovarian cancer, the PFS HR was 0.48 (95% CI, 0.38 to 0.60) for chemotherapy including PLD, weekly paclitaxel or topotecan with bevacizumab (BEV+CT) compared with the same regimen although without bevacizumab (CT). Median PFS was 6.7 months in the BEV+CT arm vs. 3.4 months in the CT arm [15].
- Statistically significant increased risks for BEV+CT vs. CT were shown for the following adverse events:
  - Grade ≥2 adverse events including hypertension, gastrointestinal perforation and fistula/abscess: RR, 3.71; 95% CI, 2.03 to 6.78) [15].
  - Grade ≥3 adverse events including hypertension, proteinuria, gastrointestinal perforation, bleeding, thromboembolic event, wound healing, reversible posterior leukoencephalopathy syndrome, congestive heart failure, and cardiac disorders: RR, 2.64; 95% CI, 1.44 to 4.84) [15].
- Based on very low quality of evidence, statistically significant improvements of ≥15% in abdominal/gastrointestinal symptoms were shown for BEV+CT vs. CT (RR, 2.33; 95% CI, 1.37 to 3.97) [15].

Interpretation of Evidence for Recommendation 5

- Based on moderate-quality evidence for PFS, there was a beneficial effect of BEV+CT.
- The above-listed recommendation is conditional in nature (i.e., "can be considered") due to the detection of adverse events with the use of BEV+CT.

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Although based on low quality of evidence, we do accept lower-tiered evidence to inform harms outcomes, thereby tempering the recommendations despite evidence for improved PFS.

FURTHER QUALIFYING STATEMENTS

Across several trials, PARP inhibitors have demonstrated a significant improvement in PFS, although we have limited phase III data in this drug class. Based on current evidence, we made a conditional recommendation on PARP inhibitors in the *BRCA*/HRD-positive patient population, and a conditional recommendation in the non-*BRCA* PARP inhibitor population. Olaparib has been approved by the United States Food & Drug Administration for recurrent ovarian cancer in germline mutations.

There is increasing evidence to support the unique nature of the numerous histologic subtypes within ovarian cancer. As evidence increases, treatment regimens will be optimized by subtype. These issues will be addressed in a PEBC guideline currently under development.

IMPLEMENTATION CONSIDERATIONS

- Cediranib was withdrawn from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) in June 2015 for cediranib as monotherapy. However, this decision does not affect cediranib as a combination treatment with other agents.
- It is our belief that patient preference should play a significant role in disease management in the setting of recurrent ovarian cancer. Since cure is seldom an endpoint in this circumstance, patients' attitudes toward the risks and benefits of chemotherapy versus palliation are relevant.
- Currently all women with high grade serous ovarian cancer should be offered *BRCA* 1 and 2 testing. This germline testing has implications for timely access to genetic counseling services and lab results. As we move to somatic testing this will have implications for the funding of pathology services to provide the test on tissue. It is highly likely that other ovarian histologies will be candidates for testing in the future.

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Systemic Therapy for Recurrent Epithelial Ovarian Cancer

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control. The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision-makers from across the province, and methodologists. The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (MOHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

JUSTIFICATION FOR GUIDELINE

Due to the awareness of new randomized trials on this topic, the CCO PEBC Gynecologic Cancer Disease Site Group (Gyne DSG) chose to update the evidence base and its recommendations for systemic therapy in this patient population.

GUIDELINE DEVELOPERS

This guideline was developed by the GDG (Appendix 1), which was convened at the request of the Gyne DSG. The project was led by a small Working Group of the Gyne DSG members, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in gynecologic oncology, medical oncology, and health research methodology. Other members of the Gyne DSG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1 and 2, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [16,17]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders. The PEBC uses the AGREE II framework [18] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along

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with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether an existing guideline could be adapted or endorsed. *A priori*, we recognized the prior Gyne DSG version of this guideline and published as part of the CCO PEBC [1]. The following sources were additionally searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the targeted peer review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through professional consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

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ACKNOWLEDGEMENTS

The Guideline 4-3 Version 4 GDG would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Sheila McNair, Hans Messersmith, Jennifer Salerno, Emily Vella, Chika Agbassi, Duvaraga Sivajohanathan, Dr. Shailendra Verma and Dr. Donna Maziak for providing feedback on draft versions.
- Fulvia Baldassare and Cindy Walker-Dilks for their help with AGREE.
- Max Chen for conducting a data audit.
- Sara Miller for copy editing.

Systemic Therapy for Recurrent Epithelial Ovarian Cancer

Section 4: Systematic Review

INTRODUCTION

In Canada, ovarian cancer is the fifth leading cause of cancer deaths among women and the leading cause of gynecologic cancer mortality. There were an estimated 2800 new cases of ovarian cancer in Canada in 2015 [19]. Ovarian cancer is usually diagnosed at an advanced stage, and most patients experience relapse after primary therapy, resulting in a survival rate of approximately 10–30% [20].

One of the most frequently documented predictors of response to chemotherapy in women with recurrent ovarian cancer is the platinum-free interval (PFI), defined as the period of time from the last dose of platinum-based therapy until disease progression [7]. However, some patients become increasingly resistant to platinum-based therapies over time and some women respond to multiple lines of treatment. Although responsiveness to platinum-based therapies would be more accurately viewed as occurring on a continuum [21], for the purposes of treatment planning and research, platinum sensitivity of patients is often stratified as follows [22]:

1. Platinum-sensitive patients: patients with a PFI of six months or longer (i.e., patients with disease that relapses ≥6 months after completion of initial therapy);
2. Platinum-resistant patients: patients with a PFI of less than six months (i.e., patients whose disease relapses <6 months after completion of initial therapy).
3. Platinum-refractory patients: patient having had progressed during previous platinum-containing therapy.

Many patients with recurrent ovarian cancer do not survive their cancers, and as a result the duration of survival (prolonged PFS) and QOL are important. Therefore, PFS is a valid study endpoint in this population. With these principles in mind, the Working Group chose PFS as one of the primary outcomes of interest.

BACKGROUND

The goal of this guideline is to provide the most up-to-date systemic therapy treatment recommendations for recurrent EOC in order to promote evidence-based practice in Ontario. Due to the awareness of new randomized trials on this topic, the CCO PEBC Gyne DSG chose to update the evidence base and recommendations for systemic therapy for this patient population. This work includes the new results of recent studies on the VEGF inhibitor bevacizumab added to combination chemotherapy. The history of work by the Gyne DSG in this topic area by CCO PEBC is shown in Appendix 2. The PEBC is funded by, but editorially independent of, CCO and the OMHTLC.

RESEARCH QUESTIONS

What is the optimal systemic therapy for women with recurrent ovarian cancer who have previously received platinum-based chemotherapy? Accordingly, the following comparisons were considered: (a) any systemic therapy option vs. another; and (b) any systemic therapy option vs. placebo.

PROTOCOL REGISTRATION

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The protocol for this systematic review was registered in The University of York's international prospective register of systematic reviews (PROSPERO) with the number CRD42016033992.

METHODS

Previous PEBC-Related Guideline

CCO's PEBC previously published a similar guideline in 2011 titled, "Optimal Chemotherapy for Recurrent Ovarian Cancer" [1], in which the research questions, outcomes, and methodology could be endorsed for our purposes. In the prior 2011 guideline by the same authors, the literature search was current as of 2011. The current guideline will search for new evidence since the previous guideline. Where new evidence does not alter the original recommendations, the prior 2011 recommendations will be endorsed. Where new evidence alters original recommendations, the prior 2011 recommendations will be modified. De novo recommendations are formulated where new evidence is available to inform new original recommendations. Appendix 3 illustrates the changes from the original guideline to this one.

Search for Existing Systematic Reviews and Primary Literature

MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched from April 1, 2011 to May 30, 2017 for systematic reviews and primary studies. The search strategy is shown in Appendix 4.

Study Selection Criteria and Process

Inclusion Criteria

- Studies published between April 1, 2011 and August 4, 2016
- English language, humans, adults ≥18 years of age
- Studies on systemic treatment for recurrent EOC including epithelial ovarian, primary peritoneal, and fallopian tube cancers
- Women who are platinum-sensitive, -resistant, and/or -refractory
- Studies that are systematic reviews, meta-analyses, or RCTs
- Studies reporting at least one outcome of interest

Exclusion Criteria

- Studies on other therapies including intraperitoneal chemotherapy, low-grade histologies, hormonal therapy, or chemotherapy with bone marrow or stem cell transplantation
- Observational studies, narrative reviews, case reports (n=1), conference abstracts, in vitro studies, or animal studies
- Non-English-language papers
- Studies in which the study methods are not well described or not clear

Included studies were those that examined systematic therapy for women with epithelial ovarian, primary peritoneal, and fallopian tube cancers, collectively called EOC [22], who fall into any of the three 'platinum' categories outlined above. Phase II or III RCTs published in English that compared one systemic therapy option with another or to a placebo were included. There was no minimum sample size specified. This systematic review of the evidence focuses on systemic therapy, and excludes intraperitoneal chemotherapy, hormonal therapy, or chemotherapy with bone marrow or stem cell transplantation. A review of the titles and abstracts that resulted from the search was conducted by EK, JS, and NC. The remaining authors reviewed the articles considered for inclusion and agreed on the full-text articles to be included.

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The following critical and important outcomes were determined *a priori*:

Critical Outcomes

- PFS

Important Outcomes

- OS
- Adverse events, e.g., grade ≥2 events and any grade for febrile neutropenia
- Health-related QOL
    - Measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Ovarian Cancer Module 28 (QLQ-OV28) and Cancer Module 30 (C30)

Patient Preferences and Values

Patient preferences and values were examined to help, if possible, reinforce/alter the prioritization of the above outcomes and clarify recommendations. A comprehensive literature review was conducted to examine the specific questions "What are patients' relative values and preferences with respect to systemic therapy for recurrent epithelial ovarian, primary peritoneal or fallopian tube cancer?" and "What outcomes are primarily important to patients, and how does the likelihood of these outcomes affect their values and preferences?" Ten studies representing five countries (Germany, United Kingdom, Sweden, Canada, and the United States) met the inclusion criteria. Although there was regional variation in preference for palliation over treatment, certain themes did emerge. Patients, even in the context of counseling and high levels of education, in general overestimated the curative capability of the chemotherapy. Patients who had previously tolerated chemotherapy well were more likely to be accepting of the side effect profile of chemotherapy. Patients were more willing to accept chemotherapy and the related side effect profile when treatment was of curative intent or when OS was increased, but patients valued both OS and PFS.

These findings, in aggregate, highlight the importance of thorough communication with patients regarding prognosis, side effect profile, and symptom management in order to help patients negotiate the decision-making process. A summary of this work is shown in Appendix 7.

Data Extraction and Assessment of Study Quality

Data were extracted by EK, JS, and NC and were audited by a project research assistant. The data elements were population, intervention, and outcome information. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the evidence including defining critical and important outcomes. The quality of included studies was assessed for critical and important outcomes using the GRADE process [23], which includes an assessment of the risk of bias [24], as well as the directness, consistency, and precision of the evidence as it related to the specified outcomes, potential for publication bias, funding source bias, and any other relevant quality or risk of bias issues. According to GRADE, the quality of evidence reflects the level of confidence or certainty we have that the estimate of an effect is correct. Given the complexity and heterogeneity of the study designs and comparisons, the GRADE strategy was used as an overall critical appraisal guide

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Due to the heterogeneity of protocols, populations, and interventions across the included studies, a meta-analysis was not considered.

RESULTS

Search for Existing Guidelines for Adaptation or Endorsement

Other Relevant Guidelines

Nine guidelines were identified. One guideline was investigated for possible endorsement. A Spanish guideline was identified that contains a brief section on recurrent disease [25]. This guideline was evaluated by three PEBC health research methodologists (NC, FB and CWD) using the AGREE instrument [18]. It was found to be of low quality. The guideline scored 33% in the Scope and Purpose domain, 11% in the Stake Holder Involvement domain, 13% in the Rigor of Development domain, 31% in the Clarity of Presentation domain, 0% in the Applicability domain, 44% in the Editorial independence domain and 0% in Overall Guideline Assessment. There is no report of a systematic search of evidence being done for the guideline or no reporting on how the recommendations were formulated. Based on the scored from the AGREE instrument and the lack of methods, the Working Group did not find this a suitable guideline to endorse. The following is a brief overview of the recommendations. The guideline states that no combination is better than another in terms of efficacy, and treatment should be chosen based on the toxicity profile. However, in patients with a relapse and a platinum-free interval of greater than six months, they state that the standard treatment is a platinum combination and bevacizumab can be added. In *BRCA* mutation-positive patients, olaparib must be considered. Patients with a platinum-free interval between six and 12 months can consider a platinum combination of trabectedin-PLD [25]. In patients with a platinum-free interval of less than six months, the guideline states that patients should be treated with sequential single-agent chemotherapy. Accepted palliative chemotherapies are PLD, weekly paclitaxel, topotecan, and gemcitabine. In patients who have not received more than two previous lines or prior bevacizumab, the addition of the latter to weekly paclitaxel, PLD, or topotecan is suggested. In platinum-resistant patients, they suggest either single-drug therapy or a combination with bevacizumab if the patient has not received this drug previously [25].

The Working Group felt that none of the following guidelines were suitable for adaptation or endorsement since the recommendations from the guidelines did not align with our research questions and methods. The European Medicines Agency advises that bevacizumab can be used for advanced or recurrent EOC in combination with certain chemotherapy medicines [26], and the United States Federal Drug Agency approves its use for platinum-resistant ovarian cancer, based on the AURELIA phase III RCT [27]. In contrast, the United Kingdom's NICE has not recommended BEV+CT for the treatment of the first recurrence of platinum-sensitive advanced ovarian cancer, citing lack of clarity around the confounding that may have led to the discrepancy between the PFS and OS results [28], and in their most recent 2016 publication, they have not recommended bevacizumab [29]. SIGN recommends that women with platinum-sensitive relapsed ovarian cancer should be treated with a platinum-based combination with paclitaxel, PLD hydrochloride, or gemcitabine. Based on advice from the Scottish Medicines Consortium, SIGN does not recommend bevacizumab (i.e., in combination with gemcitabine or paclitaxel) because of insufficient justification of the treatments' costs, among other factors [30]. However, the most recent release of the National Comprehensive Cancer Network 2015 publication has recommended bevacizumab plus chemotherapy in both platinum-sensitive and –resistant disease [31]. Canadian oncologists have published a commentary in support of approval for bevacizumab in EOC, and have issued a call for consistency in regulatory approvals for systemic therapy across jurisdictions [32]. In its

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initial report, the Pan-Canadian Oncology Drug Review concluded that the AURELIA RCT [15] demonstrated a statistically significant but clinically modest net benefit for PFS in the platinum-resistant population.

NICE published a technology appraisal guidance document in January 2016 recommending the use of olaparib for the maintenance treatment of *BRCA* 1 or 2 mutated, relapsed, platinum-sensitive ovarian, fallopian tube, and peritoneal cancer in women whose relapsed disease has responded to platinum-based chemotherapy [33].

Search for Existing Systematic Reviews and Primary Literature

One systematic review/meta-analysis [34] was identified that potentially met the inclusion criteria. However, it included data taken from a published abstract (i.e., GOG 0213 trial to be completed in March 2019) and it did not include the updated data from the 2015 publication of the Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease (OCEANS) trial. Therefore, this systematic review/meta-analysis was ultimately excluded. Thirteen other relevant systematic reviews were identified and assessed for possible adoption into the evidence base; however, these papers were excluded [35-47]. They were unsuitable because they were either too old, could not be obtained, had different inclusion criteria from ours, or included first-line treatments in their analysis.

The primary literature search yielded 36 primary research papers representing 30 studies of RCTs that met the eligibility criteria [11-15,48-78]. The Ledermann phase 2 trial of olaparib was included as four papers [58-61] and the Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy AURELIA trial was included as three papers [15,53,75]. The OCEANS trial [11,14] and the TRINOVA-1 Trial [66,67] were represented by two papers. A study flow diagram is provided in Appendix 5, Figure 1.

Study Design

A summary of the included studies is shown in Table 4-1a-d. All of the studies were either phase 2 or 3 randomized trials. Phase 3 studies that were of high quality and had low risk of bias received more weight in determining the recommendations. As previously mentioned, GRADE was used as a general guide to view the studies and as a group they were of moderate quality. The risk of bias chart for included studies is presented in Appendix 6.

Six included studies were assessments of olaparib in populations of women with serous tumour histologies. They are summarized Table 4-1a below [13,55,58,59,62,70]. The 2014 article by Ledermann et al. is a subgroup analysis of *BRCA* patients from the 2012 study [58,59].

Table 4-1a. Summary of included studies: Serous histology studies

Study	Drug Type	Intervention	Comparator
Serous			
Mirza [13] 2016 Phase 3	Niraparib (poly [ADP-ribose] polymerase inhibitor)	Niraparib 300 mg N=138 for germline *BRCA* mutation N=234 for non-germline mutation	Placebo N=65 for germline *BRCA* mutation N=116 for non-germline mutation
Oza [70] 2015 Phase 2	Olaparib (poly [ADP-ribose] polymerase inhibitor), taxane, alkylating agent	Olaparib (200 mg capsules twice daily), paclitaxel (175 mg/m^2), and carboplatin (AUC 4) (combination phase) then olaparib monotherapy	Paclitaxel (175 mg/m^2 and carboplatin (AUC 6) then no further treatment, N=81

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Study	Drug Type	Intervention	Comparator
		(400 mg capsules twice daily) until progression (maintenance phase) N=81	
Liu [62] 2014 Phase 2	Olaparib (poly [ADP-ribose] polymerase inhibitor), VEGF inhibitor	Olaparib capsules 400 mg twice daily, N=46	Cediranib 30 mg daily and olaparib capsules 200 mg twice daily, N=44
Kaye [55], 2012 Phase 2	Olaparib (poly [ADP-ribose] polymerase inhibitor) vs. anthracycline antineoplastic antibiotic doxorubicin	Olaparib 200 mg twice daily, N=32 Olaparib 400 mg twice daily, N=32	PLD 50 mg/m^2 every 28 days, N=33
Ledermann [58,60,61] 2012 Phase 2	Olaparib (poly [ADP-ribose] polymerase inhibitor)	Olaparib 400 mg twice daily, N=136	Placebo, N=129
Ledermann [59] 2014 Phase 2 This article pertains to a subset of *BRCA* patients	Olaparib (poly [ADP-ribose] polymerase inhibitor)	Olaparib 400 mg twice daily, N=136	Placebo, N=129

There were five studies of systemic treatment in patients with recurrent ovarian cancer [49,54,65,66,68]. These are summarized below in Table 4-1b

Table 4-1b. Summary of included studies: Recurrent ovarian cancer studies

Study	Drug Type	Intervention	Comparator
Recurrent			
Marth [65] 2017-06-06 Phase 3	Anthracycline antineoplastic antibiotic doxorubicin, an angiopoietin (Ang) 1 and 2 neutralizing peptibody	PLD 50 mg/m^2 + trebananib 15 mg/kg N=114	PLD 50 mg/m^2+ placebo N=109
Monk [68] 2016 Phase 2	VEGF-A, monoclonal antibody, vascular targeting agent	Bevacizumab 15 mg/kg every 3 weeks, N=53	Bevacizumab 15 mg/kg + fosbretabulin 60 mg/m^2 every 3 weeks, N=54
Coleman [49], 2014 Phase 2	VEGF-A, monoclonal antibody, taxane	Docetaxel 75 mg/m^2 + vandetanib 100 mg daily, N=63	Docetaxel 75 mg/m^2, N=66
Monk [66,67] TRINOVA-1 2014 Phase 3	An angiopoietin (Ang) 1 and 2 neutralizing peptibody, taxane	Paclitaxel 80 mg/m^2 + trebananib 15 mg/kg, N=461	Paclitaxel 80 mg/m^2 + Placebo, N=458

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Karlan [54] 2012 Phase 2	Taxane	Paclitaxel 80 mg/m^2 once weekly + AMG 386 10 mg/kg (Arm A), N=53	Paclitaxel 80 mg/m^2 + AMG 386 3 mg/kg (Arm B), N=53 Paclitaxel 80 mg/m^2 + placebo (Arm C), N=55

Seven studies addressed systemic treatment in a platinum-sensitive population [11,12,48,56,64,74,77]. These are summarized below in Table 4-1c.

Table 4-1c. Summary of included studies: Platinum-sensitive studies

Study	Drug Type	Intervention	Comparator
Platinum-Sensitive			
Vergote [77] 2016 Phase 3	Monoclonal antibody vs. taxane and antineoplastic alkylating agent	Farletuzumab 1.25 mg/kg + carboplatin/paclitaxel or docetaxel, N=376 Farletuzumab 2.5 mg/kg + carboplatin/paclitaxel or docetaxel, N=363	Placebo + carboplatin/paclitaxel or docetaxel, N=352
Aghajanian [11,14] 2012 OCEANS Trial Phase 3	VEGF-A, monoclonal antibody	Gemcitabine 1000 mg/m^2 and carboplatin (AUC 4) and bevacizumab 15 mg/kg, N=242	Gemcitabine 1000 mg/m^2 and carboplatin (AUC 4) and placebo, N=242
Mahner [64] CALYPSO 2015 Phase 3	Platinum-based + anthracycline antineoplastic antibiotic doxorubicin	Carboplatin (AUC 5) plus PLD 30 mg/m^2, N=131	Carboplatin (AUC 5) plus paclitaxel 175 mg/m^2, N=128
Ledermann [12] 2016 ICON 6 Phase 3	VEGF 1-3 receptor inhibitor vs. chemotherapy	Arm B (concurrent), platinum-based chemotherapy plus cediranib 20 mg, then switched to placebo during the maintenance phase, N=174 Arm C (concurrent plus maintenance) cediranib 20 mg during both phases N=164	Arm A (reference) platinum-based chemotherapy plus placebo during the chemotherapy phase, then placebo alone during the maintenance phase, N=118
Schwandt [74] 2014 Phase 2	Tyrosine kinase inhibitor, angiogenesis inhibitor, VEGF inhibitor, taxane, antineoplastic alkylating agent	Sorafenib 400 mg twice daily, N=14	Sorafenib 400 mg bid with carboplatin (AUC 6) and paclitaxel 175 mg/m^2 every 3 weeks, N=28
Alvarez Secord [48] 2011 Phase 2	Taxane, antineoplastic alkylating agent	Docetaxel 30 mg/m^2 and carboplatin (AUC 6) every 3 weeks, N=74	Docetaxel 30 mg/m^2, every 3 weeks for 6 cycles followed by carboplatin, N=74

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Kaye [56] 2013 Phase 2	Monoclonal antibody, taxane, antineoplastic alkylating agent, antimetabolite	Pertuzumab + paclitaxel or gemcitabine + carboplatin at the investigators' discretion, N=74	Paclitaxel or gemcitabine + carboplatin at the investigators' discretion, N=75

Twelve studies reported on patients with platinum-resistant ovarian cancer [15,50-52,57,63,69,71-73,76,78] and are summarized in Table 4-1d.

Table 4-1d. Summary of included studies: Platinum-resistant ovarian cancer studies

Study	Drug Type	Intervention	Comparator
Platinum-Resistant or -Refractory			
Pujade-Lauraine [15,53,75] AURELIA 2014 Phase 3	VEGF-A, monoclonal antibody, anthracycline antineoplastic antibiotic doxorubicin	Paclitaxel or topotecan or PLD + bevacizumab 10 mg/m^2, N=179	Paclitaxel or topotecan or PLD, N=182
Kurzeder [57] PENELOPE Trial 2016	HER2, monoclonal antibody	Pertuzumab (840-mg loading dose followed by 420 mg every 3 weeks) + selected chemotherapy (topotecan, paclitaxel, or gemcitabine), N=78	Placebo + selected chemotherapy (topotecan, paclitaxel, or gemcitabine), N=78
Colombo 2012 [50] Phase 3	Epothilone, anthracycline antineoplastic antibiotic doxorubicin	Patupilone 10 mg/m^2, N=412	PLD 50 mg/m^2, N=417
Pujade-Lauraine [72] 2016 Phase 2	Dihydropteridinone Polo-like kinase 1 (Plk1) inhibitor, chemotherapy	Volasertib 300 mg, N=54	Investigator's choice of single-agent, nonplatinum, cytotoxic chemotherapy, N=55
Vergote [78] 2013 Phase 2	Long-acting topoisomerase I-inhibitor	Etirinotecan pegol 145 mg/m^2 day 14, N=36	Etirinotecan pegol 145 mg/m^2 day 21, N=35
Gotlieb [52] 2012 Phase 2	VEGF-Trap	Aflibercept (4 mg/kg) , N=29	Placebo, N=26
Rustin [73] 2011 Phase 2	Low-molecular-weight epothilone	Sagopilone as a 3-hour infusion, N=38	Sagopilone as a half-hour infusion, N=25
Fotopoulou [51] 2014 Phase 3	Novel isoflavone, antineoplastic alkylating agent	Carboplatin + phenoxodiol 400 mg, N=70	Placebo + carboplatin, N=72
Pignata [71] 2015 Phase 2	Tyrosine kinase inhibitor; VEGF inhibitor, taxane	Paclitaxel 80 mg/m^2 + pazopanib 800 mg, N=37	Paclitaxel 80 mg/m^2, N=37

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Naumann [69] 2013 Phase 2	Folate-receptor, antineoplastic antibiotic doxorubicin	Vintafolide 2.5 mg + PLD (50 mg/m^2), N=109	PLD (50 mg/m^2), N=53
Tew [76] 2014 Phase 2	VEGF-Trap	Aflibercept 2 mg/kg, N=109	Aflibercept 4 mg/kg, N=109
Lortholary [63] 2012 Phase 2	Taxane, antineoplastic alkylating agent, topoisomerase 1 inhibitor	Paclitaxel (80 mg/m^2), N=57	Paclitaxel (80 mg/m^2) and carboplatin (AUC 5), N=51 Paclitaxel (80 mg/m^2) and topotecan (3 mg/m^2/week), N=57

Abbreviations: AUC = area under the curve; AURELIA = Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer; CALYPSO = Caelyx in Platinum Sensitive Ovarian Patients; HER2 = human epidermal growth factor receptor; ICON6 = International Collaborative for Ovarian Neoplasia; OCEANS = Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease; PENELOPE = Pertuzumab in Platinum-Resistant Low Human Epidermal Growth Factor Receptor 3 (HER3) mRNA Epithelial Ovarian Cancer; PLD = pegylated liposomal doxorubicin ; RCT = randomized controlled trial; TRINOCA-1 = Trebananib in Ovarian Cancer-1; VEGF = vascular endothelial growth factor receptor.

Serous Histology Recurrent Ovarian Cancer

There were five phase 2 trials [55,58-61,62,70] and one phase 3 trial [13] that included women with serous histology and recurrent ovarian cancer. The Ledermann study was represented by four papers [58-61]. All the trials except for the Ledermann et al. study were powered to detect a difference in treatment effects for PFS [13,55,62,70]. The 2012 study by Ledermann et al. had a p-value set at p<0.20 [58] and was not powered to detect a difference. The trial by Kaye et al. included patients with different histologies, but 75% of the patients had a serous subtype and all patients were either *BRCA* 1 or 2 mutation carriers; therefore, it was included in this group [55]. The 2014 article by Ledermann et al. is a subgroup analysis of *BRCA* patients from the 2012 study [59-61]. Olaparib is the intervention in all of the phase 2 trials and since it was compared with different agents a meta-analysis was not feasible.

Only the phase 3 study by Mirza et al. investigated the use of niraparib in a serous population [13]. The studies in this group were assessed using GRADE and were found to be of moderate quality. The results are reported in Tables 4-2 and 4-3.

Progression-Free Survival

Four trials had PFS as their primary outcome and three were powered to detect a meaningful difference [13,62,70]. All trials were conducted in platinum-sensitive patients. In the phase 3 trial by Mirza et al., niraparib significantly prolonged PFS in platinum-sensitive patients when compared with a placebo in patients with no germline *BRCA* mutations (HR, 0.45; 95% CI, 0.34 to 0.61; p<0.001) [13].

In the phase 2 trial by Oza et al., olaparib (200 mg capsules twice daily), paclitaxel, and carboplatin followed by olaparib monotherapy (400 mg capsules twice daily) until progression was compared with paclitaxel and carboplatin. PFS was significantly longer in patients receiving olaparib (HR, 0.51; 95% CI, 0.34 to 0.77; p=0.0012) [70]. In this study, PFS was analyzed by a masked, independent panel of experts [70].

The trial by Liu et al. which examined olaparib against olaparib and cediranib showed that patients in the combination arm had a higher PFS rate (9.0 months vs. 17.7 months; HR, 0.42; 95% CI, 0.23 to 0.76; p=0.005) [62]. The 2012 study by Ledermann et al. compared olaparib with placebo. PFS was 8.4 months in the olaparib group and 4.8 months for the placebo group (HR, 0.35; 95% CI, 0.25 to 0.49; p<0.001) [61].

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Overall Survival

For olaparib, the trial by Oza et al. found no significant difference in OS (HR, 1.17; 95% CI, 0.79 to 1.73; p=0.44) and overall response rate (p=0.42) [70]. In the 2012 Ledermann et al. study, the analysis of OS showed no significant difference between groups with olaparib (29.8 vs. 27.8 months; HR, 0.73; 95% CI, 0.55 to 0.96; nominal p=0.025). The threshold for significance in this study was p<0.0095 and it was not met [61].

OS was not mature and could not be reported in the Liu et al. trial examining cediranib and olaparib [62] and the Mirza et al. trial examining nirparib [13].

Response Rate

The response rate for the Oza et al. trial was not significant (p=0.42) as the proportion of patients with an objective response was similar between groups [70]. The trial by Liu et al., which examined olaparib against olaparib and cediranib, showed that patients in the combination arm had a higher response rate (47.8% vs. 79.6%; p=0.002) [62]. The Ledermann et al. 2012 study showed the following percentages for response rate: 12% for the olaparib group and 4% for the placebo group [58].

Table 4-2. Results for patients with a serous histology

Reference	Intervention	PFS	OS	Response Rate
Mirza [13] 2016-12-02 Phase 3 No germline mutation	Niraparib, N=234 Placebo, N=116	9.3 months 3.9 months HR 0.45; 95% CI 0.34 to 0.61; p<0.001	Not yet mature	NR
Oza [70] 2015 Phase 2	Olaparib 200 mg + paclitaxel + carboplatin, then olaparib (400 mg) maintenance until progression, N=81 Paclitaxel + carboplatin then no further treatment N=81	12.2 months (95% CI 9.7-15.0) 9.6 months (95% CI 9.1-9.7) HR 0.51 (95% CI 0.34-0.77); p=0.0012	33.8 months 37.6 months HR 1.17 (95% CI 0.79-1.73); p=0.44	52 (64%) 47 (58%) p=0.42
Liu [62] 2014 Phase 2	Olaparib capsules 400 mg, N=46 Cediranib 30 mg and olaparib capsules 200 mg N=44	9.0 months (95% CI 5.7-16.5) 17.7 months (95% CI 14.7-not reached) HR 0.42, 95% CI 0.23-0.76; p=0.005	Not yet mature	22 (47.8%) 35 (79.6%) (odds ratio 4.24, 95% CI 1.53-12.22; p=0.002)
Ledermann [58,61] 2012 Phase 2	olaparib 400 mg N= 136 placebo N=129	8.4 months 4.8 months HR 0.35; 95% CI, 0.25 to 0.49; p<0.001	29.8 months 27.8 months HR 0.73; 95% CI, 0.55 to 0.96; nominal P=0.025	12% 4%

Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival

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Serous Subtype and *BRCA* Mutations

The trials by Mirza, Oza and Ledermann [13,59,70] analyzed their results by subgroups of patients that had *BRCA* mutations, and the study by Kaye et al. [55] only included patients with *BRCA* 1 or 2 mutations. The three subgroup analyses included patients with platinum-sensitive ovarian cancer Ledermann [13,59,70] and the trial by Kaye et al. [55] included patients with recurrent ovarian cancer.

Progression-Free Survival

The phase 3 study by Mirza et al. demonstrated that in patients with germline *BRCA* mutations, niraparib significantly prolonged PFS compared with placebo (HR, 0.27; 95% CI, 0.17 to 0.41; p<0.001) [13].

The study by Oza et al. found a statistically significant improvement in PFS for olaparib combined with paclitaxel and carboplatin (N=20) compared with paclitaxel and carboplatin (N=21) (HR, 0.21; 95% CI, 0.08 to 0.55; p=0.0015) [70]. In the Ledermann et al. subgroup analysis that compared olaparib (n=131) with placebo (n=123), PFS was also significant for patients being treated with olaparib, 11.2 months vs. 4.3 months for the olaparib group vs. the placebo group (HR, 0.18; 0.10 to 0.31; p<0.0001) [59]. The study by Kaye et al. compared two different doses of olaparib (200 mg and 400 mg twice daily) to PLD. However, there was no statistically significant difference in PFS (HR, 0.88; 95% CI, 0.51 to 1.56; p=0.66) for combined olaparib doses vs. PLD [55].

Overall Survival

In both the Oza and Ledermann trials, OS was not statistically significant (Oza et al.: HR, 1.28; 95% CI, 0.39 to 4.18; p=0.69 [70]; Ledermann et al.: HR, 0.73; 95% CI, 0.45 to 1.17; p=0.19 [59]). In the study by Kaye et al., HRs for PLD vs. olaparib 200 mg and 400 mg were 0.66 (95% CI, 0.27 to 1.55) and 1.01 (95% CI, 0.44 to 2.27), respectively [55].

Response Rate

Only the study by Kaye et al. provided response rates: 25% for olaparib 200 mg, 31% for olaparib 400 mg, and 18% for PLD [55].

Table 4-3. Olaparib in *BRCA* 1 or 2 patients

Reference	Intervention	PFS	OS	Response Rate
Mirza [13] 2016-12-02 Phase 3 With germline mutaion	Niraparib, N=138 Placebo, N=65	21.0 months 5.5 months HR 0.27 (95% CI 0.17 to 0.41); p<0.001	Not yet mature	NR
Oza [70] 2015 Phase 2 Patients with a BRCA mutation	Olaparib 200 mg + paclitaxel + carboplatin, then olaparib (400 mg) maintenance until progression, N=20 Paclitaxel + carboplatin then no further treatment N=21	HR 0.21 (95% CI 0.08 to 0.55); p=0.0015.	HR 1.28 (95% CI 0.39 to 4.18); p=0.69	NR
Ledermann [59,61] 2014 Phase 2	Olaparib 400 mg N=131	11.2 months (95% CI 8.3 to not calculable)	34.9 months	NR

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	Placebo, N=123	4.3 months (95% CI 3.0 to 5.4); HR 0.18; 95% CI 0.10 to 0.31; p<0.0001	31.9 months, HR 0.73 (95% CI 0.45 to 1.17); nominal p=0.19	
Kaye [55] 2012 Phase 2 Patients with *BRCA* 1 or *BRCA* 2	Olaparib 200 mg N=32 Olaparib 400 mg N=32 PLD 50 mg/m^2 N=33	6.5 months (95% CI, 5.5 to 10.1 months) 8.8 months (95% CI, 5.4 to 9.2 months), 7.1 months (95% CI, 3.7 to 10.7 months) HR 0.88 (95% CI, 0.51 to 1.56); p=0.66 for combined olaparib doses versus PLD	9 deaths 11 deaths 13 deaths HR for PLD versus olaparib 200 mg 0.66 (95% CI 0.27 to 1.55) and 400 mg 1.01 (95% CI 0.44 to 2.27)	25% 31% 18%

Abbreviations: *BRCA* 1 or 2 = breast cancer gene 1 or 2; CI = confidence interval; HR = hazard ratio; NR = not reported; OS = overall survival; PLD = pegylated liposomal doxorubicin; PFS = progression-free survival

Adverse Events and Quality of Life

Adverse events and QOL are reported in Table 4-4. Treatments are comparable; however, in the Kaye et al. study, one patient in the olaparib 200 mg group died as a result of a cerebrovascular accident, which was considered to be possibly related to olaparib treatment, but deep vein thrombosis and concurrent anticoagulation treatment may have contributed. Another patient receiving olaparib 200 mg died as a result of myelodysplastic syndrome considered by the investigator to be related to olaparib; however, this patient had received extensive chemotherapy [55].

Table 4-4. Adverse events and quality of life for serous studies

Reference	Adverse events and Quality of Life		
Mirza [13] 2016	Grade 3 or 4 (%)	Niraparib	Placebo
	Nausea	11 (3.0)	2 (1.1)
	Thrombocytopenia	124 (33.8)	1 (0.6)
	Fatigue	30 (8.2)	1 (0.6)
	Neutropenia	72 (19.6)	3 (1.7)
	Abdominal pain	4 (1.1)	3 (1.7)
	Hypertension	30 (8.2)	4 (2.2)
	Quality of Life: Patient-reported outcomes were similar for both groups		
Oza [70] 2015	Grade 3 or 4 (%)	Olaparib + chemo	Chemo
	Fatigue	6 (7)	3 (4)
	Neutropenia	35 (43)	26 (35
	Anemia	7 (9)	5 (7)
	Thrombocytopenia	5 (6)	6 (8)
	Leukopenia	4 (5)	4 (5)
	Quality of Life: There were no significant differences in improvement or worsening rates between the olaparib treatment groups and the PLD group for the FACT-O Symptom Index and Trial Outcome Index scores. However, a higher improvement rate was noted for olaparib 400 mg compared with PLD for the total FACT-O score (odds ratio, 7.23; 95% CI, 1.09 to 143.3; p=0.039)		
Liu [62] 2014	Grade 3 and 4 (%)	Olaparib	Cediranib

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	Hypertension	0	18 (39)
	Diarrhea	0	10 (23)
	Fatigue	5 (11)	12 (27)
Ledermann [59-61] 2014 Phase 2	In both arms most of the patients reported no change (81%) on the TOI and other quality of life instruments. There was no statistically significant difference in time to worsening or improvement in rates in the TOI, FOSI and FACTO-O measures for *BRCA* mutation and germline *BRCA* mutation patients		
Kaye [55] 2012	Grade 3 and 4 (%)	Olaparib 200 mg	Olaparib 400 mg	Cediranib
	Nausea	1 (3)	2 (6)	2 (6)
	Fatigue	1 (3)	3 (9)	3 (9)
	Constipation	2 (6)	0	0
	Anemia	2 (6)	4(13)	0
	Palmar-plantar erythrodysesthesia syndrome	0	0	12 (38)
	Quality of Life: There were no significant differences in health-related quality of life among the treatment groups. However, the olaparib group showed a higher improvement rate compared with cediranib, p=0.039			
Ledermann [58,60] 2012	Grade 3 and 4 (%)	Olaparib	Placebo	
	Fatigue	9 (6.6)	4 (3.1)	
	Diarrhea	3 (2.2)	2 (2.3)	
	Abdominal pain	2 (1.5)	4 (3.1)	
	Anemia	7 (5.1)	1 (0.8	
	Quality of life: No differences between groups in patient-reported outcomes in quality of life questionnaires.			

Abbreviations: Chemo = chemotherapy; CI = confidence interval; FACT-O = Functional Assessment of Cancer Therapy-Ovarian; FOSI = A FACT-Ovarian Symptom Index (a subset of FACT-O containing 8 items); PLD = pegylated liposomal doxorubicin; TOI = Trial outcome index

Recurrent Ovarian Cancer – Non-Platinum-Based Treatment

There were five studies that looked at recurrent ovarian cancer. Two were phase 3 studies [65-67] and three were phase 2 studies [49,54,68]. One phase 3 study is represented by two papers [66,67]. All the trials were powered to detect a difference in treatment effects in PFS [49,54,65,66,68]. The intervention and control arms of these trials were heterogeneous; therefore, no meta-analysis was possible. Three studies assessed trebatinib, but the doses were inconsistent [54,65,66]. The studies in this group were assessed using GRADE and were found to be of moderate quality. The results are reported in Tables 4-5 and 4-6. None of the studies examined a platinum agent.

Progression-Free Survival

An open label, phase 2 study conducted in 2016 by Monk et al. compared bevacizumab with bevacizumab and fosbretabulin. Patients in the combination arm had a longer PFS (4.8 months vs. 7.3 months; HR, 0.69; 90% two-sided CI, 0.47 to 1.00; one-sided p=0.05) [68]. The 2014 Monk et al. phase 3 study, TRINOVA, which examined paclitaxel and trebananib 15 mg/kg showed a longer and statistically significant PFS with trebananib and paclitaxel (7.2 months vs. 5.4 months for paclitaxel and placebo; HR, 0.66; 95% CI, 0.57 to 0.77; p<0.0001) [66]. In the other phase 2 trial that examined trebananib, (at lower doses) and paclitaxel, PFS was longer, but not statistically significant. The HR for both arms (10 mg/kg and 3 mg/kg) combined compared with the control arm was 0.76 (95% CI, 0.52 to 1.12; p=0.165) [54]. The 2017 phase 3 ENGOT-ov-6/TRINOVA study by Marth et al. did not show any difference in PFS between arms (HR, 0.92; 95% CI, 4.8 to 8.2; p=0.57) [65]. The study by Coleman et al. comparing docetaxel

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and vandetanib with single-agent docetaxel was not significant (HR, 0.99; 80% CI, 0.79 to 1.26; p=0.49) [49].

Overall Survival

In the 2017 phase 3 ENGOT-ov-6/TRINOVA study by Marth et al., OS was 19.4 months with trebananib and 17.0 months with placebo; however, this was not significant (HR, 0.94; 95% CI, 0.64 to 1.39; p=0.76) [65]. OS was 24.6 months with bevacizumab and fosbretabulin and 22.0 months with bevacizumab in the 2016 Monk et al. trial; however, it is not known whether this was significant since no p-value was reported [68]. In both studies that examined trebananib, OS was not significant. HRs were 0.95 (95% CI, 0.81 to 1.11; p=0.52) for the phase 3 study by Monk et al. [67], 0.60 (95% CI, 0.34 to 1.06; p=0.081) for trebananib 10 mg/kg compared with placebo, and 0.77 (95% CI, 0.45 to 1.31; p=0.330) for 3 mg/kg compared with placebo [54]. The OS in the study by Coleman et al. was also not significant (HR, 1.25; 80% CI, 0.93 to 1.68; p=0.83) [49].

Response Rate

The response rate was significant in the 2017 phase 3 ENGOT-ov-6/TRINOVA study by Marth et al.; 46% in the trebananib group versus 21% in the placebo group (p<0.001) [65]. The response rates were not significant for any of the four trials and are reported in Table 4-5.

Table 4-5. Recurrent ovarian cancer

Reference	Intervention	Progression-Free Survival	Overall Survival	Response Rate
Marth [65] 2017 Phase 3 ENGOT-ov-6/TRINOVA	Trebananib + PLD N=114 Placebo + PLD N=109	7.6 months 7.2 months HR=0.92; 95% CI, 4.8-8.2; P=0.57	19.4 months 17.0 months HR 0.94; 95% CI 0.64-1.39; P=0.76	46% 21% P<0.001
Monk [68] 2016 Phase 2	Bevacizumab, N=53 Bevacizumab + fosbretabulin, N=54	4.8 months 7.3 months HR 0.69; 90% two-sided CI, 0.47 to 1.00; one-sided P=0.05	22.0 months 24.6 months HR 0.85; 90% CI 0.54 to 1.34)	28.2% among 39 patients with measurable disease 35.7% among 42 patients with measurable disease
Monk [66,67] 2014 Phase 3 TRINOVA-1	Paclitaxel and trebananib 15 mg/kg, N=461 Paclitaxel and placebo, N=458	7.2 months 5.4 months HR 0.66; 95% CI 0.57 to 0.77; p<0.0001	19.3 months 18.3 months HR 0.95, 95% CI 0.81 to 1.11; p=0.52	38% in patients with measurable lesions 30% in patients with measurable lesions
Karlan [54] 2012 Phase 2	Paclitaxel + trebananib 10 mg/kg (Arm A), N=53 Paclitaxel + trebananib 3 mg/kg (Arm B), N=53 Paclitaxel and placebo (Arm C), N=55	7.2 months (95% CI, 5.3 to 8.1 months) 5.7 months (95% CI, 4.6 to 8.0 months) 4.6 months (95% CI, 1.9 to 6.7 months)	22.5 months 20.4 months 20.9 months Arm A vs. placebo, HR 0.60 (95% CI 0.34 to 1.06); p=0.081	37% 19% 27%

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		HR for arms A and B combined vs. Arm C was 0.76 (95% CI, 0.52 to 1.12; p=0.165)	Arm B vs. placebo, HR 0.77 (95% CI 0.45 to 1.31); p=0.330	
Coleman [49] 2014 Phase 2 SWOG S0904	Docetaxel and vandetanib, N=63 Docetaxel N=63	3.0 months 3.5 months HR 0.99 (80% CI 0.79 to 1.26); p=0.49	14 months 18 months HR 1.25 (80% CI 0.93 to 1.68); p=0.83	5 (9%) 6 (12%)

Abbreviations: CI = confidence interval; HR = hazard ratio; PLD = pegylated liposomal doxorubicin

Adverse Events and Quality of Life

Adverse events and QOL are reported in Table 4-6.

Table 4-6. Adverse Events and Quality of Life

Study	Adverse events and Quality of Life			
Marth [65] 2017 Phase 3 ENGOT-ov-6/TRINOVA	Grade 3 & 4, N (%) Stomatitis Fatigue Diarrhea Dyspnea Hypokalemia Neutropenia Anemia Pleural effusion	Trebananib 8 (7) 8 (7) 4 (4) 1 fatal 5 (5) 9 (8) 9 (8) 4 (4) 6 (5)	Placebo 6 (6) 6 (6) 5 (5) 5 (5) 1 fatal 3 (3) 17 (16) 4 (4) 5 (5) 1 fatal	
	Quality of Life: When compared with placebo, trebananib did not show a decrease in quality of life.			
Monk [68] 2016 Phase 2	Grade 3 and higher adverse events were more frequent in the combination arm of bevacizumab plus fosbretabulin than in bevacizumab-only arm for hypertension (35% vs. 20%). There was one grade 3 thromboembolic event in the combination arm and one intestinal fistula in the bevacizumab-only arm.			
Monk [66] 2014 Phase 3 TRINOVA-1	Grade 3 & 4, N (%) Localized edema Nausea Fatigue Abdominal pain Neutropenia Anemia Ascites Dyspnea	Trebananib 24 (5) 8 (2) 15 (3) 21 (4) plus one grade 5 event 26 (5) 5 (1) 52 (11) 10 (2)	Placebo 4 (1) 6 (1) 17 (4) 21 (4) 40 (9) 19 (4) 34 (8) 5 (1) plus one grade 5 event	
	Quality of Life: No change in patient-reported outcomes between groups on FACT-O, OCS, and EQ5D.			
Karlan [54] 2012 Phase 2	Grade 3 & 4 N (%) Peripheral neuropathy Dyspnea GI perforation	Trebananib 10 mg/kg + paclitaxel 5 (10) 1 (2) 0	Trebananib 3 mg/kg + paclitaxel 1 (2) 5 (9) 0	Paclitaxel + placebo 2 (4) 2 (4) 1 (2)

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	Venous thromboembolic events	3 (6)	2 (4)	5 (9)
	Hypokalemia	6 (12)	6 (11)	2 (4)
Coleman [49] 2014 Phase 2 SWOG S0904	Grade 3 & 4, N (%)	Docetaxel + vandetanib	Docetaxel	
	Anemia	2 (3)	1 (1.5)	
	Febrile neutropenia	1 (1.6)	0	
	Neutrophil count decreased	28 (46)	32 (50)	
	White blood cell decreased	20 (33)	20 (31)	
	Fatigue	5 (8)	6 (9)	

Abbreviations: EQ5D = EuroQOL EQ-5D; FACT-O = Functional Assessment of Cancer Therapy-Ovarian; GI = gastrointestinal; OCS = ovarian cancer-specific subscale

Platinum-Sensitive Recurrent Ovarian Cancer

There were seven RCTs in platinum-sensitive populations. There were four phase 3 trials [11,12,14,64,77] and three phase 2 trials [48,56,74]. The OCEANS trial had two publications [11,14] for the one study. All of the trials were evaluated using GRADE and were found to be of moderate quality. However, these studies all investigated different agents, and therefore were too heterogeneous to be assessed as part of a meta-analysis. The results of the studies are reported in Table 4-7.

Progression-Free Survival

Five of the studies had PFS as the primary endpoint [11,12,48,56,77] and four of the studies were adequately powered to detect a difference in treatment effects based on PFS [11,12,56,77]. The CALYPSO trial by Mahner et al. was a subset analysis of 'very platinum-sensitive' patients from a non-inferiority trial and therefore was likely not powered appropriately given the reduced sample size [2,64]. Overall, a statistically significant beneficial effect of the experimental arm was shown in the OCEANS, ICON6, Schwandt et al., and Alvarez Secord et al. trials [11,12,48,74]. In the OCEANS trial, the median PFS in the bevacizumab and carboplatin arm was 12.4 months (95% CI, 11.4 to 12.7) and in the chemotherapy arm it was 8.4 months (95% CI, 8.3 to 9.7) (HR, 0.48; 95% CI, 0.39 to 0.61; p<0.0001) [11]. In the ICON6 trial, the main analysis was between Arm C compared with Arm A (referent), which showed a median PFS in Arm C of 11.0 months (95% CI, 10.4 to 11.7), and in Arm A of 8.7 months (95% CI, 7.7 to 9.4) (HR, 0.56; 95% CI, 0.44 to 0.72, p<0.0001) [12]. The trial by Schwandt et al. demonstrated a median 5.6-month PFS time with sorafenib and 16.8 months with sorafenib, carboplatin, and paclitaxel (p=0.012) [74]. The trial by Alvarez Secord et al., which was originally designed as a phase 3 study but was switched to a phase 2 study because of low accrual, demonstrated a longer PFS with a combination of docetaxel and carboplatin compared with a sequential administration of docetaxel and carboplatin (13.7 months vs. 8.4 months; HR, 1.62; 95% CI, 1.08 to 2.45; p=0.02) [48]. No difference was seen in the CALYPSO, Vergote, and Kaye trials [56,64,77]. A summary of the critical outcome of PFS in platinum-sensitive populations is reported in Table 4-7.

Table 4-7. Progression-free survival among platinum-sensitive trials

Study	Treatment	Progression-Free Survival	Hazard Ratio and P value

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*Ledermann [12] ICON6 2016 Phase 3	Arm A: platinum-based CT + placebo, then placebo during the maintenance phase, N=118 Arm B: platinum-based CT + cediranib, then placebo during the maintenance phase, N= 174 Arm C: once-daily oral cediranib during both phases, N= 164	8.7 months (95% CI 7.7–9.4) 9.9 months (95% CI 9.4–10.5) 11.0 months (95% CI 10.4–11.7)	0.56 (95% CI 0.44–0.72); p<0.0001 (for arms A vs. C)
Vergote [77] 2016 Phase 3	Placebo + carboplatin/paclitaxel or docetaxel, N=352 Farletuzumab 1.25 mg/kg + carboplatin paclitaxel or docetaxel, N=376 Farletuzumab 2.5 mg/kg + carboplatin/paclitaxel or docetaxel, N=363	9.0 months 9.5 months 9.7 months	Farletuzumab 1.25 vs placebo: 0.99 (95% CI0.81-1.21) Farletuzumab 2.5 vs. Placebo: 0.86 (95% CI 0.70-1.06)
Mahner [64] CALYPSO 2015 Phase 3 (subset of a non-inferiority trial)	Carboplatin + PLD, N=131 Carboplatin + paclitaxel, N=128	12.0 months 12.3 months	1.05 (95% CI, 0.79–1.40); p=0.73 for superiority
Aghajanian [11] OCEANS 2012 Phase 3	Gemcitabine + carboplatin + bevacizumab, N= 242 Gemcitabine + carboplatin + placebo, N=242	12.4 months 8.4 months	0.48 (95% CI, 0.39–0.61); p<0.0001
Schwandt [74] 2014 Phase 2	Sorafenib, N=14 Sorafenib + carboplatin + and paclitaxel, N=28	5.6 months 16.8 months	p=0.012
Alvarez Secord [48] 2012 Phase 2	Docetaxel + carboplatin (combination arm cDC); N= 74 Docetaxel followed by carboplatin (sequential arm sDC); N=74	13.7 months (95% CI, 9.9-16.8) 8.4 months (95% CI, 7.1-11.0 months)	1.62 (95% CI 1.08-2.45) P=0.02
Kaye [56] 2013 Phase 2	Pertuzumab 840 mg loading dose followed by 420 mg and either paclitaxel or gemcitabine and carboplatin at the investigators discretion, N=74 Above CT without pertuzumab, N=75	34.1 weeks 37.3 weeks	1.16 (80% CI 0.90-1.49); p=0.4487

Abbreviations: CI = confidence interval; CT = chemotherapy; PLD = pegylated liposomal doxorubicin
*Due to a drug shortage, the primary outcome in this trial was changed to progression-free survival between Arms A and C

Overall Survival and Response Rate

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The CALYPSO study was a non-inferiority study and had OS as its primary endpoint [64]. However, there were no studies that found a significant difference in OS in platinum-sensitive studies. The results are reported in Table 4-8.

The OCEANS study found a significant difference in response rate with the use of gemcitabine, carboplatin and bevacizumab [14] and so did the trial by Schwandt et al. with sorafenib, carboplatin and paclitaxel [74].

Table 4-8. Overall survival in platinum-sensitive trials

Study	Treatment	Overall Survival	Response rate
*Ledermann [12] ICON6 2016 Phase 3	Arm A: platinum-based CT + placebo, then placebo for maintenance, N=118 Arm B: platinum-based CT + cediranib, then placebo for maintenance, N=174 Arm C: once-daily oral cediranib during both phases, N=164	Overall survival data are immature: 21.0 months (95% CI 17.7–27.6) in Arm A 26.3 months (95% CI 23.8–30.0) in Arm C HR 0.77 (95% CI 0.55–1.07), p=0.11	NR
Vergote [77] 2016 Phase 3	Placebo + carboplatin/ paclitaxel or docetaxel, N=352 Farletuzumab 1.25 mg/kg + carboplatin/paclitaxel or docetaxel, N=376 Farletuzumab 2.5 mg/kg + carboplatin/paclitaxel or docetaxel, N=363	29.1 months 28.7 months 32.1 months HR 0.99 and 0.88; for farletuzumab 1.25 and 2.5 vs. placebo, respectively	NR
Mahner [64] CALYPSO 2015 Phase 3 (subset of a non-inferiority trial)	Carboplatin + PLD, N=131 Carboplatin + paclitaxel, N=128	40.2 months 43.9 months HR = 1.18, (95% CI, 0.85–1.63); p=0.33 for superiority	42% 38% p=0.46
Aghajanian [14] OCEANS 2012 Phase 3	Gemcitabine + carboplatin + bevacizumab, N=242 Gemcitabine + carboplatin + placebo, N=242	33.6 months 32.9 months HR 0.95; log-rank p=0.65	21.1% (ORR, 78.5% [190 of 242]) 57.4% (139 of 242); p=0.0001
Schwandt [74] 2014 Phase 2	Sorafenib, N=14 Sorafenib + carboplatin + paclitaxel, N=28	25.6 months 25.9 months p=0.974	15% 61% p=0.014
Alvarez Secord [48] 2012 Phase 2	Docetaxel + carboplatin (combination arm cDC); N=74	33.2 months	55.4%

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	Docetaxel followed by carboplatin (sequential arm sDC), N=74	30.1 months p=0.2	43.3%
Kaye [56] 2013 Phase 2	Pertuzumab 840 mg loading dose followed by 420 mg and either paclitaxel or gemcitabine and carboplatin at the investigators' discretion, N=74 Above CT without pertuzumab, N=75	28.2 months Not yet estimable	NR

Abbreviations: CI = confidence interval; CT = chemotherapy; HR = hazard ratio; NR = not reported; ORR = objective response rate; PLD = pegylated liposomal doxorubicin
*Due to a drug shortage, the primary outcome in this trial was changed to progression-free survival between Arms A and C

Adverse Events and Quality of Life

Adverse events and QOL are reported in Table 4-9. Adverse effects were consistent with those known for the systemic treatment. QOL was only measured in the Ledermann et al. and Alvarez Secord et al. trials. In the Alvarez Secord et al. trial, QOL was significantly different in the sequential arm compared with the combination arm (p=0.013), as measured by the Functional Assessment of Cancer Therapy–Trial Outcome Index for Ovarian cancer scores [48].

Table 4-9. Adverse events and quality of life

Study	Adverse events and quality of life				
Ledermann [12] ICON6 2016 Phase 3	Grade 3 or 4; N (%)	Chemotherapy + placebo	Cediranib	Placebo maintenance	Cediranib maintenance
	Fatigue	9 (8)	54 (16)	2 (1)	6 (6)
	Diarrhea	2 (2)	34 (10)	2 (1)	10 (12)
	Hypertension	4 (3)	38 (12)	8 (4)	5 (5)
	Febrile neutropenia	4 (3)	22 (7)	0	1 (1)
	Neutropenia	27 (23)	85 (26)	13 (7)	6 (6)
	Thrombocytopenia	3 (3)	25 (8)	4 (2)	2 (2)
	Quality of Life: Reported briefly on the global quality of life at 12 months measured by the Quality of Life Questionnaire C30. Among 235 patients with baseline and follow-up data, there was no difference between Arms C and A (Mean, 4.5 points higher in Arm C vs. Arm A, 95% CI, -2.0 to 11.0).				
Vergote [77] 2016 Phase 3	Grade 3 or 4; N (%)	Placebo	Farletuzumab 1.25 mg	Farletuzumab 2.5 mg	
	Neutropenia	145 (41.2)	167 (44.4)	139 (38.3)	
	Thrombocytopenia	28 (8.0)	49 (13.0)	42 (11.6)	
	Leukopenia	48 (13.6)	44 (11.7)	36 (9.9)	
	Febrile neutropenia	17 (4.8)	18 (4.8)	27 (7.4)	
	Anemia	35 (9.9)	38 (10.1)	37 (10.2)	
	Fatigue	10 (2.8)	15 (4.0)	17 (4.7)	
	Vomiting	8 (2.3)	15 (4.0)	10 (2.8)	
Mahner [64] CALYPSO 2015 Phase 3	Grade 3 or 4; N (%)	Carboplatin + PLD	Carboplatin + paclitaxel		
	Vomiting	5 (4)	7 (6)		

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(subset of a non-inferiority trial)	Diarrhea	2 (2)	3 (2)
	Infection without neutropenia	6 (5)	8 (6)
	Fatigue	10 (8)	6 (5)
	Leukopenia	10 (8)	25 (20)
	Neutropenia	36 (27)	51 (41)
	Anemia	7 (5)	4 (3)
Aghajanian [14] OCEANS 2012 Phase 3	Grade 3 or 4; N (%)	GC+BV arm	GC+PL arm
	Hypertension	43 (17.4)	1 (0.4)
	Neutropenia	51 (20.6)	51 (21.9)
	Proteinuria	21 (8.5)	2 (0.9)
	Venous thromboembolic events	10 (4.0)	6 (2.6)
	Fistula/abscess (any grade)	4 (1.6)	4 (1.6)
Schwandt [74] 2014 Phase 2	Grade 3 and 4, N (%)	S	S+C+P
	Anemia	0	4 (14)
	Neutropenia	1 (7)	22 (75)
	Thrombocytopenia	0	6 (22)
Alvarez Secord [48] 2012 Phase 2	Grade 3 and 4, N (%)	Combination	Sequential
	Anemia	3 (4.4)	3 (4.2)
	Neutropenia	25 (36.8)	8 (11.3)
	Thrombocytopenia	9 (13.2)	9 (12.7)
	Quality of Life: There were no significant differences in baseline scores between the groups. The sequential docetaxel + carboplatin group demonstrated significant improvements in FACT-O TOI scores compared with the combination cohort (p=0.013).		
Kaye [56] 2013 Phase 2	**Adverse events:** The most commonly reported NCI-CTC grade ≥3 adverse events were hematological toxic effects, with neutropenia being the most frequent single event. In the primary analysis, few patients (n=6, 8%) experienced adverse events during the pertuzumab infusion. Pertuzumab was not associated with increased cardiac toxicity. Treatment-related cardiac adverse events were infrequent in patients in both arms during the first six cycles of treatment (8% and 11% in Arms A and B, respectively).		

Abbreviations: FACT-O TOI = Functional Assessment of Cancer Therapy–Trial Outcome Index for Ovarian cancer; GC+BV = gemcitabine + carboplatin + bevacizumab; GC+PL = gemcitabine + carboplatin + placebo; NCI-CTC = National Cancer Institute Common Terminology Criteria; PLD = pegylated liposomal doxorubicin; S = sorafenib; S+C+P = sorafenib + carboplatin + paclitaxel

Platinum-Resistant or -Refractory Recurrent Ovarian Cancer

There were 12 RCTs in platinum-resistant or –refractory populations [15,50-52,57,63,69,71-73,76,78]. All of the trials were evaluated using the GRADE method and were found to be of moderate quality. However, they all investigated different agents and were too heterogeneous to be assessed as part of a meta-analysis.

Progression-Free Survival

Six studies had PFS as the primary outcome [15,51,57,63,69,71] and five studies were powered to detect a difference in PFS [15,51,57,69,71]. These results are reported in Table 4-10. A statistically significant difference was only seen in three trials [15,69,71]. The Pignata

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et al. trial showed that paclitaxel and pazopanib were superior over paclitaxel [71]. A statistically significant beneficial effect of the experimental arm was shown in the AURELIA trial for paclitaxel or topotecan and bevicizumab over paclitaxel or topotecan, and this was confirmed by independent radiological review [15,53]. The trial by Nauman et al. also saw a significant effect in the combination of vintafolide plus PLD over PLD alone [69]. None of the trials compared the same drugs and, therefore, the results are difficult to generalize.

Table 4-10. Progression-free survival in platinum-resistant/-refractory trials

Study	Treatment	Progression-Free Survival	Hazard Ratio and P value
Kurzeder [57] PENELOPE 2016 Phase 3	Pertuzumab (840 mg loading dose followed by 420 mg every 3 weeks), N=78 Placebo, N=78	4.3 months 2.6 months	0.74; 95% CI 0.50–1.11; p=0.14
Pujade-Lauraine [72] 2016 Phase 2	Volasertib, N=54 Investigator's choice of single-agent, non-platinum, cytotoxic chemotherapy, N=55	13.1 weeks 20.6 weeks	1.01; 95% CI 0.66–1.53
Pignata [71] 2015 Phase 2	Paclitaxel + pazopanib, N=37 Paclitaxel, N=37	6.35 months (95% CI 5.36-11.02) 3.49 months (95% CI 2.01-5.66)	0.42; 95% CI 0.25-0.69; p=0.0002
Fotopoulou [51] 2014 Phase 3	Carboplatin + phenoxodiol, N=70 Placebo + carboplatin, N=72	15.4 weeks 20.1 weeks	1.22; 95% CI 0.84-1.22 p=0.3
Pujade-Lauraine [15] 2014 AURELIA Phase 3 Investigator results Husain [53] 2016 AURELIA Phase 3 Independent radiological review results	Paclitaxel or topotecan and bevicizumab, N=179 Paclitaxel or topotecan, N=182 Paclitaxel or topotecan and bevicizumab, N=179 Paclitaxel or topotecan, N=182	6.7 months 3.4 months 8.1 months 3.9 months	0.48; 95% CI 0.38-0.60; p<0.001 0.48; 95% CI 0.37-0.63; p<0.0001
Tew [76] 2014 Phase 2	Aflibercept 2 mg/kg, N=109 Aflibercept 4 mg/kg, N=109	13.0 weeks 13.3 weeks	NR
Naumann [69] 2013 Phase 2	Vintafolide + PLD, N=109 PLD, N=53	5.0 months 2.7 months	0.63; 95% CI, 0.41-0.96; p=0.031
Vergote [78] 2013 Phase 2	Etirinotecan pegol 145 mg/m^2 Day 14, N=36 Day 21, N=35	4.1 months 5.3 months	NR

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Columbo [50] 2012 Phase 3	Patupilone, N=412 PLD, N=427	3.7 months for both arms	1.05; 95% CI 0.89-1.24
Gotlieb [52] 2012 Phase 2	Aflibercept, N=29 Placebo, N=26	6.3 (95% CI 5.9–10.9) 7.3 (6.3–14.0) weeks	NR
Rustin [73] 2011 Phase 2	Sagopilone as a 3-hour infusion, N=38 Sagopilone as a half-hour infusion, N=25	91 days 68 days	NR
Lortholary [63] CARTAXHY 2010 Phase 2	Paclitaxel, N=57 Paclitaxel + carboplatin, N=51 Paclitaxel + topotecan, N=57	3.7 months 4.8 months 5.4 months	Among the treatment arms: HR 0.922; 95% CI 0.765-1.111; p=0.46 Between monotherapy and combination therapy: HR 0.951; 95% CI 0.686-1.318; p=0.76

Abbreviations: CI = confidence interval; HR = hazard ratio; NR = not reported; PLD = pegylated liposomal doxorubicin

Overall Survival and Response Rate

Only the study by Columbo et al. was powered to detect a difference in OS [50]. Nevertheless, none of the studies showed a statistically significant difference between the arms. The results are reported in Table 4-11.

The response rate was significant in only the Pignata et al. trial for the paclitaxel and pazopanib arm (p=0.008). It should be noted that this was a small phase 2 trial [71].

Table 4-11. Overall survival and response rate in platinum-resistant/-refractory trials

Study	Treatment	Overall Survival	Response rate
Kurzeder [57] PENELOPE 2016 Phase 3	Pertuzumab (840 mg loading dose followed by 420 mg every 3 weeks), N=78 Placebo, N=78	Interim OS 10.3 months 7.9 months stratified HR 0.84; 95% CI 0.53-1.32; p=0.44	Not reported
Pujade-Lauraine [72] 2016 Phase 2	Volasertib, N=54 Investigator's choice of single-agent, non-platinum, cytotoxic chemotherapy, N=55	NR	13.0% 14.5%
Pignata [71] 2015 Phase 2	Paclitaxel + pazopanib, N=37 Paclitaxel, N=37	19.1 months 13.7 months HR 0.60; 95% CI 0.32-1.13; p=0.056	N=20 (56%) N=9 (25%) p=0.008
Fotopoulou [51] 2014 Phase 3	Carboplatin + phenoxodiol, N=70	38.3 weeks	0%

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	Placebo + carboplatin, N=72	45.7 weeks HR 1.2; 95% CI 0.83-1.73; p=0.33	1.4%
Pujade-Lauraine [15] AURELIA 2014 Phase 3	Paclitaxel or topotecan and bevicizumab, N=179 Paclitaxel or topotecan, N=182	16.6 months 13.3 months HR 0.85; 95% CI 0.66-1.08; p<0.174	30.9% 12.6%
Tew [76] 2014 Phase 2	Aflibercept 2 mg/kg, N=109 Aflibercept 4 mg/kg, N=109	59.0 weeks 49.3 weeks	1.7% 6.3%
Naumann [69] 2013 Phase 2	Vintafolide + PLD, N=109 PLD, N=53	Not powered for OS	18% 12%
Vergote [78] 2013 Phase 2	Etirinotecan pegol 145 mg/m^2 Day 14, N=36 Day 21, N=35	10 months 11.7 months	20% 19%
Columbo [50] 2012 Phase 3	Patupilone, N=412 PLD, N=427	13.2 months 12.7 months HR 0.93; 95% CI 0.79-1.09; p=0.195	64 (15.5%) 33 (7.9%)
Gotlieb [52] 2012 Phase 2	Aflibercept, N=29 Placebo, N=26	Estimate 16.0 weeks (95% CI 7.6-17.7) 12.9 weeks (95% CI 6.6-17.7)	
Rustin [73] 2011 Phase 2	Sagopilone as a 3-hour infusion, N=38 Sagopilone as a half-hour infusion, N=25	211 days 238 days	18% 13%
Lortholary [63] CARTAXHY 2010 Phase 2	Paclitaxel, N=57 Paclitaxel + carboplatin, N=51 Paclitaxel + topotecan, N=57	19.9 months 15.2 months 18.6 months (HR 1.080; 95% CI 0.873–1.336; p=0.29). Survival for the P arm compared with the combination arms was 19.9 months vs. 16.2 months, respectively (HR 1.282; 95% CI 0.879–1.870; p=0.20)	35% 37% 39%

Adverse Events

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Adverse events and QOL are reported in Table 4-12. One patient in the Pignata et al. study had ileal perforation in the paclitaxel and pazopanib group [71].

Table 4-12. Adverse events and quality of life

Study	*Adverse Events*			
Kurzeder [57] PENELOPE 2016 Phase 3	Grade 3 and 4, N (%)	Pertuzumab	Placebo	
	Fatigue	6 (7.8)	9 (11.8)	
	Neutropenia	24 (31.2)	16 (21.1)	
	Abdominal pain	2 (2.6)	2 (2.6)	
	Hypertension	4 (5.4)	3 (3.9)	
	Leukopenia	5 (6.5)	7 (9.2)	
Pujade-Lauraine [72] 2016 Phase 2	Grade 3 and 4, N (%)	Volasertib	Choice	
	Anemia	8 (14.8)	1 (1.8)	
	Neutropenia	24 (44.4)	3 (5.5)	
	Thrombocytopenia	9 (16.7)	2 (3.6)	
	Leukopenia	9 (16.7)	0	
	Quality of Life: Both arms showed similar effects on QOL. The hazard ratios for time to deterioration and endpoints favoured volasertib; however, the numbers of patients completing questionnaires were too small to show any valid conclusions.			
		Volasertib	Choice	HR (95% CI)
	Global Health/QOL	15 (27.8)	18 (32.7)	0.80 (0.40-1.61)
	Fatigue	14 (25.9)	14 (25.5)	0.78 (0.37-1.65)
	Pain	11 (20.4)	14 (25.5)	0.86 (0.39-1.93)
	Abdominal bloating	12 (22.2)	17 (30.9)	0.69 (0.33–1.47)
Pignata [71] 2015 Phase 2	Grade 3 and 4, N (%)	Paclitaxel	Paclitaxel and pazopanib	
	Anemia	5 (14)	2 (5)	
	Leukopenia	1 (3)	4 (11)	
	Neutropenia	1 (3)	11 (30)	
	Hypertension	0	3 (8)	
	Fatigue	2 (6)	4 (11)	
Fotopoulou [51] 2014 Phase 3	Grade 3 and 4, N (%)	Phenoxodiol	Placebo	
	Blood and lymphatic system disorders	8 (11.3)	10 (15.1)	
	Anemia	0	0	
	Leukopenia	0	0	
	Neutropenia	6 (8.5)	6 (9.1)	
	Thrombocytopenia	2 (2.8)	6 (9.1)	
	GI disorders	2 (2.8)	4 (6.1)	
	Diarrhea	0 (0.0)	1 (1.5)	
	Vomiting	1 (1.4)	2 (3.0)	
	Quality of Life: No significant differences between groups for QOL			
Pujade-Lauraine [15] AURELIA 2014 Phase 3	Grade 3 and 4, N (%)	Bev+CT	CT	
	GI perforation	3 (2)	0	
	Fistula	2 (1)	0	
	Bleeding	2 (1)	2 (1)	
	Thromboembolic event	9 (5)	8 (4)	
	Neutropenia	(16)	(17)	

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	Fatigue	(4)	(10)
	Quality of Life: There were significantly more patients in the BEV+CT arm that had at least a 15% improvement in abdominal symptoms at 8 to 9 weeks among those that completed a baseline questionnaire (BEV+CT, n=34/155 patients [21.9%] vs. CT, n=15/162 [9.3%], p=0.002), despite 35% of patients not having sufficient symptoms at baseline to allow for a 15% improvement. Similar results were shown when missing questionnaires were classified as 'no improvement' (N=361). When analysis was restricted to only those patients who had completed questionnaires at baseline and at 8/9 weeks follow-up (N=206), there was no difference in abdominal symptoms. Quality considerations include a disproportionate percentage of missing results in the CT arm that were classified as "not improved". There was no difference in health-related QOL when using the EORTC QLQ-C30 global health status at any time period up to 30 weeks between the study groups In a subgroup of 113 patients (31%) with ascites at baseline, nine patients (17%) treated with CT alone underwent paracentesis after starting study treatment compared with one patient (2%) receiving BEV-CT.		
Tew [76] 2014 Phase 2	Grade 3 and 4, N (%) Hypertension Fatigue Nausea Diarrhea Abdominal pain	Aflibercept 2 mg/kg 27 (25.5) 6 (5.7) 0 1 (0.9) 1 (0.9)	Aflibercept 4 mg/kg 30 (27.5) 4 (3.7) 1 (0.9) 3 (2.8) 1 (0.9)
	Quality of Life: No clinically relevant differences in FACT-O QOL.		
Naumann [69] 2013 Phase 2	Grade 3 and 4 N Anemia Leukopenia Neutropenia Thrombocytopenia Fatigue	Vintafolide + PLD 9 9 23 4 9	PLD 8 0 10 4 6
Vergote [78] 2013 Phase 2	Grade 3 and 4, N (%) Dehydration Diarrhea Fatigue Nausea Abdominal pain Neutropenia Vomiting	Etirinotecan pegol day 14 10 (27.8) 11 (30.6) 5 (13.9) 9 (25.0) 5 (13.9) 5 (13.9) 4 (11.1)	Etirinotecan pegol day 21 7 (20.0) 5 (14.3) 8 (22.9) 4 (11.4) 7 (20.0) 3 (8.6) 4 (11.4)
Columbo [50] 2012 Phase 3	Grade 3 and 4, N (%) Diarrhea Nausea Vomiting Abdominal pain Fatigue Neutropenia	Patupilone 103 (25.6) 33 (8.2) 32 (8.0) 31 (7.7) 42 (10.4) 12 (3.0)	PLD 9 (2.2) 24 (5.9) 24 (5.9) 35 (8.6) 34 (8.3) 41 (10.0)
Gotlieb [52]	Grade 3 and 4 N (%)	Aflibercept	Placebo

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2012 Phase 2	Vomiting Fatigue Abdominal pain Dyspnea Hypertension GI perforation/ fistula Venous thromboembolism	2 (7) 4 (13) 2 (7) 6 (20) 2 (7) 3 (10) 2 (7)	2 (8) 11 (44) 1 (4) 2 (8) 0 1 (4) 0	
Rustin [73] 2011 Phase 2	Grade 3 and 4, N (%) Anemia Neutropenia Thrombocytopenia	Sagopilone 3 hour 1 (4) 0 1 (4)	Sagopilone 30 min 1 (4) 1 (4) 1 (4)	
Lortholary [63] CARTAXHY 2010 Phase 2	Grade 3 and 4, N Leukopenia Neutropenia Anemia Thrombocytopenia Vomiting Fatigue	Paclitaxel 7 13 6 2 17 59	Paclitaxel + carboplatin 31 54 19 4 20 61	Paclitaxel + topotecan 27 42 29 7 25 70
	Quality of Life: Among symptom and functional scales, patients on paclitaxel experienced improvements in attitude to disease and insomnia and worsening of dyspnea and peripheral neuropathy; patients on paclitaxel + carboplatin experienced improvements in constipation, abdominal/GI symptoms, appetite loss, pain, and emotional functioning; and patients on paclitaxel + topotecan experienced improvements in pain and sexuality.			

Abbreviations: AURELIA = Avastin Use in Platinum-Resistant Ovarian Cancer; Bev+CT = bevacizumab with gemcitabine and carboplatin; CT = gemcitabine and carboplatin; EORTC = European Organisation for Research and Treatment of Cancer; FACT-O = Functional Assessment of Cancer Therapy-Ovarian; GI = gastrointestinal; PLD = pegylated liposomal doxorubicin; QLQ-C30 = Quality of Life Questionnaire Core 30; QOL = quality of life

DISCUSSION

This update of a previous PEBC guideline [1] for chemotherapy for recurrent EOC was undertaken to incorporate the findings of the newest RCTs. Thirty-six RCTs of 30 individual studies fully published since the last guidelines search in 2011 met the inclusion criteria [11-15,48-78].

As previously stated, PFS was one of the primary outcomes of interest in this guideline. The Working Group chose this outcome over OS in part because OS is a reflection of multiple sequential treatments and not a reflection of upfront treatment. Currently, there are insufficient data to conclude that PFS is a reasonable surrogate for OS in second- or third-line therapy trials; however, PFS may be a valuable outcome on its own in terms of symptom relief and as reported by some patients [79]. There exists some previously published guidance for making recommendations in this context. Ocana et al. (2011) suggests that three months is the minimum amount of PFS improvement that would be important to clinicians in the case of a reasonably well-tolerated drug [80]. The Society of Gynecologic Oncology recommends the following [79]:

- In the case of a statistically significant difference in PFS and QOL improvements, a potential therapeutic agent should be approved in the case of platinum-sensitive disease, and considered in the case of platinum-resistant disease.

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- Where PFS is statistically significant and there is a clinically meaningful magnitude of effect, an agent should be considered for either population.

Based on the evidence found in the systematic review, the critical outcome of PFS showed statistically significant improvement with BEV+CT compared with CT in two phase 3 trials. Recommendations regarding bevacizumab were determined by weighing the evidence for a significant benefit in the critical outcome of PFS against a higher frequency of adverse events [11,15]. A single trial looking at niraparib, a PARP inhibitor, demonstrates a significant difference in PFS [13].

Recurrent ovarian cancer is increasingly viewed as the 'chronic' model of cancer; therefore, the toxicity of treatment and health-related QOL were designated as important outcomes in this palliative setting [50]. Health-related QOL was reported in the AURELIA trial, with a statistically significant benefit for patients receiving the intervention. However, this was based on very low-quality evidence. When reviewing the evidence in aggregate, we accept low-quality of evidence for identifying harms according to the precautionary principle of "do no harm". Therefore, the recommendations can be considered conditional recommendations due to the trade-offs between the identified benefits (PFS and health-related QOL outcomes) and risks (adverse events), as shown in our evidence analysis and critical appraisal.

Our recommendations with regard to platinum-sensitive recurrent ovarian cancer are heavily weighted on our prior 2011 guideline recommendations [1]. Although new supporting evidence was identified as part of the OCEANS trial [11] in terms of a benefit on PFS, there was a toxicity profile that precluded a modified recommendation (Recommendation 3). Thus, for platinum-sensitive recurrent ovarian cancer, our prior recommendations are endorsed in this current guideline. With regard to platinum-resistant or –refractory recurrent ovarian cancer, we were able to only make a conditional recommendation based on the results of the AURELIA trial that took into account the clinical, harms, and health-related QOL outcomes [15,75].

Olaparib is an oral PARP inhibitor that has shown antitumour activity in patients with high-grade serous ovarian cancer. The European Medicines Agency Committee for Medicinal Products for Human Use has recommended approval of this drug for **maintenance** treatment for women with either a germline or somatic *BRCA* mutation-associated platinum-sensitive recurrent ovarian cancer after having a response to platinum-based chemotherapy, based on a post hoc analysis showing that patients in the target population who have a *BRCA* mutation have the greatest likelihood of benefitting [59]. Olaparib has been authorized in the European Union since December 2014 as maintenance therapy for patients with *BRCA* 1 or *BRCA* 2 mutations who have platinum-sensitive recurrent disease [81], and NICE in 2016 has recommended olaparib 'as an option' for platinum-sensitive recurrent ovarian cancer [33]. While this guideline did not search conference abstracts, the Working Group was aware of the results of the phase 3 SOLO2 trial presented in March 2017 at the Society of Gynecologic Oncology. This was a double-blind randomized trial where patients with platinum-sensitive relapsed ovarian cancer and a *BRCA* mutation were randomized to either olaparib or placebo. The results from a blinded independent central review showed that patients treated with olaparib had a longer PFS than patients treated with placebo (19.1 months vs. 5.5 months; HR, 0.30; 95% CI, 0.22 to 0.41; $p<0.0001$) [82,83].

Olaparib has not yet been recommended in the United States for this indication, and the results of further trials are anticipated.

CONCLUSIONS

This guideline includes results from newer phase 2 and 3 trials for the treatment of recurrent ovarian cancer. The body of evidence from trials that include olaparib and bevacizumab consistently show a benefit to PFS without a corresponding benefit to OS. The

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Working Group for this guideline designated PFS, which is associated with symptom control, as a critical outcome. Therefore, a finding of net benefit can be concluded based on significant PFS differences. However, this benefit is not without identified harms. Bevacizumab has been associated with increased risks of gastrointestinal perforation, and fistulae [15,75], and cediranib has been associated with increased fatigue, neutropenia, diarrhea, hypertension, febrile neutropenia, and thrombocytopenia [12]. Given that, patient involvement in the decision-making process must take into consideration the side effect profile of these medications within the context of an improved PFS but minimal change in OS.

There are numerous ongoing trials in VEGF inhibitors and PARP inhibitors, as well as other mediators of the tumour immune environment (see below). Although at present it is not possible to determine which of these interventions will prove to be significant, it is clear that the landscape of interventions in this setting is changing rapidly. We continue to encourage the involvement of patients in clinic trials to improve outcomes in this population.

Ongoing Clinical Trials

Protocol ID and Title	Study details
NCT00954174 Paclitaxel and Carboplatin or Ifosfamide in Treating Patients With Newly Diagnosed Persistent or Recurrent Uterine, Ovarian, Fallopian Tube, or Peritoneal Cavity Cancer	This randomized phase III trial studies paclitaxel and carboplatin to see how well it works compared with paclitaxel and ifosfamide in treating patients with newly diagnosed persistent or recurrent uterine, ovarian, fallopian tube, or peritoneal cavity cancer. Drugs used in chemotherapy, such as paclitaxel, carboplatin, and ifosfamide, work in different ways to stop the growth of tumour cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. It is not yet known whether paclitaxel is more effective when given with carboplatin or ifosfamide in treating patients with uterine, ovarian, fallopian tube, or peritoneal cavity cancer.
NCT02502266 Refractory Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (COCOS) (CCTG OVC.2)	This randomized phase II/III trial studies how well cediranib maleate and olaparib work when given together or separately, and compares them with standard chemotherapy in treating patients with ovarian, fallopian tube, or primary peritoneal cancer that has returned after receiving chemotherapy with drugs that contain platinum (platinum-resistant) or continued to grow while being treated with platinum-based chemotherapy drugs (platinum-refractory). Cediranib maleate and olaparib may stop the growth of tumour cells by blocking enzymes needed for cell growth. Drugs used in chemotherapy work in different ways to stop the growth of tumour cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. It is not yet known whether giving cediranib maleate and olaparib together may cause more damage to cancer cells when compared with either drug alone or standard chemotherapy.
NCT00565851 Carboplatin, Paclitaxel and Gemcitabine Hydrochloride With or Without Bevacizumab After Surgery in Treating Patients With Recurrent Ovarian Epithelial Cancer, Primary Peritoneal Cavity Cancer, or Fallopian Tube Cancer	This randomized phase III trial studies carboplatin, paclitaxel, and gemcitabine hydrochloride when given together with or without bevacizumab after surgery to see how well it works in treating patients with ovarian epithelial cancer, primary peritoneal cavity cancer, or fallopian tube cancer that has come back. Drugs used in chemotherapy, such as carboplatin, Paclitaxel, and gemcitabine hydrochloride work in different ways to stop the growth of tumour cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. Monoclonal antibodies, such as bevacizumab, may block tumour growth in different ways by targeting certain cells. It is not yet known whether combination chemotherapy is more effective when given with or without bevacizumab after surgery in treating patients with ovarian epithelial cancer, primary peritoneal cavity cancer, or fallopian tube cancer.
NCT02101788 Trametinib in Treating Patients With Recurrent or Progressive Low-Grade Ovarian Cancer or Peritoneal Cavity Cancer	This randomized phase II/III trial studies how well trametinib works and compares it to standard treatment with either letrozole, tamoxifen citrate, paclitaxel, pegylated liposomal doxorubicin hydrochloride, or topotecan hydrochloride in treating patients with low-grade ovarian cancer or peritoneal cavity cancer that has come back, become worse, or spread to other parts of the body. Trametinib may stop the growth of tumor cells by blocking some of

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	the enzymes needed for cell growth. It is not yet known whether trametinib is more effective than standard therapy in treating patients with ovarian or peritoneal cavity cancer.
NCT01281254 AMG 386 (Trebananib) in Ovarian Cancer (TRINOVA-2)	To determine if AMG 386 plus pegylated liposomal doxorubicin (PLD) is superior to placebo plus PLD as measured by progression-free survival (PFS) The hypothesis for this study is that AMG 386 plus PLD will prolong PFS compared with placebo plus PLD in women with recurrent partially platinum sensitive or resistant epithelial ovarian, primary peritoneal, or fallopian tube cancer.
NCT00382811 OVATURE (OVArian TUmor REsponse) A Phase III Study of Weekly Carboplatin With and Without Phenoxodiol in Patients With Platinum-Resistant, Recurrent Epithelial Ovarian Cancer (OVATURE)	The purpose of this project is to see if weekly carboplatin compared with phenoxodiol in combination with weekly carboplatin, is effective against late stage ovarian cancer and to see what, if any, side effects of treatment may result.
NCT00045461 Combination Chemotherapy With or Without Whole-Body Hyperthermia in Treating Patients With Recurrent Ovarian Epithelial, Fallopian Tube, or Peritoneal Cancer	Randomized phase II/III trial to compare the effectiveness of chemotherapy with or without whole-body hyperthermia in treating patients who have recurrent ovarian epithelial, fallopian tube, or peritoneal cancer.
NCT01611766 Surgery or Chemotherapy in Recurrent Ovarian Cancer (SOC 1 Trial)?	The purpose of this study is to evaluate the role of secondary cytoreduction (SCR) and validate the risk model of patient selection criteria in platinum-sensitive recurrent ovarian cancer.
NCT01837251 Evaluation of Optimal Treatment With Bevacizumab in Patients With Platinum-sensitive Recurrent Ovarian Cancer	Evaluation of the best therapeutic index for patients with platinum-sensitive ovarian cancer when treatment with bevacizumab and gemcitabine/carboplatin or with bevacizumab and PLD/carboplatin.
NCT02641639 FOCUS: PCC + Bevacizumab + CA4P Versus PCC + Bevacizumab + Placebo for Subjects With Platinum Resistant Ovarian Cancer	This is a multicenter, multinational, randomized, double-blind, 2-arm, parallel-group, Phase 2/3 study to evaluate the efficacy and safety of PCC plus bevacizumab and CA4P versus PCC plus bevacizumab and placebo in subjects with platinum-resistant ovarian cancers (prOC). Subjects with platinum-resistant, recurrent, epithelial ovarian, primary peritoneal or fallopian tube cancer will be randomized 1:1 to receive PCC plus bevacizumab and CA4P or PCC plus bevacizumab and placebo. Subjects will be stratified by selected chemotherapy (PLD vs. paclitaxel), platinum free interval (< 3 vs. 3 to 6 months from last platinum therapy to subsequent progression), and line of therapy (2nd vs. 3rd). This is a 2-part study, consisting of a phase 2, exploratory study (Part 1) followed by a phase 3, pivotal study (Part 2). Both parts of the study will have similar overall design. Approximately 80 subjects will be randomized into Part 1 and approximately 356 subjects will be randomized into Part 2.
NCT01684878 Pertuzumab in Platinum-Resistant Low Human Epidermal Growth Factor Receptor 3 (HER3) Messenger Ribonucleic Acid (mRNA) Epithelial Ovarian Cancer (PENELOPE)	This two-part, multicenter study will evaluate the safety, tolerability and efficacy of pertuzumab in combination with standard chemotherapy in women with recurrent platinum-resistant epithelial ovarian cancer. In the non-randomized Part 1 safety run-in, participants will receive pertuzumab plus either topotecan or paclitaxel. In the randomized, double-blind Part 2 of the study, participants will receive either pertuzumab or placebo in combination with chemotherapy (topotecan, paclitaxel, or gemcitabine).
NCT02446600 Olaparib or Cediranib Maleate and Olaparib Compared With Standard Platinum-Based Chemotherapy in Treating Patients With Recurrent Platinum-Sensitive Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (CCTG OVC.1)	This randomized phase III trial studies olaparib or cediranib maleate and olaparib to see how well they work compared with standard platinum-based chemotherapy in treating patients with platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer that has come back. Olaparib and cediranib maleate may stop the growth of tumour cells by blocking some of the enzymes needed for cell growth. Cediranib maleate may stop the growth of ovarian, fallopian tube, or primary peritoneal cancer by blocking the growth of new blood vessels necessary for tumor growth. Drugs used in chemotherapy, such as carboplatin, paclitaxel, gemcitabine hydrochloride, and pegylated liposomal

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	doxorubicin hydrochloride work in different ways to stop the growth of tumor cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. It is not yet known whether olaparib or cediranib maleate and olaparib is more effective than standard platinum-based chemotherapy in treating patients with platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer.
NCT00262990 Patupilone Versus Doxorubicin in Patients With Ovarian, Primary Fallopian, or Peritoneal Cancer	The objective of this study is to assess the safety and efficacy of patupilone compared to pegylated liposomal doxorubicin. Additionally, this study will assess the ability of patupilone to extend the survival time and potential beneficial effects in women who have nonresponsive or recurrent ovarian, primary fallopian, or primary peritoneal cancer.
NCT00043082 S0200 Carboplatin With or Without Doxil in Patients With Recurrent Ovarian Cancer	Randomized phase III trial to determine the effectiveness of carboplatin with or without liposomal doxorubicin in treating patients who have recurrent ovarian epithelial or primary peritoneal cancer.
NCT01840943 A Study to Compare CAELYX With Topotecan HCL in Patients With Recurrent Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy	The purpose of this study is to compare the effectiveness between CAELYX and topotecan hydrochloride (HCl) in Chinese participants with recurrent epithelial ovarian carcinoma following failure of first-line, platinum-based chemotherapy, who have received no more than one prior platinum-based regimen therapy.
NCT01081262 Carboplatin and Paclitaxel or Oxaliplatin and Capecitabine With or Without Bevacizumab as First-Line Therapy in Treating Patients With Newly Diagnosed Stage II-IV or Recurrent Stage I Epithelial Ovarian or Fallopian Tube Cancer	This randomized phase III trial studies carboplatin given together with paclitaxel with or without bevacizumab to see how well it works compared with oxaliplatin given together with capecitabine with or without bevacizumab as first-line therapy in treating patients with newly diagnosed stage II-IV, or recurrent (has come back) stage I epithelial ovarian or fallopian tube cancer. Drugs used in chemotherapy, such as carboplatin, paclitaxel, oxaliplatin, and capecitabine, work in different ways to stop the growth of tumour cells, either by killing the cells or by stopping them from dividing. Monoclonal antibodies, such as bevacizumab, may block tumour growth in different ways by targeting certain cells. It is not yet known which regimen of combination chemotherapy given together with or without bevacizumab is more effective in treating epithelial ovarian cancer or fallopian tube cancer.
NCT00327444 Study of the Effect of Intravenous AVE0005 (VEGF Trap) in Advanced Ovarian Cancer Patients With Recurrent Symptomatic Malignant Ascites	This study was designed to characterize the effect of aflibercept in participants with advanced chemoresistant ovarian cancer. Primary objective: Compare the effect of aflibercept (ziv-aflibercept, AVE0005, VEGF trap, ZALTRAP®) to placebo treatment on repeat paracentesis in symptomatic malignant ascites in participants with advanced ovarian cancer Secondary objectives: Safety, tolerability, paracentesis-related parameters, participant-reported outcome.
NCT00191607 A Randomized Trial for Patients With Platinum Resistant Ovarian, Fallopian or Primary Peritoneal Cancer.	This trial compares two chemotherapy agents for the treatment of recurrent ovarian, fallopian or primary peritoneal cancer in patients that have received and are no longer responding to platinum-based treatment. The purpose of this trial is to compare progression-free survival (PFS) between gemcitabine and liposomal doxorubicin. PFS is defined as the period from study entry until disease progression
NCT00002895 Early Chemotherapy Based on CA 125 Level Alone Compared With Delayed Chemotherapy in Treating Patients With Recurrent Ovarian Epithelial , Fallopian Tube, or Primary Peritoneal Cancer	RATIONALE: It is not yet known if treatment for recurrent ovarian epithelial, fallopian tube, or primary peritoneal cancer is more effective if it is begun when blood levels of CA 125 become elevated rather than waiting for other indicators of disease recurrence. PURPOSE: This randomized phase III trial is studying early chemotherapy based on blood levels of CA 125 alone to see how well it works compared to chemotherapy based on conventional clinical indicators in patients with recurrent ovarian epithelial, fallopian tube, or primary peritoneal cancer.
NCT01204749 TRINOVA-1: A Study of AMG 386 or Placebo, in Combination With Weekly	The purpose of this study is to determine if treatment with paclitaxel plus AMG 386 is superior to paclitaxel plus placebo in women with recurrent partially

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Paclitaxel Chemotherapy, as Treatment for Ovarian Cancer, Primary Peritoneal Cancer and Fallopian Tube Cancer	platinum-sensitive or -resistant epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. AMG 386 is a man-made medication that is designed to stop the development of blood vessels in cancer tissues. Cancer tissues rely on the development of new blood vessels, a process called angiogenesis, to obtain a supply of oxygen and nutrients to grow.
NCT01802749 Bevacizumab Beyond Progression in Platinum Sensitive Ovarian Cancer (MITO16MANGO2b)	This study aims to evaluate whether administering bevacizumab in combination with chemotherapy in second-line therapy to patients with recurrent ovarian cancer who have received first-line bevacizumab will be more effective than chemotherapy alone.
NCT00657878 Efficacy Study of Chemotherapy to Treat Ovarian Cancer Recurrence by Prolonging the Platinum Free Interval (MITO-8)	Liposomal Doxorubicin Versus Carboplatin/Paclitaxel in Patients With Ovarian Cancer Recurrence Between 6 and 12 Months After Previous Platinum Based Therapy: Phase III Randomized Multicenter Study Amendment Title Protocol Version 2.0: Phase III international multicenter randomized study testing the effect on survival of prolonging platinum-free interval in patients with ovarian cancer recurring between 6 and 12 months after previous platinum based chemotherapy.
NCT01116648 Cediranib Maleate and Olaparib in Treating Patients With Recurrent Ovarian, Fallopian Tube, or Peritoneal Cancer or Recurrent Triple-Negative Breast Cancer	This partially randomized phase I/II trial studies the side effects and the best dose of cediranib maleate and olaparib and to see how well cediranib maleate and olaparib work compared to olaparib alone in treating patients with ovarian, fallopian tube, peritoneal, or triple-negative breast cancer that has returned after a period of improvement. Cediranib maleate may help keep cancer cells from growing by affecting their blood supply. Olaparib may stop cancer cells from growing abnormally. The combination of cediranib maleate and olaparib may help to keep cancer from growing.
NCT02282020 Olaparib Treatment in Relapsed Germline Breast Cancer Susceptibility Gene (BRCA) Mutated Ovarian Cancer Patients Who Have Progressed at Least 6 Months After Last Platinum Treatment and Have Received at Least 2 Prior Platinum Treatments. (SOLO3)	Comparison of olaparib vs. physician's choice of single agent standard of care non-platinum based chemotherapy in patients with germline breast cancer susceptibility gene (*gBRCA*) mutated ovarian cancer who have progressed at least 6 months after the last platinum based chemotherapy. Patient should have received at least 2 prior lines of platinum based chemotherapy. The aim of the study is to assess the efficacy and safety of olaparib tablets.
NCT02822157 Circulating Tumor DNA Guiding (Olaparib) Lynparza® Treatment in Ovarian Cancer (CLIO)	This is a randomized, open-label, two-arm study in patients with relapsed epithelial ovarian tumours. Patients will be randomized in a 1:1 ratio to receive olaparib or standard chemotherapy with the possibility of crossover at the time of progression.
NCT02485990 Study of Tremelimumab Alone or Combined With Olaparib for Patients With Persistent EOC (Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Carcinoma)	This study will be looking at what dose of tremelimumab and olaparib is safe and effective in patients with persistent EOC (epithelial ovarian, fallopian tube or primary peritoneal carcinoma)
NCT01874353 parib Treatment in BRCA Mutated Ovarian Cancer Patients After Complete or Partial Response to Platinum Chemotherapy	Comparison of olaparib against a placebo in patients with ovarian cancer whose cancer has already improved by taking platinum based chemotherapy. The patients must also have a fault in their DNA which codes for the BRCA protein. The BRCA protein helps mend broken DNA in the cells of the body; if this protein does not work properly it can increase the chance of getting cancer. The aim of this study is to see whether patients taking olaparib tablets last longer until their cancer gets worse, compared to those taking the placebo tablet. The study is also looking to see if there is an overall improvement to how long the patients survive whilst taking olaparib tablets compared to the placebo tablets; and the quality of their life whilst living with ovarian cancer.
NCT00753545	The primary purpose of this study to determine if AZD2281 is effective and well tolerated in maintaining the improvement in your cancer after previous platinum-based chemotherapy.

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Assessment of Efficacy of AZD2281 in Platinum Sensitive Relapsed Serous Ovarian Cancer	
NCT01081951 Study to Compare the Efficacy and Safety of Olaparib When Given in Combination With Carboplatin and Paclitaxel, Compared With Carboplatin and Paclitaxel in Patients With Advanced Ovarian Cancer	To compare the efficacy of olaparib in combination with paclitaxel and carboplatin (AUC4) when compared with carboplatin (AUC6) and paclitaxel alone in patients with advanced ovarian cancer.
NCT01844986 Olaparib Maintenance Monotherapy in Patients With BRCA Mutated Ovarian Cancer Following First Line Platinum Based Chemotherapy. (SOLO-1)	A phase III, randomized, double-blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in patients with BRCA mutated advanced (FIGO Stage III-IV) ovarian cancer following first-line platinum-based chemotherapy.
NCT01891344 A Phase 2, Open-Label Study of Rucaparib in Patients With Platinum-Sensitive, Relapsed, High-Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (ARIEL2)	The purpose of this study is to determine which patients with ovarian, fallopian tube, and primary peritoneal cancer will best respond to treatment with rucaparib.
NCT02903004 Trial on Trabectedin (ET-743) vs Clinician's Choice Chemotherapy in Recurrent Ovarian, Primary Peritoneal or Fallopian Tube Cancers of BRCA Mutated or BRCAness Phenotype Patients _MITO-23 (Mito23)	This is an open-label, prospective, multicenter, randomized Phase III, clinical trial evaluating the efficacy and safety of trabectedin in BRCA1 and BRCA2 mutation carrier and BRCAness phenotype advanced ovarian cancer patients in comparison to physician' choice chemotherapy. Arm A: Trabectedin 1.3 mg/mq d1 q 21 in 3 hours (central line) Arm B: Pegylated Liposomal Doxorubicin 40 mg/mq q 28 or Topotecan 4 mg/mq dd 1,8,15 q 28 or Gemcitabine 1000 mg/mq dd 1, 8, 15 q 28 Weekly Paclitaxel 80 mg/mq gg 1, 8, 15 q 28 Carboplatin AUC 5-6 q 21 or 28
NCT02839707 Pegylated Liposomal Doxorubicin Hydrochloride With Atezolizumab and/or Bevacizumab in Treating Patients With Recurrent Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	This randomized phase II/III trial studies how well pegylated liposomal doxorubicin hydrochloride with atezolizumab and/or bevacizumab work in treating patients with ovarian, fallopian tube, or primary peritoneal cancer that has come back. Drugs used in chemotherapy, such as pegylated liposomal doxorubicin hydrochloride, work in different ways to stop the growth of cancer cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. block tumor growth Monoclonal antibodies, such as atezolizumab and bevacizumab, may interfere with the ability of tumor cells to grow and spread. It is not yet known which combination will work better in treating patients with ovarian, fallopian tube, or primary peritoneal cancer.

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Systemic Therapy for Recurrent Epithelial Ovarian Cancer

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC RAP (Appendix A1b and c). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the six members of the GDG Expert Panel, 4 members cast votes and 2 abstained, for a total of 75% response in February 2017. Of those that cast votes, 4 approved the document (75%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. A comment was made about the phrase "Inhibitors of the VEGF pathway". PARPi do not affect the VEGF pathway so either rename the title to something like "Targeted Agents" or move somewhere else.	We have made this change
2. A comment was made about the objective response rate in Table 4-8 as it was confusing.	We decided to leave this in and no changes were made.
3. Several comments were made to include a new abstract in the study results.	While this guideline did not search abstracts, details of this study are discussed in the Discussion.
4. A comment was made about niraparib and cediranib having the same level of toxicity.	We made this change to clarify that cediranib does have more toxicity.
5. A study should be added to ongoing studies.	We have made this change.
6. A comment was made about duplicate trials in the ongoing studies section.	We have made this changed and removed them.
8. A comment was made about removing "RCT" in the recommendations and changing it to clinical trial as not every clinical trial is an RCT.	We have made this change
9. Several comments were made about funding for cedaranib, and niraparib.	We have decided not to make recommendations based on available funding, but to let the literature speak for itself.
10. Qualifying statement for recommendation #5 sounds like a motherhood statement.	We have made this change to improve the clarity.
11. A comment was made about the duplicate recommendations that patients participate in clinical trials if possible.	We have made this change.
12. A comment was made about recommendation #3 and 4 being confusing.	We have made this change.
13. A comment was made that no attempt has been made to separate out low grade from the other types; therefore, there is no mention of hormonal treatment.	We have changed this to improve clarity.

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14. A comment was made about defining germline or somatic testing in recommendation #4.	No changes were made since it is not the purpose of this guideline to define germline or somatic testing.
15. A comment was made about changing the subsection from serous to high-grade serous.	No changes were made as not all the studies were on patients with high-grade serous carcinoma.
16. A comment was made about adding the histological subtypes in ovarian cancer.	No changes were made, as this will be addressed in another guideline that is currently underway.
17. A comment was made about including the ARIEL2 Part 1 study, and updates to the AURELIA study.	The ARIEL2 Part 1 study is not randomized and therefore will not be included; updates to the AURELIA study have been made.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in February 2017. The RAP approved the document. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. Recommendation 4 is too vague and should be changed.	We have moved modified the recommendation.
2. Minor stylistic and logical wording comments.	We have made these changes.
3. A comment was made about why the guidelines was found in the search were not endorsed.	We have made these changes.
4. A comment was made to clarify which studies were most relevant in Ontario.	We have made these changes.
5. A comment was made about how these recommendations are different from the ones in the previous version.	We have made these changes.
6. A comment was made on the implementation considerations of cediranib since funding was withdrawn.	We have made this change.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Five targeted peer reviewers from Ontario who are considered to be clinical and methodological experts on the topic were identified by the Working Group. Four agreed to be the reviewers (Appendix 1-d). Four responses were received. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=4)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				1	3

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2. Rate the guideline presentation.			1	1	2
3. Rate the guideline recommendations.		1		1	2
4. Rate the completeness of reporting.			1		3
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				1	3
6. Rate the overall quality of the guideline report.			1		3
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.		1			3
8. I would recommend this guideline for use in practice.		1			3
9. What are the barriers or enablers to the implementation of this guideline report?	• Practical advice focus. • Recommendation 2 is critical. Barriers to opportunities for participation in clinical trials include: education of patients and clinicians (which this guideline goes a long way toward enabling) and institutional funding to make clinical trials for ovarian cancer available across the province. Recommendation 4 involves biologic therapies, none of which are currently funded by the province of Ontario. Bevacizumab and olaparib are Health Canada approved. The main barrier to implementation of this recommendation is drug availability/funding. • Barriers are current funding for some of the medications; however, this will hopefully change in the near future. Also need to ensure this document gets to the end users. Barrier with knowledge translation. • Although data demonstrate the PFS benefit, and the guideline is clear with respect to discussing the complexity of patient preference in the recurrent ovarian cancer setting, implementation is difficult given that bevacizumab in the recurrent setting has not been approved on a provincial level. Difficult to reconcile recommendations in guidelines and barrier of cost.				

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Table 5-4. Responses to comments from targeted peer reviewers.

Comments	Responses
1. A comment was made about separating the guideline by PFI (platinum-sensitive vs. -resistant) then by agents: 1) PARP inhibitor; 2) Antiangiogenic; and 3) Other.	We have discussed and decided to keep the categories as they currently are.

2. A comment was made about the presenting the data from platinum-resistant trials separately in an appendix since apart from AURELIA, none of these trials are particularly relevant.	We have discussed and decided to keep the studies in the table and not move them to an appendix.
3. Several suggestions were made to change the wording of the recommendation #4.	We have made this change.
4. Several suggestions were made about incorporating the SOLO2 data. These data were presented at SGO in abstract form, and suggested PFS benefit to olaparib maintenance vs. placebo in the platinum-sensitive *BRCA* mutation population. These data add weight to the recommendation for PARP inhibitor maintenance. As these data have not been published, they should not be included in the systematic review. Given the relevance of these data, however, I would suggest some reference to "emerging data" in the discussion (Section 4).	This has been added into the discussion and as one of the ongoing trials.
5. A comment was made that bevacizumab is to be recommended for platinum-resistant recurrent disease for patients who meet AURELIA eligibility criteria. Quality of life benefit and improvement in ascites should be highlighted.	We have made these changes in the appropriate table.
6. A comment was made that PARP inhibitors for *BRCA*1 or 2 mutation should be changed to somatic and germline.	We have made these changes.
7.A comment was made that Table 4-1 was confusing and should be separated into different tables to go along with the text.	We have made these changes.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All medical oncologists who treat ovarian cancer in the PEBC database were contacted by email to inform them of the survey. One hundred twenty seven medical oncologists in Ontario were contacted. Twenty-one (16.5%) responses were received. Eight stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 13 people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	N=13 (10%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				5 (38.4%)	8 (61.5%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	2 (15.3%)	1 (7.6%)	4 (30.7%)	3 (23.0%)	3 (23.0%)
3. I would recommend this guideline for use in practice.			4 (30.7%)	3 (23.0%)	6 (46.1%)
4. What are the barriers or enablers to the implementation of this guideline report?	• Some of the drugs are not funded. • Time and length of guidelines are barriers. Online access is an enabler. • Cost and availability				

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	• Access to some of the biologic therapies off study. • Ability to participate in trial, i.e., academic vs. community hospital offering chemotherapy, ability of hospital to offer targeted agents. • Cost effectiveness and hospital policies. Would be nice to have clearly delineated first- and second-line options, rather than a menu of various options. • If olaparib is recommended, then molecular testing should be expanded from the single Ontario laboratory currently conducting this testing. I would appreciate the addition of a statement under "Implementation Considerations" regarding the laboratory implications of this report.

Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

Comments	Responses
1. Several comments were made about access to funding of olaparib in Ontario.	We have decided not to make recommendations based on available funding, but to let the literature speak for itself.
2. Recommendation #4 states "PARP inhibitors could be considered for prolonging progression-free survival in those with known *BRCA* 1 or 2 mutations". It should be clarified what is meant by "known mutations" - germline, somatic, or both.	We have made this change.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Members of the Working Group, the Gynecologic Cancer Guideline Development Group Expert Panel, Report Approval Panel, external reviewers and their conflict of interest declarations.

Table A1-a. Members of the Working Group

Name	Affiliation	Declarations of interest
Dr. Julie Francis Gynecologic Oncologist	Queen's University and Kingston General Hospital, Kingston, Ontario	None
Nadia Coakley Health Research Methodologist	Program in Evidence-Based Care McMaster University, Hamilton, Ontario	None
Erin Kennedy Health Research Methodologist	Program in Evidence-Based Care McMaster University, Hamilton, Ontario	None
Dr. Laurie Elit Gynecologic Oncologist	McMaster University and Juravinski Cancer Centre, Hamilton, Ontario	*Professional interest:* Received financial or material support (of $5,000 or more in a single year. *Professional interest:* Principal investigator for a clinical trial involving the objects of study. Received grants or other research support, either as principal or co-investigator, in any amount, from a relevant business entity Provided advice or guidance regarding the objects of study in a public capacity.
Dr. Helen MacKay Medical Oncologist	Odette Cancer Centre, Sunnybrook Health Sciences Toronto, Ontario	None

Table A1-b: Gynecologic Cancer Guideline Development Group Expert Panel

Name	Affiliation	Declarations of Interest
Dr. Allan Covens	Odette Cancer Centre, Sunnybrook Health Sciences Toronto, Ontario	*Professional interest:* Principal investigator for a clinical trial involving the objects of study
Dr. Hal Hirte	Juravinski Cancer Centre, Hamilton, Ontario	*Professional interest:* Principal investigator for a clinical trial involving the objects of study
Dr. Tien Le	The Ottawa Hospital-General Campus, Ottawa, Ontario	*Financial interest:* Received any grants or other research support, either as principal or co-investigator, in any amount. *Professional interest:* Principal investigator for a clinical trial involving the objects of study.
Dr. Anthony Fyles	Princess Margaret Hospital, Toronto, Ontario	None

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Table A1-c External Review Targeted Peer Reviewers

Name	Affiliation	Declarations of interest
Melissa Brouwers	Program in Evidence-Based Care McMaster University, Hamilton, Ontario	None
Dr. Donna Maziak	The Ottawa Hospital-General Campus, Ottawa, Ontario	None
Dr. Shailendra Verma	The Ottawa Hospital Regional Cancer Centre, Ottawa, Ontario	None

Table A1-d External Review Targeted Peer Reviewers

Name	Affiliation	Declarations of interest
Jim Biagi	Queen's University and Kingston General Hospital, Kingston, Ontario	None
Sarah Ferguson	Princess Margaret Hospital, Toronto, Ontario	None
Lilian Gien	Odette Cancer Centre, Sunnybrook Health Sciences Toronto, Ontario	None
Stephen Welch	London Regional Cancer Program, London, Ontario	*Financial interest:* Received honorarium of less than $1,000 in the past five years from a relevant business entity. *Professional interest:* Principal investigator for local clinical trials involving the objects of study.

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Appendix 2: Conflict of Interest

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, expert panel members, and internal and external reviewers were asked to disclose potential conflicts of interest. Only one author (LE) had a conflict of interest. LE 1) received support from AstraZeneca for a student project on the process of referral to Cancer Risk Assessment Clinics for women with ovarian, fallopian tube, or primary peritoneal cancer; 2) is a site Principal investigator for the ARIEL, a study involving a PARPi in recurrent ovarian cancer; and 3) attended interactions sponsored by AstraZeneca where the goal was to brainstorm how to decrease wait times for genetic counseling and testing.

For the Expert Panel, one member declared they had no conflicts of interest (AF) and three (AC, HH, and TL) declared conflicts. AC has reported being a Principal investigator for clinical trials involving the objects of study (recurrent ovarian cancer): The AstraZeneca Solo trials and trials involving bevacizumab. HH has reported being a Principal investigator for clinical trials involving the objects of study (recurrent ovarian cancer): pegylated liposomal doxorubicin - NCIC OV.17 gemcitabine - NCIC OV.14 PARP inhibitors - SOLO-2. TL has reported receiving grants or other research support, either as Principal or co-investigator, in any amount from Roche Canada and AstraZeneca as well as being a Principal investigator for a clinical trial involving the objects of study (recurrent ovarian cancer) on the ARIEL studies.

For the RAP review the members declared they had no conflicts of interest (MB, DM, and SV)

For the Targeted Peer Review, three members declared they had no conflicts of interest (JB,SF, LG) and one member declared conflicts (SW). SW received an honorarium of less than $1,000 in the past five years from a relevant business entity and was a Principal investigator for local clinical trials involving the objects of study (recurrent ovarian cancer).

The COIs declared above did not disqualify the individuals from carrying out a designated role in the development of this guideline, in accordance with the PEBC COI Policy.

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Appendix 3: Document History

Narrative History

- An evidence summary for this topic was originally completed by the PEBC in 2001. At that time, there was not enough evidence to make recommendations.
- In 2003, the document was updated to incorporate preliminary results from the International Collaborative Ovarian Neoplasm Group 4 (ICON4) randomized trial, which found a survival advantage with carboplatin-paclitaxel compared with carboplatin alone.
- In 2006, a new guideline incorporating full results of ICON4, and results from National Cancer Institute of Canada OV15 trial (OV15), which found a PFS advantage with the combination of carboplatin-gemcitabine compared with carboplatin alone in platinum-sensitive patients, was developed to replace the 2001 evidence summary. A recommendation was made for platinum-based combination chemotherapy to be considered for patients with prior platinum sensitivity, provided there are no contraindications. Recommendations for platinum-refractory and platinum-resistant patients included non-platinum-based regimens, such as single-agent PLD.
- In the 2011 version, recommendations were nearly the same as 2006, except for the addition of carboplatin plus PLD as a treatment option for platinum-sensitive recurrent ovarian cancer, and the addition of single-agent gemcitabine as a treatment option for platinum-resistant ovarian cancer. Findings of an individual patient data meta-analysis conducted by Raja et al in 2013 support the recommendation for combination chemotherapy [43].
- See Table A3 below for a tabulated history.

Table A3: Chronological History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS
	Search Dates	Data	
Original Evidence Summary 2001	1984 to June 2001	Evidence Summary	Fung Kee Fung M, Johnston ME, Eisenhauer EA, Elit L, Hirte HW, Rosen B. Chemotherapy for recurrent epithelial ovarian cancer previously treated with platinum—a systematic review of the evidence from randomized trials. Eur J Gynaecol Oncol. 2002:23(2);104-10.
Version 1 2003	MEDLINE 1984 to February 2004, EMBASE 1980 through week 10, 2004	Full Report	Web publication.
V2 2006	MEDLINE 1966 to March 2006, EMBASE 1988 to March 2006	New data added to original Full Report	1. Updated web publication. 2. Fung-Kee-Fung M, Oliver T, Elit L, Oza A, Hirte HW, Bryson P, et al. The optimal chemotherapy treatment for women with recurrent ovarian cancer: a clinical practice guideline. Curr Oncol. 2007 Aug;14(5):195-208.
V3 2011	2006 to March 2011	New data added to Version 2	Updated web publication.
V4 2016	March 2011 to October 2015	New data added to Version 3	Updated web publication.

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Appendix 4: Literature Search Strategy

The original literature search was conducted on October 16, 2015 and an updated literature search was conducted on May 30, 2016 (as shown below). Searched databases: Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® 1946 to Present and Embase and EBM Reviews - Cochrane Database of Systematic Reviews

1 ovarian neoplasms/
2 ovarian.ti.
3 neoplasm.mp.
4 cancer.mp.
5 neoplasm recurrence local/
6 neoplasm metastasis/
7 recurrent.mp.
8 relapse.mp.
9 resistance.mp.
10 drug therapy/
11 antineoplastic agents/
12 chemotherapy.mp.
13 2 and (3 or 4)
14 1 or 13
15 5 or 6 or 7 or 8 or 9
16 10 or 11 or 12
17 14 and 15 and 16
18 limit 17 to yr="2015 -Current"
19 remove duplicates from 18
20 random:.af.
21 19 and 20

Note: Patient preferences and values were searched separately, as shown in Appendix 7.

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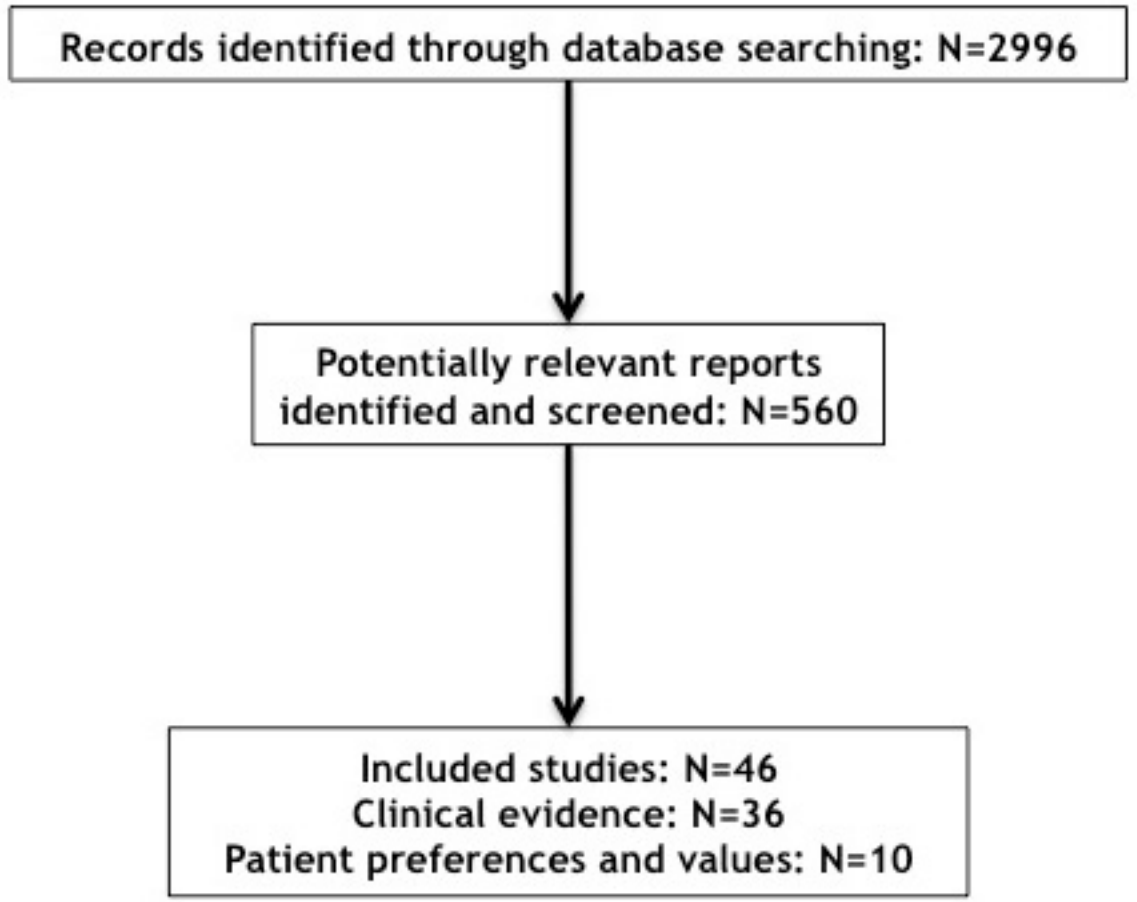
Appendix 5: PRISMA Flow

(*Note: includes work on patient preferences and values as shown in Appendix 8)



Appendix 6: Risk of Bias judgments for eligible randomized studies by the Cochrane Collaboration Risk of Bias tool

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting
Serous						
Mirza [13] 2016 – Phase 3	Unclear	Unclear	Low	Low	Low	Low
Oza [70] 2015 – Phase 2	Unclear	Low	Unclear	Unclear	High*	Low
Liu [62] 2014 – Phase 2	Low	Low	Low	Low	Low	Low
Lederman [58] 2012 – Phase 2	Low	Low	Low	Low	Low	Low
Lederman [59] 2014 – Phase 2	Low	Low	Low	Low	Low	Low
Kaye [55] 2012 – Phase 2	Low	Low	Unclear	Unclear	Low	Low
Recurrent						
Marth 2017 ENGOT-ov-6/TRINOVA-2 – Phase 3	Unclear	Low	Low	Low	Low	Low
Monk [66] 2014 TRINOVA –Phase 3	Low	Low	Low	Low	Low	Low
Monk [68] 2016 – Phase 2	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Karlan [54] 2012 – Phase 2	Unclear	Low	Low	Low	Low	Low
Coleman [49] 2014 – Phase 2	Low	Low	Low	Low	Low	Low
Platinum Sensitive						
Vergote [77] 2016 – Phase 3	Unclear	Unclear	Low	Low	Unclear	Low
Aghajanian [11] 2012 OCEANS – Phase 3	Low	Low	Low	Low	Unclear	Low
Mahner [64] 2015 Calypso based on Pujade-Lauraine [2] 2010 – Phase 3	High^	Low	Unclear	Unclear	Unclear	Low
Lederman [12] 2016 ICON 6 –Phase 3	Low	Low	Low	Low	Low	Low
Schwandt [74] 2014 – Phase 2	Unclear	Unclear	Unclear	Unclear	Low	Low
Alvares-Secord [48] 2012 –Phase 2	Low	Unclear	Unclear	Unclear	Low	Low
Kaye [56]2013 – Phase 2	Unclear	Unclear	Unclear	Unclear	Low	Low
Platinum Resistant						
Vergote [78] 2013 – Phase 2	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Rustin [73] 2011 – Phase 2	Low	Unclear	Unclear	Unclear	Unclear	Low
Gotlieb [52] 2012 – Phase 2	Low	Low	Low	Low	Low	Low
Pujade-Lauraine [15] 2014 AURELIA – Phase 3	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Columbo [50] 2012 – Phase 3	Low	Low	Low	Low	Unclear	Low

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	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting
Fotopoulou [51] 2014 OVATURE – Phase 3	Unclear	Unclear	Low	Low	Low	Low
Kurzeder [57] 2016 PENELOPE – Phase 3	Unclear	Unclear	Low	Low	Unclear	Low
Lortholary [63] 2012 – Phase 2	Unclear	Low	Low	Low	Low	Low
Naumann [69] 2013 – Phase 2	Unclear	Low	Unclear	Unclear	Unclear	Low
Pignata [71] 2015 – Phase 2	Unclear	Low	Unclear	Unclear	Low	Low
Pujade-Lauraine [72] 2016 – Phase 2	High¶	Unclear	Unclear	Unclear	Low	Low
Tew [76] 2014 – Phase 2 refill	Unclear	Unclear	Low	Unclear	Unclear	Low

*8 patients in the chemotherapy-alone arm chose to withdraw from the study compared with 2 in the olaparib group.
^This was a non-inferiority trial.
¶Patients were randomized to either volasertib or investigator's choice of a single-agent non-platinum chemotherapy agent.

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Appendix 7: Patient Values and Preferences

Methods

A literature search was conducted to examine patient preferences and values in recurrent ovarian cancer.

Search Strategy

Ovid MEDLINE and EMBASE, CINAHL, and PsycINFO were searched from January 1, 2000 to December 13, 2016 for any English-language studies of values, preferences, or expectations of women for any treatment of palliative care for platinum-sensitive recurrent or refractory ovarian cancer, using a search strategy adapted from Selva et al. [84].

Study Eligibility

Reference lists of included studies were also scanned for additional citations. Studies of women being treated for a first incidence of ovarian cancer were excluded. Studies were screened by EK and NC, and the study authors confirmed eligibility. The protocol for this study was registered as PROSPERO number CRD42016033223.

Data and analysis and quality assessment

Data were extracted by EK and NC and audited by a project research assistant. Due to the heterogeneity of study designs and the lack of an established methodology for assessing study quality for a systematic review of patient values and preferences [85], a specific tool was not used for the assessment of risk of bias and other indicators of study quality. The many different study designs made it difficult to synthesize the data using an established methodology. Rather, methodological characteristics of included studies, and any potential limitations of the included studies were abstracted. Potential quality issues included limited sample size, inconsistency of results, lack of generalizability, lack of understanding on the part of participants, inconsistency of options presented to participants, and selection bias.

We reported the results on an individual study basis and grouped similar findings under appropriate headings in the results section, which were then used to contextualize the findings of the quantitative literature review and inform recommendations. It did not appear that findings differed significantly by study methodology. Selection bias was reported as a potential problem in at least one study [86]. Limitations that could result in limited generalizability include publication date. Older studies such as Donovan et al. (published in 2002, before the era of biological agents) may not provide direct evidence regarding current treatment preferences [87]. Another bias is geographic area. The findings of Penson et al. show that preferences differ between the United Kingdom and the United States, and that patient preferences can be specific to a geographic area [86]. Therefore, studies published outside Ontario should be interpreted with caution, as they may not be relevant to our own population. However, another study showed that Canadian values for health states were in between United States and United Kingdom values [88]. There were several biases found in the Herzog et al. online study. The study was completed online and therefore suffered from selection bias. Only participants who had access to the Internet and were able to navigate the survey could complete it. This potentially excludes a large section of the population. In addition, people could have fabricated answers, leading to problems with interpretation [79].

Characteristics of Included Studies

The search yielded a total of 1021 articles. After title and abstract screening, 49 full-text studies were retained. Of these, 10 studies that were designed to elicit values, preferences, or expectations for treatment of recurrent ovarian cancer met the inclusion

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criteria. The studies were conducted in Germany [89], the United States [86,87,90,91], Canada [92,93], Sweden [94], and the United Kingdom [86,95]. Methods used to elicit values, preferences, and expectations included an expectations checklist, questionnaires, interviews, time trade-offs and visual analogue scales instruments, discrete-choice experiments, decision boards, QOL questionnaires, patient interviews, and an online survey. There was one study that used qualitative methods [94]. The studies included patients who were experiencing recurrent ovarian cancer and were required to make a treatment decision. There were five cross-sectional studies [86,87,90,91,95], one prospective cohort study [92], one study of patient interviews [96], one QOL substudy from a larger trial [89] and one web-based questionnaire [79]. The studies varied in size from four women in one of the qualitative studies [94] to a survey that included 1400 participants [79]. The main findings of the studies can be seen in Table A7-1.

Summary of Findings

Expectations of Treatment

Baumann et al. found a very high expectation for healing among patients in an analysis of data collected before recurrent ovarian cancer patients were randomized to carboplatin-paclitaxel or carboplatin-PLD as part of the CALYPSO phase III randomized controlled trial. This high expectation of healing was stated by 92% of patients who completed the Expectations Checklist [89]. In another study, where the stated goal of treatment was palliative rather than curative, 42% of a population described as "highly educated" expected that chemotherapy would have a moderately high or high likelihood of curing their disease. In this study, 58% of patients expected that chemotherapy would make them feel better, 62% of patients expected that it would delay problems, and 65% of patients expected that it would make them live longer [92]. However, only seven of 27 patients in this study, who were mostly stage III, actually experienced a response to treatment. In another study [86], patients thought that standard chemotherapy for a second recurrence of ovarian cancer produced remission in 50% and cure in 15% of patients. By comparison, in the same study, staff reported an expectation of 20% and 0%, respectively. In the Elit et al. study [93], one-half of cancer patients acknowledged that they would never be cancer-free and many saw the goal of treatment as prolonging life. Fifty-eight percent of patients saw treatment as having the potential to control cancer, 19% to extend life, and 15% to control symptoms. Twenty-four percent of patients in the United States and United Kingdom reported that they would not consider palliative care as an option when considering the goals of treatment [86].

The study by Herzog et al. found that OS and PFS were both seen as important treatment outcomes and women expected and wanted large differences with treatment. In this large, online, cross-sectional study of 1400 women with a current or previous history of ovarian cancer, the overwhelming majority (>70%) expected five or more months' difference in the median variables of PFS and OS when asked what was "minimally acceptable" [79]. When the patients were asked about toxicity, there was a noteworthy change in what they would accept depending on whether the treatment was delivered in a "curative" setting [79]. It was ascertained that patients receiving curative therapy would accept twice the toxicity of those receiving palliative therapy. In addition, patients recognized that stable disease was a vital parameter; however, it was less suitable to those in remission relative to those who had their disease recur [79].

The study by Elit et al. showed that patient preference was strongly influenced by previous experience with ovarian cancer [93]. The study found that women understood that the goal of treatment at recurrence was to prolong life. This was in contrast with a desire for a cure when they were first diagnosed. Nevertheless, the women were overwhelmed with information at both diagnoses. They were not interested in the details and trusted their health teams [93].

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Time Trade-Offs and Utility Scores

The Havrilesky et al. 2014 study investigated what women would trade off for a reduction in adverse effects. The study found that women were willing to agree to a reduction in PFS of 6.7 months (95% CI, 5.4 to 8.3 months) to go from severe nausea and vomiting to mild nausea and vomiting during treatment [90]. Women were also willing to take a reduction of 5.0 months in PFS (95% CI, 3.9 to 6.2 months) to go from severe peripheral neuropathy to mild neuropathy and a reduction of 3.7 months (95% CI, 2.6 to 5.0 months) of PFS for a decrease from severe to moderate abdominal symptoms. This clearly shows the patients' preference as approximately 25% of women ranked something other than PFS as the most important [90].

In the 2009 Havrilesky et al. study, which used patients with ovarian cancer and healthy volunteers, found that women who had experienced a particular adverse effect assigned a more favourable utility scores than those who had not [91]. Grade 2 alopecia and grade 1-2 peripheral neuropathy had the highest time trade-off utility (0.97) versus febrile neutropenia, which had the lowest (0.67) [91]. In the Jenkins et al. study, patients were bothered most by fatigue. However, patients whose ovarian cancer had recurred were found to be less troubled by adverse effects than patients receiving first-line treatment [95]. The context for this preference is given in a qualitative study, which found that women would tolerate the hardships of treatment because they understood that "the continuation of treatment was the prerequisite for life," and they preferred to continue treatment until the side effects became intolerable [94].

The Donovan et al. study [87] explored the choice of patients receiving first-line therapy and patients who had not been diagnosed with ovarian cancer in a hypothetical recurrent setting. Patients could choose between salvage therapy (aimed at slowing disease progression), or palliative care (stressing the management of symptoms rather than disease control). When compared with the non-cancer controls, patients with ovarian cancer overwhelmingly chose and preferred salvage therapy. The patients with ovarian cancer indicated that they would consider switching from salvage therapy to palliative care when the median survival associated with salvage therapy was reduced to five months. However, the non-cancer controls stated that they would consider switching considerably sooner, at eight months. This switch point was not correlated with psychological or spiritual well-being, life satisfaction, or QOL [87].

Additional Perspectives on Patients' Preferences

A study by Penson et al. compared the perceptions of physicians and nurses with those of patients, and found that the physicians and nurses rating of life prolongation of three months to one year to be much less acceptable than patient ratings ($p<0.001$) [86]. Both the patients and the physicians and nurses gave symptoms improvement the same rating. The study also concluded that patients are generally more tolerant of grade II chemotherapy-induced adverse events such as nausea, anorexia, diarrhea, and rash than are physicians and nurses. The same was also true of severe adverse events. They were tolerable to 12% of physicians and nurses compared with 34% of patients ($p=0.0016$) [86]. When asked whether they wanted chemotherapy if they were asymptomatic and had a rising CA125, both staff and patients chose chemotherapy, even when it was of no proven benefit [86]. When accounting for geographical differences, the Penson et al. study showed that 74% of United Kingdom patients, versus 45% of United States patients, were ready to consider hospice care, and to see palliative care integrated with cancer care more frequently [86]. However, these results should be approached cautiously as this study is from 2004 and attitudes toward palliative care are different today.

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Summary

There were few studies that met the inclusion criteria for this review. However, there were some general trends that may inform the development of guideline recommendations for this patient population, such as the unrealistically high expectations of patients may affect their expectations of being cured and influence their treatment preferences. Elit et al. found that patients valued the sharing of survival information [96], and Stewart et al. [97] found that women wanted detailed information concerning their disease and its treatment.

Based on these findings, the significant PFS advantage of three to four months reported in two recently published phase III trials would be acceptable to a proportion of the patient population. However, this proportion could vary depending on the accuracy of the patients' understanding of the intentions and goals of treatment, and on their level of tolerance for adverse effects.

Attention should be paid to formalizing patient preferences into the cancer decision-making model. Developing an integrated model could assist in individualizing care based on each patient's priorities.

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Table A7-1. Characteristics of Included Studies and Summary of Results

Study, Year [ref], location	Study Population	Study Design	Methods for Eliciting Preferences	Therapy	Summary of Key Results
Baumann [89], 2012 (abstract), Germany	97 of 299 German patients enrolled in CALYPSO (recurrent platinum-sensitive). 10% of total study population of 976.	German QOL Substudy of CALYPSO phase III RCT	Fact–O, EORTC QLQ C-30, OV-28 and Expectations Checklist (J R Soc Med 2000; 93:621-8)	Carboplatin paclitaxel or carboplatin-PLD	"Healing expectation" was stated by 92% at start of study. 68% found this expectation fulfilled at end of study. This was followed by tumour and symptom control and pain and emotional control. Pain and emotional control were correlated with QOL.
Donovan [87], 2002 USA	Women recently diagnosed with and being treated with first-line therapy for OC and non-cancer controls	Cross-sectional study	All patients completed profile of mood states, system of belief inventory and satisfaction with life scale. Only cancer patients completed functional assessment of chronic illness therapy-spiritual well-being scale and FACT-O. All patients completed a modified TTO to determine switch point and decision board including choices in the event of ROC.	Salvage therapy compared to palliative care	86% of cancer patients indicated initial preference for salvage therapy if recurrence happened. Cancer patients were five times more likely to choose salvage therapy compared to noncancer controls. In both groups of women who initially chose salvage treatment over palliative care, both groups would switch to palliative care with median survival time reduction of 10 months to 12 weeks. Those who initially chose palliative care would switch to salvage therapy if the median survival was 62 weeks. QOL was not associated with the treatment switchpoint. 25% would never switch to palliative care. A small proportion considered QOL to be of greater importance than quantity. The shorter the expected period of survival with salvage therapy, the higher the expectation of QOL with treatment.
Doyle [92], 2001 Canada	27 mostly stage III patients from Princess Margaret and Toronto General hospitals entered if they were about to	Prospective Cohort	Questionnaires (EORTC QLQ C-30 and FACT-O) administered to evaluate patient expectations at baseline and at each	Chemotherapy For ROC (primary goal was palliative, treatment would not be curative)	Most felt that chemotherapy would make them feel better (58%), would delay further problems (62%), make them live longer (65%), or have a moderately high or high likelihood of curing their disease (42%).

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Study, Year [ref], location	Study Population	Study Design	Methods for Eliciting Preferences	Therapy	Summary of Key Results
	start second- or third-line chemotherapy.		visit before the next course of chemotherapy and at home 1 week after each treatment. Also elicited changes in QOL.		Seven of 27 experienced response.
Ekwall [94], 2014 USA	4 women living with ROC over 2 years (starting approximately 3 years after first recurrence)	Qualitative study (phenomeno-logical approach)	Participants were interviewed twice	Chemotherapy for ROC	The women stated that even if they wanted a break in treatment they understood that they needed to go through treatment for a better chance at survival. They also stated when the adverse events from treatment became too burdensome it would be time to stop treatment.
Elit [93], 2010 Canada	26 patients of any age who were within 2 months of their first diagnosis of ROC (at Juravinski Cancer Centre).	Cross-sectional qualitative case study	Semi-structured interviews		95% of participants with a recurrence understood that treatment was not a cure, but a way of prolonging life. Half of the patients with a recurrence stated that they would never be cancer free.
Havrilesky [91], 2009 USA	37 women without a history of OC, and 13 women with a prior diagnosis of OC	Interviews by a single trained researcher	TTO and VAS questionnaires	Chemotherapy treatment	Patients who had experienced specific toxicities assigned more favourable utility scores than those who had not. Alopecia grade 2 and peripheral neuropathy (grade 1-2) had the highest time trade-off utility (0.97) versus the lowest: febrile neutropenia (0.67).
Havrilesky [90], 2014 USA	95 women (45 recurrent)	Cross-sectional	Ratings, rankings, discrete-choice experiment	2 different treatment scenarios characterized by 7 attributes: mode of administration, frequency, peripheral neuropathy,	Patients were willing to trade significant PFS time for reductions in treatment-related toxicity. Of symptoms, the rank of importance was: fatigue, abdominal symptoms, nausea and vomiting, and peripheral neuropathy. Participants stated they would accept a reduction in PFS of 6.7 months (95% CI, 5.4-8.3 months) to go from severe nausea and vomiting during treatment to a mild nausea

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Study, Year [ref], location	Study Population	Study Design	Methods for Eliciting Preferences	Therapy	Summary of Key Results
				nausea and vomiting, fatigue, abdominal discomfort and PFS, patient-reported outcome (PRO), FACT-O and MDASI questionnaires	and vomiting. A reduction of 5.0 months of PFS to go from severe peripheral neuropathy to mild neuropathy (95% CI, 3.9-6.2 months). A reduction of 3.7 months of PFS to go from severe to moderate abdominal symptoms (95% CI, 2.6-5.0 months).
Herzog [79], 2014 USA	1400 completed questionnaires	Cross-sectional; conducted in the context of a discussion regarding appropriate clinical trials endpoints in OC and which endpoints cancer patients find relevant	Brief online survey	Not stated	Overall survival and PFS were both seen as important treatment outcomes and women expected and wanted large differences with treatment (>70% of respondents stated that 5 or more months was "minimally acceptable"). Patients receiving curative therapy would accept twice the toxicity of those receiving palliative therapy.
Jenkins [95], 2013 (ADVOCATE study), UK	202 patient interviews (141 with experience of second and subsequent chemotherapies) 66 clinicians interviewed	Cross-sectional	Online survey with oncologists; structured interviews with patients including EORTC QLQC30, OV28 and EORTC INFO25 questionnaires	Survey included patients with stage II-IV OC recently completed or currently receiving chemotherapy (58%). 59% received more	Fatigue was most troublesome side effect for patients. Recurring patients were less bothered by side effects and less likely to report side effects.

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Study, Year [ref], location	Study Population	Study Design	Methods for Eliciting Preferences	Therapy	Summary of Key Results
				than one course of chemotherapy	
Penson [86], 2004 USA, UK	122 patients and 37 staff in USA; 39 patients and 25 staff in UK (61% with recurrence)	Cross-sectional exploratory study	Questionnaire developed by research team	Chemotherapy	The data suggest that a lot of desire for active treatment does not comes medical culture or staff, but from the patients who have very high expectations of treatment. Patients were found to be generally very tolerant of grade II chemotherapy-induced toxicity and staff was less tolerant than patients of nausea, anorexia, diarrhea, and rash" For severe adverse effects the staff found them less acceptable than patients (12% vs. 34%, p=0.0016). Staff rated life prolongation by 3 months to 1 year very much less acceptable than patients did. Patients thought that standard chemotherapy for a second recurrence of OC produced remission in 50% and cure in 15% of patients. Staff reported 20% and 0%, respectively. 24% of both US and UK patients stated that palliative care would never be an option for them.

CALYPSO = Caelyx in Platinum Sensitive Ovarian Patients, CI = confidence interval, EORTC QLQ C-30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, FACT-O = Functional Assessment of Cancer Therapy-Ovarian, OC = ovarian cancer, OS = overall survival, PFS = progression-free survival, PLD = pegylated liposomal doxorubicin, QOL = quality of life, RCT = randomized controlled trial, ROC = recurrent ovarian cancer, TTO = time trade-off, VAS = visual analogue scale.

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Example: Medline Search Strategy

1. Ovarian Neoplasms/
2. ovarian.ti.
3. neoplasm.mp.
4. cancer.mp.
5. neoplasm recurrence local/
6. neoplasm metastasis/
7. recurrent.mp.
8. relapse.mp.
9. resistance.mp.
10. drug therapy/
11. antineoplastic agents/
12. chemotherapy.mp.
13. 2 and (3 or 4)
14. 1 or 13
15. 5 or 6 or 7 or 8 or 9
16. 10 or 11 or 12
17. 14 and 15 and 16
18. limit 17 to yr="2011 - 2015"
19. remove duplicates from 18
20. attitude to health/
21. patient participation/
22. patient preference/
23. preference*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
24. (choice or value or "health state value" or valuation or expectation or attitude or acceptability or knowledge or "point of view" or "user participation" or "patient participation" or "patient perception*" or "health perception" or "users view" or "patient view").mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
25. decision making/
26. ("decision making" or "discrete choice" or "decision board" or "decision analysis" or "decision-support" or "decision tool" or "decision aid" or "discrete-choice").mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
27. decision support techniques/
28. value of life/
29. ("health utility" or "gamble" or "prospect theory" or "preference score" or "preference elicitation" or "utility value" or "utility score" or "utility estimat*" or "health state" or "health state utility" or "feeling thermomet*" or "best-worst scaling" or "standard gamble" or "time trade-off" or "probability trade-off" or "utility score").mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
30. ("preference based" or "preference score" or "multiattribute" or "EuroQol 5D" or "EQ 5D" or "SF6D" or "HUI" or "15D").mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
31. 19 and (or/21-30)
32. 19 and (or/21-24)
33. 19 and (25 or 26)
34. 19 and (27 or 28 or 29)
35. 19 and 30
36. limit 17 to yr="2000 - 2015"
37. 36 and (or/21-30)
38. remove duplicates from 37

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