Ontario Health
Cancer Care Ontario

Guideline 4-18

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

Consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma

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An assessment conducted in November 2023 deferred the review of Guideline 4-18. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 4-18 comprises 5 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/67196

Section 1:	**Recommendations Summary**
Section 2:	**Guideline**
Section 3:	**Guideline Methods Overview**
Section 4:	**Evidence Review**
Section 5:	**Internal and External Review**

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2. Hirte H, Yao X, Ferguson SE, May T, Elit L. An Ontario Health (Cancer Care Ontario) clinical practice guideline: consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma. Curr Oncol. 2021;28:1114-1124.

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Consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma

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 provide guidance for consolidation or maintenance systemic therapy in patients with newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma (collectively, EOC)

TARGET POPULATION

These recommendations apply to patients with newly diagnosed stage II, III, or IV EOC after first-line therapy with cytoreductive surgery and adjuvant therapy (patients who require neoadjuvant therapy before cytoreductive surgery also qualify for this guideline).

INTENDED USERS

Intended users of this guideline are gynecologic oncologists, medical oncologists, and other clinicians who are involved in the treatment of the target patients in the province of Ontario.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Please note:

We are unable to specify the patient population by histological types for different maintenance therapy recommendations. The majority of patients in the eligible studies are high-grade serous.

All Program in Evidence-Based Care (PEBC) documents are maintained and updated through an annual assessment and subsequent review process (see the details in **Section 3: Guideline Methods Overview**). When new evidence that can impact the recommendations is available, the recommendations should be updated as soon as possible. The definition of strength of recommendations for this guideline is listed in Appendix 1.

I. Consolidation therapy

Recommendation 1 (Strength: Recommendation)
Consolidation therapy with chemotherapy should ***NOT*** be recommended in the target population.
Qualifying statements
The investigated consolidation chemotherapy agents include epidoxorubicin alone, cisplatin alone, topotecan alone, paclitaxel alone, 5-fluorouracil plus cisplatin, and paclitaxel plus cisplatin/carboplatin.

II. Maintenance therapy

A. Agents are RECOMMENDED

Recommendation 2 (Strength: Recommendation)
Maintenance therapy with olaparib 300 mg twice a day by mouth for up to two years or until progression should be recommended in newly diagnosed stage III, or IV EOC patients with *BRCA1/2* mutation (somatic or germline), who are in complete remission or partial remission status after the first-line therapy with cytoreductive surgery and adjuvant therapy (patients who require neoadjuvant therapy before cytoreductive surgery also qualify for this recommendation).
Qualifying statement
Patients who have no evidence of disease at two years stopped using olaparib, but patients who have a partial response at two years can continue receiving it. The strength of recommendation will be reconsidered when overall survival (OS) data are available.

Recommendation 3 (Strength: Weak Recommendation)
Maintenance therapy with niraparib 200 to 300 mg by mouth daily for three years or until progression can be recommended in newly diagnosed stage III, or IV EOC patients in complete remission or partial remission status after the first-line therapy with cytoreductive surgery and adjuvant therapy (patients who require neoadjuvant therapy before cytoreductive surgery, and who are inoperable also qualify for this recommendation).
Qualifying statement
The strength of recommendation will be reconsidered when OS data are available.

Recommendation 4 (Strength: Weak Recommendation)
Concurrent use of bevacizumab 7.5 mg/kg intravenously three-weekly with adjuvant therapy for six cycles and continued use for up to 12 cycles or until progression as maintenance therapy can be recommended in newly diagnosed high-risk stage III, or IV EOC patients.
Qualifying Statement
The definition of high-risk stage III or stage IV patients in the eligible study (ICON7 trial) was defined as stage III with residual disease >1 cm, inoperable stage III, or stage IV EOC (total 30 [6%] inoperable stage III or IV patients).

Recommendation 5 (Strength: Weak Recommendation)
Concurrent use of veliparib 150 mg twice a day by mouth with adjuvant therapy for six cycles, and continued use of 400 mg twice a day by mouth for 30 cycles as maintenance therapy can be recommended in newly diagnosed stage III, or IV EOC patients with homologous-recombination deficiency.
Qualifying statement
The strength of recommendation will be reconsidered when OS data are available.

B. Agents are NOT recommended

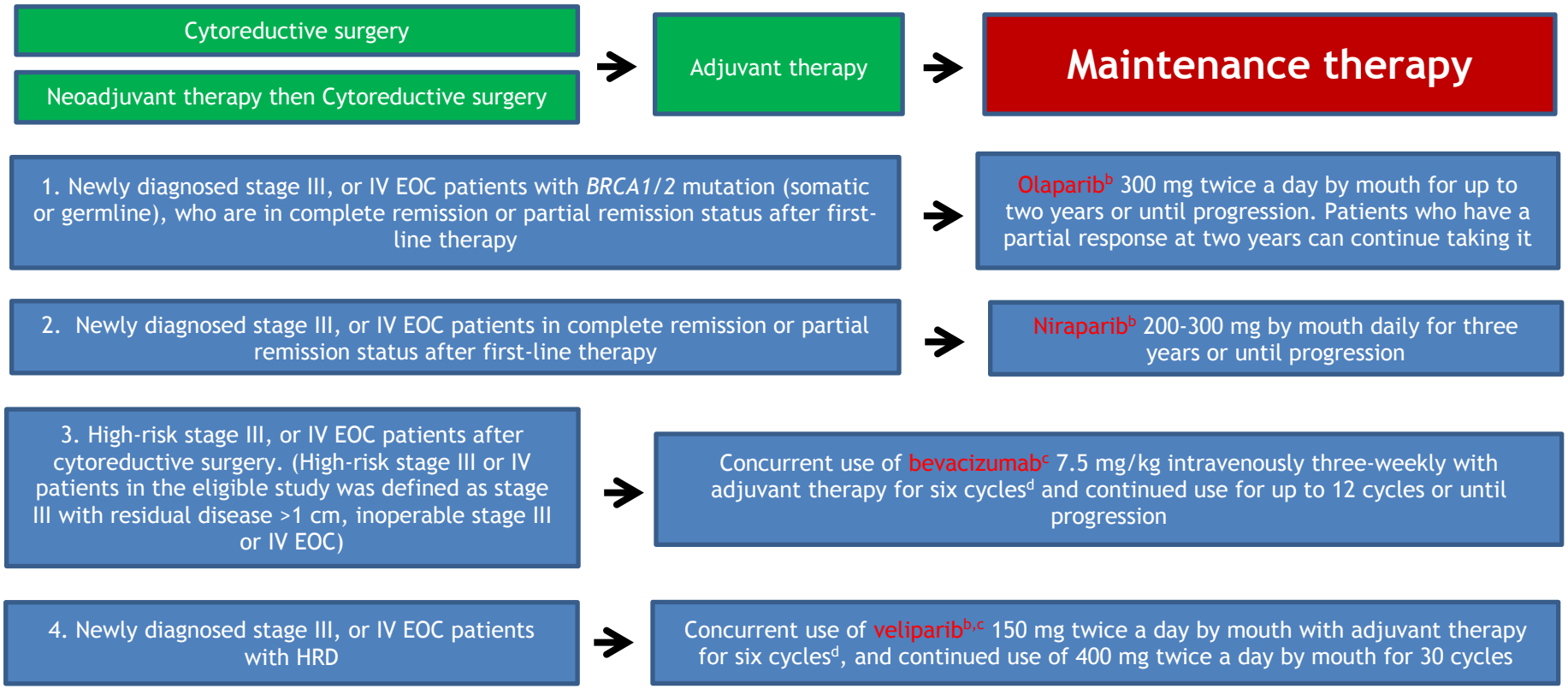
Recommendation 6 (Strength: Recommendation)
Pazopanib should ***NOT*** be recommended for use as maintenance therapy in the target population.

Recommendation 7 (Strength: Recommendation)
Maintenance therapy with interferon-alpha, erlotinib, abagovomab, oregovomab, or sorafenib, should ***NOT*** be recommended in the target population.

Recommendation 8 (Strength: Recommendation)
Concurrent use of nintedanib with adjuvant therapy and continued use as maintenance therapy should ***NOT*** be recommended in patients with newly diagnosed stage III with residual >1 cm or stage IV EOC.

Recommendation 9 (Strength: Recommendation)
Concurrent use of lonafarnib, enzastaurin, or trebananib with adjuvant therapy and continued use as maintenance therapy should ***NOT*** be recommended in the target population.

Diagram of options for recommended maintenance therapy agents in patients with newly diagnosed stage III or IV EOC[a]



Abbreviations: EOC, epithelial ovary, fallopian tube, or primary peritoneal carcinoma; HRD, homologous-recombination deficiency.

[a] Although we included stage II patient in our research questions, there is no evidence of maintenance therapy agents in this target population. The details of strength of recommendations are in Sections 2 and 4. The cost-effectiveness, and therapy agent and test resource issues are beyond the scope of this guideline. Green part represents current standard care period (We refer another Program in Evidence-Based Care's guideline 4-1 version 2 regarding neoadjuvant therapy and adjuvant therapy); Red part represents maintenance therapy period; and blue part represents our recommendations for target populations.

[b] The final OS data are immature; about 95% of patients are serous.

[c] Due to the lack of evidence, we do not know if bevacizumab or veliparib should be taken after adjuvant therapy as maintenance therapy option.

[d] A cycle means three weeks.

Consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To provide guidance for consolidation or maintenance systemic therapy in patients with newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma (collectively, EOC)

TARGET POPULATION

These recommendations apply to patients with newly diagnosed stage II, III, or IV EOC after first-line therapy with cytoreductive surgery and adjuvant therapy (patients who require neoadjuvant therapy before cytoreductive surgery also qualify for this guideline).

INTENDED USERS

Intended users of this guideline are gynecologic oncologists, medical oncologists, and other clinicians who are involved in the treatment of the target patients in the province of Ontario.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Please note:

We are unable to specify the patient population by histological types for different maintenance therapy recommendations. The majority of patients in the eligible studies are high-grade serous.

All Program in Evidence-Based Care (PEBC) documents are maintained and updated through an annual assessment and subsequent review process (see the details in **Section 3: Guideline Methods Overview**). When new evidence that can impact the recommendations is available, the recommendations should be updated as soon as possible.

I. Consolidation therapy

Recommendation 1 (Strength: Recommendation)
Consolidation therapy with chemotherapy should ***NOT*** be recommended in the target population.
Qualifying statements
The investigated consolidation chemotherapy agents include epidoxorubicin alone, cisplatin alone, topotecan alone, paclitaxel alone, 5-fluorouracil plus cisplatin, and paclitaxel plus cisplatin/carboplatin.
Key Evidence for Recommendation 1
Eight trials (nine full-text publications) investigated consolidation therapy with chemotherapy [1-9]. The certainty of the aggregate study evidence for each intervention comparison was moderate to low based on the GRADE approach [10] (details in Section 4). • Six trials enrolled patients with either complete response or without progressive disease after completing first-line therapy with surgery and adjuvant therapy [1, 3-6, 8, 9]. The SWOG-9701/GOG-178 trial reported that consolidation therapy, consisting of a monthly cycle of paclitaxel for 12 cycles, led to a longer progression-free survival

(PFS) than that for three cycles (22 months versus [vs.] 14 months; hazard ratio [HR], 0.68; p<0.01), but there was no benefit in overall survival (OS) (53 months vs. 48 months; HR, 0.88; p=0.40) [3, 4]. However, the authors of the trial admitted that the trial did not have sufficient power to support its conclusion. Additionally, the After-6 Protocol 1 trial did not find that PFS and OS benefit from paclitaxel as consolidation therapy for six cycles compared with observation [6]. Four other trials did not identify any statistically significant results for PFS and OS for paclitaxel plus cisplatin/carboplatin, epidoxorubicin alone, 5-fluorouracil plus cisplatin, or cisplatin alone [1, 5, 8, 9]. The SWOG-9701/GOG-178 trial [3, 4] indicated greater Grade 3 or higher hematologic adverse effects in the experimental group, but not for neurologic adverse effects. The other five studies did not report or compare the adverse effect outcomes between two groups [1, 5, 6, 8, 9]. No trials reported quality of life (QoL) outcomes.

- The AGO-OVAR 7 trial and MITO-1 trial examined topotecan [2, 7]. The AGO-OVAR 7 trial did not clarify patients' remission status after completing surgery and adjuvant paclitaxel and carboplatin [7]. Both trials showed that compared with observation, topotecan consolidation therapy did not result in improved PFS or OS. The AGO-OVAR 7 trial also reported that consolidation topotecan did not improve QoL, but led to more anemia, neutropenia, and thrombocytopenia [7].

Justification for Recommendation 1

- In this patient population, the evidence does not show any benefit of consolidation therapy with additional chemotherapy after completion of adjuvant therapy. Rather, it can cause more adverse effects and is more costly. Therefore, the Working Group members recommend against using consolidation therapy with chemotherapy. The Patient Consultation Group agreed with this recommendation.

II. Maintenance therapy

A. Agents are RECOMMENDED

Recommendation 2 (Strength: Recommendation)

Maintenance therapy with olaparib 300 mg twice a day by mouth for up to two years or until progression should be recommended in newly diagnosed stage III, or IV EOC patients with *BRCA1/2* mutation (somatic or germline), who are in complete remission or partial remission status after first-line therapy with cytoreductive surgery and adjuvant therapy (patients who require neoadjuvant therapy before cytoreductive surgery also qualify for this recommendation).

Qualifying statement

Patients who have no evidence of disease at two years stopped using olaparib, but patients who have a partial response at two years can continue receiving it.
The strength of recommendation will be reconsidered when OS data are available.

Key Evidence for Recommendation 2

The SOLO1 trial [11] and PAOLA-1 trial [12] investigated the efficacy of olaparib. The certainty of evidence of these two trials is high when evaluated using GRADE approach (details in Section 4).

- The SOLO1trial recruited 391 patients with *BRCA1*, *BRCA2*, or both mutations (somatic or germline) (>95% of them were high-grade serous) [11]. Patients who had no evidence of disease at two years stopped receiving the olaparib, but patients who had a partial response at two years were permitted to continue receiving the trial intervention in a blinded manner. Patients who took olaparib alone as a maintenance

therapy had a higher PFS rate than those in the placebo group (60% vs. 27%; HR, 0.3; 95% confidence interval [CI], 0.23 to 0.41; p<0.01), and the sensitivity analysis of investigator-assessed PFS showed the difference was 36.1 months (49.9 months vs. 13.8 months; p<0.01) between two groups. But the final OS data are immature. Patients in the olaparib group had more anemia and any Grade 3 adverse effects. There was no clinically meaningful difference between the two groups when QoL was measured at two years. The subgroup analysis showed that patients with either *BRCA1* or *BRCA2* received a greater PFS benefit in the olaparib group than in the placebo group. Another subgroup analysis did not find a significant association between tumour stage (i.e., stage III or IV) and effect magnitude of olaparib (Tables in Section 4).

- The PAOLA-1 trial [12] enrolled 806 patients. All patients received bevacizumab 15 mg/kg three-weekly with platinum-based chemotherapy as adjuvant therapy, and after that, all patients continued receiving bevacizumab for up to another 11 months or until progression. At the end of adjuvant therapy, patients with complete or partial remission were randomized to receive olaparib as maintenance therapy for 24 months versus placebo. Olaparib led to higher PFS compared with placebo (22.1 months vs. 16.6 months; HR, 0.59; 95% CI, 0.49 to 0.72; p<0.01). Data for OS are to date not yet available. Patients in the experimental group had more Grade 3 and more anemia adverse effects. There was no statistically significant difference in QoL between the two groups. Subgroup analyses showed that patients with homologous-recombination deficiency (HRD) had better PFS in the olaparib group than those in the placebo group. Patients with either *BRCA1* or *BRCA2* mutation also had better PFS in the olaparib group than in the placebo group (Tables in Section 4).

Justification for Recommendation 2

- In the SOLO1 trial, the OS at the time of the interim analysis did not reach the statistical significance, and the final OS data are immature. The Patients' Consultation Group emphasizes that OS is the most important outcome from a patient perspective. However, the effect magnitude of olaparib for PFS is large (36-month difference between two groups) in patients with *BRCA1/2* mutation with manageable adverse effects. Thus, the Working Group and Expert panel members make "Recommendation" for olaparib at present instead of "Weak Recommendaiton".
- In their discussion section, the authors of the PAOLA-1 trial realized the potential contamination bias due to additional bevacizumab therapy and the lack of an arm with olaparib monotherapy. Thus, it is unclear whether olaparib maintenance therapy alone will have benefit in patients with HRD versus patients without HRD.
- In the PAOLA-1 trial, we are unable to identify an additional desirable effect from bevacizumab; thus, we do not recommend olaparib plus bevacizumab as maintenance therapy at present.

Recommendation 3 (Strength: Weak Recommendation)

Maintenance therapy with niraparib 200 to 300 mg by mouth daily for three years or until progression can be recommended in newly diagnosed stage III, or IV EOC patients in complete remission or partial remission status after first-line therapy with cytoreductive surgery and adjuvant therapy (patients who require neoadjuvant therapy before cytoreductive surgery, and who are inoperable also qualify for this recommendation).

Qualifying statement

The strength of recommendation will be reconsidered when OS data are available.

Key Evidence for Recommendation 3

The PRIMA/ENGOT-OV26/GOG-3012 trial investigated the efficacy of niraparib. The certainty of evidence of the trial is high (details in Section 4).

- The trial randomized 733 patients (about 95% of them are serous) to niraparib versus placebo [13]. Three hundred seventy-three patients had HRD. The results indicated that niraparib led to higher PFS in all patients (13.8 months vs. 8.2 months; HR, 0.62; 95% CI, 0.50 to 0.76). The subgroup analyses showed that niraparib had PFS benefit among patients with HRD and patients without HRD, and patients with or without *BRCA1/2* mutation, compared with placebo. Thus, HRD or *BRCA1/2* mutation is not a confounder. However, the OS data are not yet mature. Compared with placebo, niraparib led to more Grade 3 or higher adverse effects on treatment-related adverse effects, anemia, neutropenia, and thrombocytopenia. There was no difference in QoL between the two groups.

Justification for Recommendation 3

- Although niraparib significantly improved PFS in all patients, it increased the risk of adverse effects. Less than 25% of Expert Panel and External Review members wanted to make "Recommendation" rather than "Weak Recommendation". The median PFS was 13.8 months in the niraparib group, but the authors' estimation of the median PFS for the overall patients in the placebo was 14 months. Since the median follow-up duration in this trial is 13.8 months only and the OS data are immature, the Working Group members make a weak recommendation for use of niraparib at present. The Patients' Consultation Group emphasizes the results of OS and agrees with this recommendation.

Recommendation 4 (Strength: Weak Recommendation)

Concurrent use of bevacizumab 7.5 mg/kg intravenously three-weekly with adjuvant therapy for six cycles and continued use for up to 12 cycles or until progression as maintenance therapy can be recommended in newly diagnosed high-risk stage III, or IV EOC patients.

Qualifying Statement

The definition of high-risk stage III or stage IV patients in the eligible study (ICON7 trial) was defined as stage III with residual disease >1 cm, inoperable stage III, or stage IV EOC (total 30 [6%] inoperable stage III or IV patients).

Key Evidence for Recommendation 4

Two large RCTs (ICON7 and GOG-0218) with eight papers investigated effectiveness of bevacizumab as concurrent and maintenance therapy [14-21]. The aggregate study evidence certainty was moderate (details in Section 4).

- The ICON7 trial randomized 1528 target patients to six cycles of adjuvant paclitaxel plus carboplatin versus paclitaxel plus carboplatin plus concurrent bevacizumab 7.5 mg/kg, followed in both arms by maintenance therapy with bevacizumab for 12 cycles or until disease progression versus placebo [15, 18-20]. At median 4.1-year follow-up, no PFS or OS benefit was found for maintenance bevacizumab. Patients in the bevacizumab group presented with more Grade 3 or 4 adverse effects.
- The pre-planned subgroup analysis of the ICON7 trial showed that among the 502 high-risk patients (defined as stage III with residual >1 cm or stage IV), bevacizumab maintenance therapy led to longer PFS (restricted mean survival time [RMST]: 20.0 months vs. 15.9 months; HR, 0.73; 95% CI, 0.61 to 0.88) and OS (RMST, 39.3 months vs. 34.5 months; HR, 0.78; 95% CI, 0.63 to 0.97). For non-high-risk patients (defined as stage III with residual ≤1 cm or stage I-II), there was no statistical difference for PFS or OS between the two groups. The p-value of 0.01 for the interaction test

demonstrated the benefit in bevacizumab in the high-risk patients. Additionally, QoL measurements indicated a worse score in patients in the bevacizumab group. The subgroup analysis for histological subtypes found no benefit of bevacizumab for OS outcome in 80 patients with low-grade serous tumours (RMST, 50.5 vs. 50.4 months) or 159 patients with clear cell tumours (RMST, 47.6 months vs. 48.0 months) (Tables in Section 4).

- The GOG-0218 trial recruited 1873 patients [14, 16, 17, 21]. After surgery, 625 patients were in the control group (CG, received paclitaxel and carboplatin for six cycles, plus placebo from cycle two to up to cycle 22), 623 patients were in the experimental group 1 (EG1, received paclitaxel and carboplatin from cycle two to cycle six, plus bevacizumab 15 mg/kg from cycle 2 to cycle 22), and 625 patients were in the experimental group 2 (EG2, received paclitaxel and carboplatin for six cycles, plus bevacizumab from cycle two to cycle six and then placebo from cycle 7 to up to cycle 22). Overall, patients in EG1 had a better PFS result than those in CG (14.1 vs. 10.3 months; HR, 0.72; 95% CI, 0.63 to 0.82), but the final results showed no benefit for OS (43.4 vs. 41.1 months) at median follow-up of 8.6 years. At the same time, there was no benefit for either PFS or OS in patients in the EG2 when compared with those in the CG. More GRADE 3 or 4 adverse effect of neutropenia occurred in EG1. There were no significant differences across the three treatment groups for QoL.
- The subgroup analyses of the GOG-0218 trial showed that patients with or without a *BRCA* mutation in the EG1 had greater PFS than those in the CG. Patients in the EG1 experienced greater PFS than those in the CG with stage III or IV, respectively; but bevacizumab only had OS benefit in patients with stage IV disease (42.8 vs. 32.6 months). With respect to histological subtypes, only the serous tumour subgroup rather than non-serous tumours had benefit for PFS but not for OS for patients in EG1 compared with CG (Tables in Section 4).

Justification for Recommendation 4

- Both trials randomized patients before adjuvant chemotherapy and investigators did not inform the readers regarding how many patients had progression in each group after adjuvant therapy who were then not qualified to receive maintenance therapy. Thus, there is some uncertainty about the effect of bevacizumab. Since there was no statistical difference between EG2 and CG for PFS or OS, there is uncertainty about the utility of bevacizumab given concurrently with cytotoxic chemotherapy.
- These two RCTs used different doses for bevacizumab (7.5 mg/kg in the ICON7 trial and 15 mg/kg in the GOG-0218 trial). There is no direct comparison between doses of bevacizumab in these two studies. However, the lower dose would be favoured if it caused fewer undesirable effects or cost less. Therefore, the Working Group members suggest using the lower dose of 7.5 mg/kg for bevacizumab.
- Less than 25% of Expert Panel and External Review members wanted to make "Recommendation" rather than "Weak Recommendation". After considering the above desirable and undesirable effects of the maintenance therapy, the certainty of evidence, health equity, acceptability, feasibility, generalizability in Ontario, and patient preference, the Working Group members make a weak recommendation. The Patients' Consultation Group agrees with this recommendation.

Recommendation 5 (Strength: Weak Recommendation)

Concurrent use of veliparib 150 mg twice a day by mouth with adjuvant therapy for six cycles, and continued use of 400 mg twice a day by mouth for 30 cycles as maintenance therapy can be recommended in newly diagnosed stage III, or IV EOC patients with HRD.

Qualifying statement
The strength of recommendation will be reconsidered when OS data are available.
Key Evidence for Recommendation 5
The VELIA/GOG-3005 trial investigated the efficacy of veliparib given either concurrently with adjuvant chemotherapy for six cycles (EG2), or concurrently and as maintenance therapy after adjuvant chemotherapy for up to 36 cycles (EG1) and compared with adjuvant chemotherapy alone (CG) [22]. The certainty of evidence of the trial is moderate (details in Section 4). • The trial recruited 1140 patients into three arms. At median 28-month follow-up, patients in EG1 had a higher PFS than patients in CG (23.5 months vs. 17.3 months; HR, 0.69; 95% CI, 0.56 to 0.83). There was no PFS benefit in EG2 when compared with CG. Veliparib led to more Grade 3 or 4 adverse effects including neutropenia, thrombocytopenia, nausea, and vomiting. No clinical significant difference was found for QoL. • The subgroup analysis showed the PFS benefit in patients with *BRCA1/2* mutation when compared with patients without *BRCA1/2* mutation. The subgroup analyses also showed that intervention in EG1 led to higher PFS in patients with HRD and patients with stage III, rather than in patients with non-HRD or stage IV when comparing with intervention in CG, but the interaction test's p-value was not statistically significant for both subgroup analyses (Tables in Section 4).
Justification for Recommendation 5
• Although veliparib showed benefits for PFS, no OS results are available at present and it has adverse effects. • This trial randomized patients before adjuvant therapy and analyzed patients including disease progression after adjuvant therapy. The investigators did not inform the readers of how many patients had progression in each group after adjuvant therapy who were not qualified to receive maintenance therapy. Thus, there is some uncertainty about the effect of veliparib. • It is not clear what the benefit of concurrent veliparib with adjuvant chemotherapy was. This EG2 did not demonstrate a PFS benefit compared with the CG. Also, since there was no maintenance-alone arm, it is unclear what benefit was conferred by EG1 as compared with veliparib given as a maintenance treatment alone. • Only one trial is available for veliparib; therefore, the doses listed in the recommendation are derived from this RCT. • Less than 25% of Expert Panel and External Review members wanted to make "Recommendation" rather than "Weak Recommendation". However, the Working Group members stay with a weak recommendation at present after considering the above factors, patients' values, health equity, acceptability, feasibility, and generalizability in Ontario.

B. Agents are NOT recommended

Recommendation 6 (Strength: Recommendation)
Pazopanib should ***NOT*** be recommended for use as maintenance therapy in the target population.
Key Evidence for Recommendation 6
Two trials investigated maintenance therapy with pazopanib. The evidence certainty was moderate for the AGO-OVAR16 trial [23-26] and low for the East Asian Study [27] (details in Section 4).

- The AGO-OVAR16 trial compared pazopanib 800 mg/day by mouth for up to 24 months with placebo in 940 patients. At median 24.3 months, pazopanib resulted in greater PFS (17.9 months vs. 12.3 months; HR, 0.77; p<0.01), but no benefit for final OS analysis at seven years. Patients in the pazopanib group had more neutropenia, thrombocytopenia, and any Grade 3 or higher adverse effects. QoL results were inconsistent. In the subgroup analyses, there was no desirable effect from pazopanib in patients with *BRCA1/2* mutation for PFS, but it led to benefits for patients without *BRCA1/2* (17.7 months vs. 14.1 months, p=0.02).
- Kim et al. combined patients from an East Asian Study with Asian patients from the AGO-OVAR16 trial [27]. No benefit was found for PFS, but a trend of worsening OS was found in the pazopanib group (HR, 1.71; 95% CI, 1.01 to 2.88; p=0.047 at median 24.3 months) (Tables in Section 4).

Justification for Recommendation 6

- Although pazopanib can improve PFS in non-Asian patients without *BRCA1/2* (median improved time, 3.6 months), it has severe adverse effects, no benefit for OS and results in a worse outcome in Asian patients. The Patients' Consultation Group was greatly concerned about the benefit versus harm. After considering the certainty of evidence, balance of the benefits and harms, and patient preference, the Working Group members recommend not to use pazopanib in the target population in Ontario.

Recommendation 7 (Strength: Recommendation)

Maintenance therapy with interferon-alpha, erlotinib, abagovomab, oregovomab, or sorafenib, should ***NOT*** be recommended in the target population.

Key Evidence for Recommendation 7

This group included seven trials with nine full-text publications [28-36]. The aggregate study evidence certainty for each intervention comparison was moderate to low after using the GRADE approach [10] (details in Section 4).

- Two trials with a total of 368 patients did not find benefit from maintenance therapy with alpha-interferon for PFS or OS, respectively [28, 33].
- One trial recruited 835 patients to investigate the effectiveness of erlotinib and did not indicate any benefit for PFS or OS. Worse QoL scores were reported in the erlotinib group than those in the observation group [36].
- The MIMOSA trial found no statistically significant difference for PFS, OS, or any serious adverse effects between the maintenance group of abagovomab and the placebo group [35]. Another trial reported no statistically significant difference for time to relapse, OS, any serious adverse effects, and QoL between the maintenance group of oregovomab and the placebo group [29-31].
- Two phase II trials with a total sample size of 331 investigated the efficacy of sorafenib as maintenance therapy in target patients [32, 34]. Both studies showed that there was no benefit from maintenance therapy with sorafenib on PFS or OS, respectively. Both trials recruited stage III or IV targeted patients.

Justification for Recommendation 7

- From the existing evidence, the Working Group members believe that there are no benefits but some harms and more costs for the above maintenance therapy in newly diagnosed EOC patients. Thus, the Working Group recommends against using them. The Patients' Consultation Group agrees with this recommendation.

Recommendation 8 (Strength: Recommendation)
Concurrent use of nintedanib with adjuvant therapy and continued use as maintenance therapy should ***NOT*** be recommended in patients with newly diagnosed stage III with residual >1 cm or stage IV EOC.
Key Evidence for Recommendation 8
Two trials investigated the effectiveness of nintedanib in EOC patients: one was the AGO-OVAR12 trial [23, 37] and the other was the CHIVA trial that was just published as a conference abstract in the 2019 American Society of Clinical Oncology annual meeting [38]. The aggregate study evidence certainty in the AGO-OVAR12 was high (details in Section 4). • The AGO-OVAR12 trial [23, 37] with a sample size of 1366 reported that at a median five-year follow-up, patients in the nintedanib group had a greater PFS than those in the placebo group (17.6 vs. 16.6; HR, 0.86; 95% CI, 0.75 to 0.98), but the time difference was 1.0 month between the two groups. The subgroup analysis with 527 patients showed that there was no statistical difference between the two groups in high-risk patients for PFS, but nintedanib led to a higher PFS in 839 non-high-risk patients (27.7 vs. 21.7 months; HR, 0.77; $p<0.05$). The p-value of 0.04 for the interaction test indicated that different risk patients react differently to nintedanib. There is no benefit for OS in overall patients and different subgroup patients. Patients in the nintedanib maintenance group had more Grade 3 or higher adverse effects of anemia, neutropenia, and thrombocytopenia (Table 4-2 in Section 4). The QoL was not affected during treatment with nintedanib measured by EORTC QLQ-C30 (Table 4-2). • The CHIVA trial recruited 188 patients [38]. Its conclusions were that the additional nintedanib led to worse PFS (14.4 vs. 16.8; HR, 1.50; $p=0.02$) and worse OS (37.7 vs. 44.1 months; HR, 1.54; $p=0.053$) results in patients with stage III or IV ovarian cancer, and increased any Grade 3 or higher toxicity (92% vs. 71%) (Table 4-2).
Justification for Recommendation 8
• This AGO-OVAR12 trial randomized patients before adjuvant therapy and analyzed patients including disease progression after adjuvant therapy. The investigators did not inform the readers of how many patients had progression in each group after adjuvant therapy who were then not qualified to receive maintenance therapy. Thus, the Patients' Consultation Group was concerned about the benefit against harm in this subgroup of non-high-risk patients. Also, the CHIVA trial showed worse survival results. • After considering the certainty of evidence, balancing the benefit and harms, and patient preference, the Working Group members recommend not to use nintedanib.

Recommendation 9 (Strength: Recommendation)
Concurrent use of lonafarnib, enzastaurin, or trebananib with adjuvant therapy and continued use as maintenance therapy should ***NOT*** be recommended in the target population.
Key Evidence for Recommendation 9
Three trials are in this category [39-41]. Their aggregate study evidence certainty was moderate to low (details in Section 4). • One trial with 105 patients did not find any benefit of lonafarnib for PFS and OS compared with observation [39]. • One trial with 142 patients did not find that additional enzastaurin as an adjuvant and maintenance therapy could improve PFS when compared with no maintenance therapy [41].

• The TRINOVA-3/ENGOT-OV2/GOG-3001 enrolled 678 patients to investigate the efficacy of trebananib [40]. No benefit was found for PFS or OS outcomes. However, trebananib led to more fatal treatment-emergent adverse events, but not for hematological, gastrointestinal, neurological, or any Grade 3 or 4 adverse effects. No significant difference was reported for QoL. The subgroup analyses showed no statistically significant difference between intervention and control group for different primary tumour locations (ovarian, primary peritoneal, and fallopian tube), histological subtypes (serous and non-serous), and disease stages (stage IIIA/B and stage IIIC/IV) (Tables in Section 4).
Justification for Recommendation 9
• From the existing evidence, the Working Group members found that there are no benefits, some harms, and more cost for the above maintenance therapy. Thus, the Working Group recommends not using these agents in the target population in Ontario.

RELATED GUIDELINES

- 4-1 version 2 Neoadjuvant and adjuvant systemic therapy for newly diagnosed stage II, III, or IV EOC (ongoing).
- 4-3 version 4 Systemic therapy for recurrent epithelial ovarian cancer.

FURTHER RESEARCH

High-quality RCTs to investigate the different doses and duration of therapies for known agents that led to benefits for survival as maintenance therapy are needed. Also, high-quality RCTs to investigate new effective maintenance agents are needed, especially for those that can improve OS. These studies could also provide treatment guidance for different histological types or molecular subsets in the target population. Additionally, high-quality RCTs are needed to investigate safe and effective combination maintenance therapies. Following this, network meta-analyses can be conducted to indicate which agent is optimal among PARP inhibitors, between PARP inhibitors and Anti-VEGF monoclonal antibody, and even for some subgroup patients, such as patients with *BRCA1/2* mutation.

GUIDELINE LIMITATIONS

The cost-effectiveness of therapy agents and test resource issues are beyond the scope of the PEBC guideline. The Working Group members leave resource consideration to other decision makers.

Consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma

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, Ontario Health (Cancer Care Ontario) (OH [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, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

GUIDELINE DEVELOPERS

This guideline was developed by the Ovarian Cancer GDG (Appendix 2), which was convened at the request of the Gynecologic Cancer Advisory Committee.

The project was led by a small Working Group of the Ovarian Cancer GDG, 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 Ovarian Cancer GDG 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 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 [42, 43]. 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 [44] 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 and to improve the completeness and transparency of reporting in practice guidelines.

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 evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test, and take into account the certainty

of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability and feasibility of implementation. A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations, dissemination issues, etc.) is provided along 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 Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. Evidence-based guidelines with systematic reviews that addressed the research question (see Section 4) were included. Guidelines older than three years (published before 2016) were excluded. Guidelines based on consensus or expert opinion were excluded.

The following sources were searched for guidelines from January 2016 to March 15 2019 with the search term of ovarian cancer: National Institute for Health and Care Excellence Evidence Search (NICE), Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, ASCO, National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, and Cancer Council Australia – Cancer Guidelines Wiki. No existing guideline met the inclusion criteria.

GUIDELINE REVIEW AND APPROVAL

Patient and Caregiver-specific Consultation Group

Six patients/survivors/caregivers participated in the Consultation Group. They reviewed copies of the draft recommendations and provided feedback on its comprehensibility, appropriateness, and feasibility to the health research methodologist who relayed the feedback to the Working Group for consideration.

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.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and will be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is

intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), ECRI Institute, and the Guidelines International Network (GIN) Library.

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- Sara Miller for copy editing.

Consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma

Section 4: Systematic Review

INTRODUCTION

Ovarian cancer is a leading cause of death among gynecological cancers worldwide [13]. In 2020, 3100 women are estimated to be diagnosed with ovarian cancer in Canada, including 1300 in Ontario. This will result in 1950 deaths in Canada, including in Ontario [45]. Currently, for patients with newly diagnosed stage II, III, and IV ovarian cancer, the standard first-line treatment strategies are cytoreductive surgery, and taxane and platinum-based chemotherapy [26]. However, around 70% of stage III and IV patients have a relapse within three years after completing adjuvant chemotherapy, which will lead to death later [11]. In an effort to reduce this high relapse rate, a number of strategies have been employed. These include: i) consolidating the initial response to initial therapy by continuing with additional cycles of the same chemotherapy regimen, or switching to alternative chemotherapy agents for an additional period of time; or ii) maintaining the response to initial therapy by continuing treatment with agents that may affect the growth and progression of any residual cancer, including agents affecting cellular proliferation, angiogenesis, DNA repair, and the immune response. Thus, whether consolidation (defined as being given after cancer has disappeared following the initial therapy) or maintenance therapy (defined as being given to help prevent a cancer recurrence after it has disappeared following initial therapy, which may be given for a long duration) with acceptable adverse effects can increase survival and improve patients' reported outcomes becomes an important clinical question [46]. Additionally, other questions would include: which agents should be considered and at what doses and schedule, what is the best administration method, and what is the ideal duration of treatment. Consideration would also be given to assessing the effects according to histological subtypes, stage, and mutation status.

The Working Group of the Ovarian Cancer GDG (including one medical oncologist: HH; three gynecologic oncologists: LE, SF, TM; and XY) developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objective of this guideline (Section 2), the Working Group derived the research question(s) outlined below. The systematic review has been registered on the website of the international prospective register of systematic reviews (www.crd.york.ac.uk/prospero) as CRD42019135079.

RESEARCH QUESTIONS

Does consolidation or maintenance systemic therapy improve OS, PFS, and patient-reported outcomes, with acceptable adverse effects in the target population? If so, what is the optimal regimen for maintenance therapy (dose/schedule/frequency)?

- In the target population, do patients with *BRCA1/2* mutation (somatic or germline mutation) or HRD have different optimal regimens for maintenance therapy and outcomes compared with patients without BRCA mutation or HRD?
- Do patients with different histological subtypes (low-grade serous, endometrioid, clear cell, mucinous, undifferentiated/unclassifiable) or different stages have different optimal regimens for maintenance systemic therapy and outcomes?

The outcomes of OS and PFS were rated as "CRITICAL", and adverse effects and patient-reported outcomes (i.e., QoL) were rated as "IMPORTANT" by the Working Group before the literature was searched. For adverse effects, the Working Group members decided to report Grade 3 or higher of the following seven adverse effects if available because they are relevant to the systemic therapy for patients with ovarian cancer: treatment-related death, anemia, neutropenia/leukopenia, thrombocytopenia, nausea, vomiting, and neuropathy.

PATIENT POPULATION

This included patients with newly diagnosed stage II, III, or IV EOC after surgery and completion of adjuvant therapy (patients who needed neoadjuvant therapy before surgery qualified for this guideline as well).

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Systematic Reviews

A search was conducted for existing systematic reviews and meta-analyses. The MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and PROSPERO databases were searched from January 2003 to August 28, 2019. The search strategies are reported in Appendix 3. There are many systematic reviews and meta-analyses relevant to our research questions. However, none included all the systemic therapy options. Thus, to work efficiently, the Working Group decided not to include any of the existing systematic reviews.

Search for Primary Literature

Literature Search Strategy

MEDLINE, EMBASE, and the Cochrane Library were searched for relevant evidence from January 2003 to August 28, 2019. PubMed was searched from January 1, 2018 to October 4, 2019. The full search strategies are reported in Appendix 3. In addition, the proceedings of the ASCO, Society of Gynaecologic Oncology, European Society Gynaecologic Oncology, and European Society for Medical Oncology annual meetings were searched for abstract reports of relevant studies from January 1, 2017 to October 4, 2019. The website of Clinicaltrials.gov was searched for trials that were ongoing, unpublished, or incomplete on October 4, 2019 2020.

Study Selection Criteria and Process

Inclusion Criteria

An article or abstract was eligible for inclusion if it met all the following pre-planned criteria:

1. An RCT with a minimum analyzed sample size for each group of 30.
2. Included patients of newly diagnosed stage II, III, or IV EOC after surgery and completion of first-line systemic therapy.

Exclusion Criteria

An article or abstract was excluded if it met any of the following pre-planned criteria:

1. It was published in a language other than English.
2. The paper only reported patient-reported outcomes from a previous RCT that was published before January 2003.

3. Studies recruited >20% recurrent (including relapsed, drug-sensitive, drug-resistant, drug-persistent, drug-refractory patients), inoperable, or stage I patients but did not have a subgroup analysis for patients with newly diagnosed EOC on stage II to IV.

A review of the titles and abstracts was conducted by one reviewer (XY). For studies that warranted full-text review, XY reviewed each article and discussed with the other Working Group members to confirm the final study selections. The reference lists of eligible papers were manually searched for further included articles.

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by XY, with all extracted data and information audited subsequently by an independent auditor. Risk of bias per outcome for each included study was assessed by the Cochrane Collaboration tools for randomized studies [47].

Synthesizing the Evidence

Statistical analyses were executed with the statistical software package STATA version 15.1 [48]. When clinically and methodologically homogeneous results from two or more studies were available, a meta-analysis was conducted. When meta-analysis was inappropriate due to clinical heterogeneity, the results of each study were presented individually in a descriptive fashion. HRs, rather than the number of events at a specific time, were the preferred statistic for meta-analysis, and were used as reported. HR was expressed with a ratio of <1.0 indicating that patients in the experimental group had a lower probability of experiencing an event; conversely, an HR >1.0 suggested that patients in the control arm had a lower probability of experiencing an event.

When a meta-analysis was conducted, the chi-squared (X^2) test was used to test the null hypothesis of homogeneity, and a probability level less than or equal to 10% ($p \leq 0.10$) was considered indicative of statistical heterogeneity. If heterogeneity was detected, then the I^2 index was used to quantify the percentage of the variability in the effect estimates that was due to heterogeneity. A two-sided significance level of $\alpha=0.05$ was assumed.

Assessment of the Certainty of the Evidence

The certainty of the evidence per outcome for each comparison, taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias was assessed by using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach [10].

RESULTS

Primary Literature Search Results

There were 12,675 citations from the medical databases search. After reviewing the titles and abstracts, 238 articles needed full-text screening and three conference abstracts met the inclusion criteria. Of 238 papers, 41 full-text articles met the pre-planned study selection criteria [1-9, 11, 12, 14-37, 39-41, 49-51]. However, in one study, the investigated drug of tanomastat was no longer available [50]. In another study [51], patients were randomized twice. After the patients were randomized for the second time and took different interventions from that at the first randomization, the first randomization was broken. Thus, it is inappropriate for the authors to analyze data at the end of the study for the two arms from the first randomization. Additionally, almost all the patients who had complete remission and were randomized the second time were included in Nicoletto 2004 [5], which was already included in our systematic review. Therefore, data from these two trials were not included in this guideline.

Six eligible conference abstracts were identified from the four pre-planned proceedings of conferences. Combined with three eligible abstracts from the literature search, nine conference abstracts were eligible. Among them, two were duplicated; four were covered by the included full-text articles; one abstract had a significant error (maintenance therapy of tamoxifen increased the median PFS by 6.3 months with the 95% CI of 4.5 months to 6.1 months, which did not make sense) and no response was received after we contacted the original authors [52]; another abstract's full text was published after our literature search date [12]. Six trials had more than one publication due to different outcomes and follow-up times. Thus, a total of 27 trials from 40 full-text articles [1-9, 11, 12, 14-41, 49] and one additional trial from a conference abstract [38], were finally analyzed in this systematic review. The trials and patients characteristics are listed in Table 4-1. A modified PRISMA flow diagram with reasons for study exclusion is listed in Appendix 4.

Risk of bias assessment for individual study

The results of risk of bias assessment for each comparison of 26 trials are shown in Appendix 5. One trial for maintenance therapy that was only published as a conference abstract did not have sufficient data to evaluate the risk of bias.

Consolidation therapy with chemotherapy

Eight trials (nine full-text publications) investigated consolidation therapy with chemotherapy [1-9]. Two of these were phase II trials [1, 5]. The randomization procedure was unclear for two trials [5, 9]. The allocation concealment was unclear for five trials [3-6, 8, 9]. All the trials had low bias with respect to patient follow-up, but patients and outcomes assessments were unblinded. For the selective reporting domain, one trial stated that PFS and OS were the primary outcomes, but only reported the OS result [1]. Overall, the risk of bias ranged from moderate to high for these eight trials. The aggregate study evidence certainty for each comparison of interventions was moderate to low after considering the other four factors (inconsistency, indirectness, imprecision, and publication bias) together from the GRADE approach. The traditional GRADE summary tables for each outcome were not presented because of the large number of different interventions, cycles, doses, follow-up period, patient populations, and the outcome report time and methods involved in this guideline. For the same reason, meta-analyses or network meta-analyses were inappropriate to perform.

Maintenance therapy

Thirty-one full-text publications for 19 RCTs studied maintenance therapy [11-37, 39-41, 49]. Five trials were phase II trials [27, 32, 34, 39, 41]. The randomization procedure was unclear in four trials [27, 28, 32, 33]. The allocation concealment was unclear in 13 trials with 19 articles [14-17, 21-28, 32-36, 40, 41] Patients in six trials were unblinded [15, 18-20, 28, 32, 33, 36] All the trials had low bias on patient follow-up. For selecting reporting bias domain, all but one trial [28] had low risk. Overall, the risk of bias was high for three trials [28, 32, 33] moderate for 12 trials [14-27, 34-36, 39-41], and low for three trials [11, 29-31, 37, 49]. The aggregate study evidence certainty for each comparison of interventions ranged from low to high after considering four other factors (inconsistency, indirectness, imprecision, and publication bias) together from the GRADE approach. The traditional GRADE summary tables for each outcome were not presented because of the large number of different interventions, cycles, doses, follow-up period, patient populations, and the outcome report time and methods involved in this guideline. Again, for the same reason, meta-analyses or network meta-analyses were inappropriate to perform.

Outcomes

The study designs and patient characteristics of the 28 RCTs are listed in Table 4-1. The available outcomes of OS, PFS, adverse effects, and patient-reported outcomes are presented in Table 4-2. Subgroup analyses are shown in Tables 4-3, 4-4, and 4-5.

Consolidation therapy with chemotherapy

Eight trials with nine full-text publications met our inclusion criteria (section 1 in Tables 4-1 and 4-2) [1-9]. Van der Burg et al's trial with a sample size of 234 compared consolidation therapy of six cycles with three cycles of paclitaxel plus cisplatin/carboplatin, and did not find statistically significant benefit for PFS and OS at median follow-up time of 10.3 years [9]. The SWOG-9701/GOG-178 trials recruited 296 patients and reported that consolidation therapy with paclitaxel given in a monthly cycle for 12 cycles led to longer PFS than that for three cycles (22 months vs. 14 months; HR, 0.68; $p<0.01$), but no statistically significant benefit for OS (53 months vs. 48 months; HR, 0.88; $p=0.40$) [3, 4]. Also, this trial did not recruit a sufficient number of patients to meet their sample size calculation (n=450), which made their results uncertain. The rest of the four trials, with a sample size range from 121 to 200 for each trial, compared consolidation therapy of intravenous (IV) paclitaxel in the Pecorelli 2009 trial [6], IV epidoxorubicin in the Bolis 2006 trial [1], IV 5-fluorouracil and then cisplatin in the Nicoletto 2004 trial [5], or intraperitoneal cisplatin in the EORTC-55875 trial [8] with observation, respectively. No trial found that the additional consolidation therapy resulted in longer PFS or OS. No trial measured QoL (Table 4-2).

The Bolis 2006 trial, Nicoletto 2004 trial, and EORTC-55875 trial reported Grade 3 or higher adverse effects for the consolidation therapy group only [1, 5, 8](Table 4-2). Two trials did not report adverse effects [6, 9]. The SWOG-9701/GOG-178 trial did not find a statistically significant difference in hematological adverse effects between the two groups, but the experimental group had more neurologic adverse effects (6% vs. 1%; $p<0.05$) [3, 4]. No subgroup analysis was reported among the six RCTs.

Two other trials (AGO-OVAR 7 [7] and MITO-1 [2]) with a total of 1581 patients, compared two different IV topotecan regimens (1.5 mg/m^2 and 1.25 mg/m^2) with observation. Both showed that maintenance therapy of topotecan did not lead to greater PFS and OS and did not improve QoL, but caused more anemia, neutropenia, and thrombocytopenia adverse effects in the AGO-OVAR 7 trial [7] (Table 4-2). The AGO-OVAR 7 trial performed a subgroup analysis by cancer stage [7]. Among non-high-risk patients (defined as stage IIB-III with a residual ≤1 cm) and high-risk patients (defined stage IIB-III with a residual >1 cm or stage IV), no statistically significant results were found between the two groups (Table 4-3).

Maintenance therapy

A. Patients without disease progression randomized after first-line therapy with surgery and adjuvant therapy (patients who require neoadjuvant therapy before surgery also qualify for this guideline).

Twelve trials with 17 full-text publications met our inclusion criteria (section 2.1. in Tables 4-1 and 4-2) [11, 12, 15, 23-36].

1. Interferon-alpha

The Alberts et al. 2006 trial enrolled 70 patients with stage III ovarian cancer, and followed them for a median of 12 years [28]. The Hall et al. 2004 trial recruited 298 patients with stage I to IV ovarian cancer and followed them for a median of two years [33]. Neither study found any benefit for maintenance therapy with interferon on survival and neither reported QoL outcomes.

2. Epidermal growth factor receptor inhibitor — erlotinib
   The Vergote 2014 et al trial with 835 patients compared maintenance therapy of erlotinib 150 mg/day to two years with observation intervention [36]. No survival benefit was found but worse QoL scores were reported in the erlotinib group.

3. Monoclonal antibody targeted to CA-125 — abagovomab and oregovomab

Compared with placebo, the MIMOSA trial investigated the effectiveness of abagovomab as maintenance therapy in 888 patients with 87% at stage III and 13% at stage IV [35]. There was no statistically significant difference for PFS, OS, or any serious adverse effects between the two groups at median two-year follow-up. No QOL was measured.

The Berek et al trial investigated the effectiveness of oregovomab in 371 patients with 92% at stage III, 7% at stage IV, and 1% at stage I-II, compared with placebo [29-31]. There was also no statistically significant difference for time to relapse, OS, any serious adverse effects, and QoL between the two groups at a median of 2.5 years.

4. Poly ADP ribose polymerase (PARP) inhibitor — olaparib and niraparib

4.1. Olaparib

The SOLO1 trial recruited 391 patients with a germline or somatic mutation in *BRCA1* or *BRCA2*, or both [11]. Among them, 85% of patients were stage III and 15% stage IV. For histological subtype, 95% of patients were serous, 3% were endometrioid, and the rest were mixed serous and endometrioid. Patients who took olaparib 300 mg twice a day for a median of 24.6 months had a lower rate of freedom from progression or death than those in the placebo group (60% vs. 27%; HR, 0.3; 95% CI, 0.23 to 0.41; $p<0.01$). The sensitivity analysis of investigator-assessed PFS showed the difference was 36.1 months (49.9 months vs. 13.8 months; $p<0.01$) between two groups. The interim analysis for OS did not reach a statistically significant difference (84% vs. 80%; HR, 0.95; 95% CI, 0.60 to 1.53). Patients in the olaparib group had more anemia and any Grade 3 adverse effects. However, there was no clinical difference in QoL when measured at two years (Table 4-2). The subgroup analysis showed that patients with either *BRCA1* or *BRCA2* separately received a greater PFS rate in the experimental group (HR, 0.40; 95% CI, 0.29 to 0.56; and HR, 0.20; 95% CI, 0.10 to 0.38, respectively) (Table 4-3). Another subgroup analysis found that olaparib led to a greater PFS rate in patients either with stage III (HR, 0.32; 95% CI, 0.24 to 0.44) or stage IV ovarian cancer (HR, 0.49; 95% CI, 0.25 to 0.94), respectively (Table 4-4).

In the PAOLA-1/ENGOT-OV25 trial [12], all patients (n=806) received bevacizumab 15 mg/kg three-weekly with platinum-based chemotherapy as adjuvant therapy, then kept bevacizumab alone for up to another 11 months. At the end of adjuvant therapy, only patients in complete or partial remission were randomized to receive olaparib or placebo as maintenance therapy for up to 24 months. Olaparib led to higher PFS compared with placebo (22.1 months vs. 16.6 months; HR, 0.59; 95% CI, 0.49 to 0.72; $p<0.01$). The data for OS are not available. Patients in the experimental group had higher Grade 3 or anemia adverse effects. There was no statistically significant difference found for QoL between the two groups (Table 4-2). Subgroup analyses showed that patients with HRD treated with olaparib had greater PFS (37.2 months vs. 17.7 month; HR, 0.33; 95% CI, 0.25 to 0.45; $p<0.05$), but not in patients without HRD (16.9 months vs. 16.0 month; HR, 0.92; 95% CI, 0.72 to 1.17; $p>0.05$) (Table 4-3). Patients with either the *BRCA1* or *BRCA2* mutation treated with olaparib had greater PFS than those without, and patients with the *BRCA1* mutation had greater PFS than patients with the *BRCA2* mutation (Table 4-3).

4.2. Niraparib

The PRIMA/ENGOT-OV26/GOG-3012 trial enrolled 733 patients and 373 of them had HRD. Niraparib led to higher PFS in all patients (13.8 months vs. 8.2 months; HR, 0.62; 95% CI, 0.50 to 0.76; p<0.01) [13]. The final OS data are not yet mature. Compared with placebo, niraparib resulted in more Grade 3 or higher adverse effects on treatment-related anemia, neutropenia, and thrombocytopenia. There was no difference in QoL between the two groups (Table 4-2).

The subgroup analysis showed that niraparib in patients with or without HRD, or in patients with or without the *BRCA1/2* mutation had better PFS results when compared with placebo (Table 4-3). In Table 4-4, HR is lower in patients with stage III (HR, 0.54; 95% CI, 0.42 to 0.70; p<0.05) than that in those with stage IV (HR, 0.79; 95% CI, 0.55 to 1.12; p>0.05), but the p-value of the interaction test is not statistically significant, indicating that stage is not a confounder that impacts the effect of niraparib.

5. Vascular endothelial growth factor receptor tyrosine kinase inhibitors — pazopanib and sorafenib

The AGO-OVAR16 trial compared pazopanib 800 mg/day by mouth to 24 months with placebo in 940 European, Asian, North American, and Australian patients [23-26]. At a median 24.3-month follow-up, pazopanib resulted in greater PFS (17.9 months; 95% CI, 15.9 months to 21.8 months vs. 12.3 months; 95% CI, 11.8 months to 17.7 months, and HR, 0.77; p<0.01), but no benefit for OS (59.1 months; 95% CI, 53.5 months to 71.6 months vs. 64.0 months; 95% CI, 56.0 months to 75.7 months, and HR, 0.960; p=0.64) at final analysis at mean seven-year follow-up. Patients in the experimental group had more neutropenia, thrombocytopenia, and any Grade 3 or higher adverse effects (p<0.01, p=0.03, and p<0.01, respectively). The QoL assessment favoured the pazopanib group measured by the European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire - Cancer30 (EORTC QoL-C30), but favoured the placebo group measured by the Quality of Life Questionnaire ovarian cancer module (QLQ-OV28). It showed no difference between the two groups by the EuroQoL-5 dimensions-3 levels tool (EQ-5D-3L) at 25 months.

Kim et al. investigated the efficacy of pazopanib as maintenance therapy in East Asian target patients, and combined the East Asian patients from the AGO-OVAR16 trial together (a total sample size of 350) [27]. No benefit was found for PFS (HR, 1.11; 95% CI, 0.82 to 1.52; p=0.49), but a worse OS result was found in the pazopanib group (HR, 1.71; 95% CI, 1.01 to 2.88; p=0.047) at median 24.3-month follow-up and a worse trend for OS (HR, 1.33; 95% CI, 0.86 to 2.05; p=0.19) at sven-year follow-up.

Both the AGO-OVAR16 trial and the East Asian study had a subgroup analysis for patients with *BRCA1/2* and non-*BRCA1/2* (Table 4-3). In the AGO-OVAR16 trial [25], patients with *BRCA1/2* had greater PFS than those without *BRCA1/2* (30.3 months vs. 14.1 months; HR, 0.48; 95% CI, 0.29 to 0.78; p<0.01) in the placebo group; there was a similar trend (30.2 vs. 17.7 months; p=0.07) in the pazopanib group. There was benefit of pazopanib for PFS in the non-*BRCA1/2* subgroup (17.7 vs. 14.1; p=0.02), but no benefit in the *BRCA1/2* subgroup (30.2 vs. 30.3; p=0.41). It indicates that patients with *BRCA1/2* may have a better prognosis than those without *BRCA1/2* after the first-line therapy, regardless of whether they have maintenance therapy. In the East Asian study [27], no benefit was found in the *BRCA1/2* group or in the non-*BRCA1/2* group.

Two other trials (the Hainsworth 2015 trial [32] and the Herzog 2013 trial [34]) investigated the efficacy of sorafenib as maintenance therapy in target patients. One trial started sorafenib 400 mg twice per day by mouth on completion of adjuvant therapy and only patients without progression were randomized to continue sorafenib as maintenance therapy to one year (n=43) or to an observation group (n=42) [32]. Another phase II trial randomized 246 patients into the same sorafenib treatment strategy group and the placebo group [34].

Neither of these studies showed a benefit of maintenance therapy with sorafenib on PFS and OS at 2.5 years or three years follow-up (Table 4-2).

B. Patients randomized before adjuvant chemotherapy

Seven trials from 14 full-text publications [14-22, 37, 39-41, 49] and one conference abstract [38], met our inclusion criteria (section 2.2. in Tables 4-1 and 4-2).

1. Anti-VEGF monoclonal antibody — bevacizumab

Two large RCTs (the ICON7 and GOG-0218 trials) investigated effectiveness of bevacizumab as maintenance therapy. The ICON7 trial randomized 1528 target patients into either paclitaxel plus carboplatin as adjuvant therapy without maintenance therapy or paclitaxel plus carboplatin plus bevacizumab 7.5 mg/kg as adjuvant therapy for six cycles and then maintenance therapy with bevacizumab for up to 12 further cycles [15, 18-20]. At median 4.1-year follow-up, no benefit was found for either PFS (HR, 0.93; 95% CI, 0.83 to 1.05) or OS (HR, 0.99; 95% CI, 0.85 to 1.14) for overall patients. Patients in the bevacizumab group presented more Grade 3 or 4 adverse effects than those in the control group (66% vs. 54%, p=0.01), but not for neutropenia and thrombocytopenia, respectively. At week 54, the mean global QoL score was 6.4 higher in the CG group (p<0.01). At week 76, 374 (24%) were assessed and no difference was found between the two groups (Table 4-2).

Subgroup analysis showed that among 502 high-risk patients (defined as stage III with residual >1 cm, or stage IV, including 30 [6%] inoperable patients), bevacizumab led to longer PFS (RMST, 20.0 months vs. 15.9 months; HR, 0.73; 95% CI, 0.61 to 0.88) and OS (RMST, 39.3 months vs. 34.5 months; HR, 0.78; 95% CI, 0.63 to 0.97; p=0.03) (Table 4-4). For non-high-risk patients (defined as stage III with residual ≤1 cm or stage I-II), there was no statistical difference for PFS or OS between the two groups. The p-value of 0.01 of the interaction test approved the benefit of bevacizumab in high-risk patients.

The ICON7 trial also reported subgroup analysis for histological types (Table 4-5). No benefit of bevacizumab was reported for OS outcome in 80 patients with low-grade serous tumours (RMST, 50.5 vs. 50.4 months) or 159 patients with clear cell tumours (RMST, 47.6 vs. 48.0 months).

The GOG-0218 trial recruited 1873 stage III-IV patients [14, 16, 17, 21]. After surgery, 625 patients received paclitaxel and carboplatin for six cycles in the CG, 623 patients received bevacizumab 15 mg/kg from cycle 2 to cycle 22 in EG1 in addition to treatment in CG, 625 patients received bevacizumab from cycle 2 to cycle 6 in the EG2 in addition to the CG treatment. Overall, patients in EG1 had a better PFS result than those in the CG (14.1 vs. 10.3 months; HR, 0.72; 95% CI, 0.63 to 0.82; p<0.01), but the final results showed no benefit for OS (43.4 vs. 41.1 months; HR, 0.96; p=0.53) at a median follow-up of 8.6 years. Patients in EG1 experienced more Grade 3 or 4 neutropenia and fatal adverse effects than those in the CG, but did not reach statistical significance (Table 4-2). A total of 1388 (74%) patients completed QoL assessment at six months, and there were no significant differences across the three treatment groups (Table 4-2).

The GOG-0218 trial reported several subgroup analyses. Analysis by gene mutation (*BRCA* and other HRD), revealed that with or without a mutation, patients in EG1 had greater PFS than those in placebo. However, the p-value was not statistically significant in the subgroup of patients with the mutation (Table 4-3). By clinical stage, concurrent and maintenance therapy with bevacizumab led to greater PFS than placebo in patients with stage III with residual ≤1 cm, stage III residual >1 cm, or stage IV, at median 1.5 years, respectively; and greater OS in patients with stage IV (42.8 vs. 32.6 month) at median 8.6 years (Table 4-4). By histological

subtype, in the serous tumour subgroup, only one statistically significant result was reported that patients in EG1 had better PFS than those in the CG (Table 4-5).

2. PARP inhibitor — veliparib

The VELIA/GOG-3005 trial recruited 382 patients to receive paclitaxel plus carboplatin three-weekly plus veliparib 150 mg twice a day by mouth for six cycles followed by veliparib 400 mg twice a day to 30 cycles (EG1); 383 patients received paclitaxel plus carboplatin three-weekly plus veliparib 150 mg twice a day by mouth for six cycles followed by placebo (EG2); and 375 patients in the CG received placebo instead of veliparib [22](Table 4-1). At median follow-up of 28 months, patients in EG1 had a greater PFS than those in the placebo group (23.5 months vs. 17.3 months; HR, 0.69; 95% CI, 0.56 to 0.83; p<0.01); data for OS were not mature. There was no PFS benefit found in EG2 when compared with CG (15.2 months vs. 17.3 months; HR, 1.07; 95% CI, 0.90 to 1.29; p>0.05). However, veliparib led to more Grade 3 and 4 adverse effects of neutropenia, thrombocytopenia, nausea, vomiting, and any adverse effects. No clinically significant difference was found in QoL assessed by National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Ovarian Symptom Index-18 (Table 4-2).

The subgroup analysis favoured veliparib regardless of a patient's *BRCA* mutation status, but the PFS benefit in patients with *BRCA1/2* mutation was greater than that in wild-type *BRCA1/2* patients (interaction test p=0.02 [Table 4-3]). The subgroup analyses also showed that veliparib led to greater PFS in patients with HRD and patients with stage III disease, rather than in patients without HRD or stage IV disease. However, the interaction test's p-value was not statistically significant for both subgroup analyses (Table 4-3 and Table 4-4). It is possible that the small sample size may not have allowed identification of the difference between the two groups.

3. Farnesyltransferase inhibitor — lonafarnib

The Meier et al. 2012 trial with 105 patients investigated the efficacy of lonafarnib as maintenance therapy but did not find any benefit in PFS (14.2 vs. 17.8 months; HR, 1.28; 95% CI, 0.83 to 2.0; p=0.27) or OS (34.4 vs. 47.3 months; HR, 1.61; 95% CI, 0.91 to 2.50; p=0.08), when compared with observation [39]. No QoL outcomes were reported.

4. Protein kinase C-beta inhibitor — enzastaurin

The Vergote 2013 trial with 142 patients did not find that additional enzastaurin as an adjuvant and maintenance therapy could improve PFS when compared with no maintenance therapy (18.9 vs. 15.2 months; HR, 0.80; 95% CI, 0.50 to 1.29; p=0.37) [41]. No QoL outcomes were reported.

5. Triple angiokinase inhibitor — nintedanib

Two trials (the AGO-OVAR 12 and CHIVA trials) investigated the effectiveness of nintedanib in the target patients. The AGO-OVAR12 trial [37, 49] with a sample size of 1366 reported that at a median five-year follow-up, patients in the nintedanib group had greater PFS than those in the placebo group (17.6 vs. 16.6; HR, 0.86; 95% CI, 0.75 to 0.98; p=0.03), but the average absolute different time was only 1.0 month between the two groups. No benefit was found for OS at median five years (median 62.0 months vs. 62.8 months; HR, 0.99; 95% CI, 0.83 to 1.17; p=0.86). Patients in the nintedanib maintenance group experienced more Grade 3 or greater adverse effects of anemia, neutropenia, and thrombocytopenia. The QoL was not affected during treatment with nintedanib measured by EORTC QLQ-C30 (Table 4-2). The subgroup analysis showed that there was no statistical difference between the two groups in high-risk patients for PFS (12.7 months vs. 11.3 months; HR, 1.03; p=NS), but nintedanib led to higher PFS in non-high-risk patients (27.7 vs. 21.7 months; HR, 0.77; p-value <0.05). The p-

value of the interaction test was statistically significant (p=0.04) and supported the benefit of nintedanib in non-high-risk patients.

The CHIVA trial with a sample size of 188 was published as an abstract in ASCO annual meeting [38]. Its conclusions were that the addition of nintedanib led to worse PFS (14.4 months vs. 16.8 months; HR, 1.50; p=0.02) and OS (37.7 months vs. 44.1 months; HR, 1.54; p=0.053) in patients with stage III or IV ovarian cancer, and patients experienced greater Grade 3 or higher toxicities (92% vs. 71%) (Table 4-2).

6. Angiopoietin inhibitor — trebananib

The TRINOVA trial enrolled 678 patients to receive paclitaxel plus carboplatin three-weekly plus trebananib 15 mg/kg intravenously weekly for 18 weeks, followed by trebananib alone to 18 months; 337 patients in the control group received placebo instead of trebananib [40](Table 4-1). At a median of 27.4 months, no statistically significant difference was found between the two groups for PFS (15.9 months vs. 15.0 months; HR, 0.93; 95% CI, 0.79 to 1.09; p=0.36); data for OS were not mature. Trebananib led to more fatal treatment-related adverse events, but not for hematological, gastrointestinal, neurological, or any Grade 3 or 4 adverse effects. No significant difference was reported for QoL (Table 4-2).

The subgroup analyses showed no statistically significant difference between intervention and control group for different primary tumour locations (ovarian, primary peritoneal, and fallopian tube), histological subtypes (serous and non-serous), and disease stages (stage IIIA/B and stage IIIC/IV) (Table 4-3 and Table 4-4).

Ongoing, Unpublished, or Incomplete Studies

The National Cancer Institute Clinical Trials Database (http://www.clinicaltrials.gov/) was searched on October 4, 2019 for potential trials meeting the selection criteria for this systematic review. There are 25 ongoing, unpublished, or incomplete trials that should be checked for potential inclusion in a future update of this guideline (Appendix 5).

DISCUSSION

This systematic review focuses on the effectiveness of consolidation and maintenance therapy agents in patients with newly diagnosed stage II, III, or IV EOC after completion of first-line therapy with surgery and adjuvant therapy (patients who require neoadjuvant therapy before surgery also qualify for this guideline). For consolidation therapy with chemotherapy, the existing evidence from eight trials with nine full–text publications does not show benefit from the additional chemotherapy, and causes more adverse effects. Thus, the use of this approach cannot be recommended in routine clinical practice. For maintenance therapy, based on current medical evidence, (Tables 4-2 to 4-5), we believe that one of four medical agents can be used as a maintenance therapy in the target population: olaparib, niraparib, bevacizumab, and veliparib. Table 4-6 summarizes their usage, treatment time, and appropriate patient population. It should be noted that as the data from a number of the PARP inhibitor studies mature, the evidence to support their use in this target population may be strengthened. Following this, network meta-analyses can be performed to indicate which agent is optimal among PARP inhibitors, between PARP inhibitors and Anti-VEGF monoclonal antibody, and even for some subgroup patients, such as patients with *BRCA1/2* mutation.

There are several limitations to this systematic review. First, although we only included RCTs, the risk of bias ranged from low to high using the Cochrane Collaboration tools for randomized studies (Appendix 5). This led to the overall certainty of evidence for each comparison being high for two RCTs [11, 37, 47, 49] and either moderate or low for others after combining the consideration of inconsistency, indirectness, imprecision, and publication bias.

Second, in 19 of 29 trials, patients with complete remission, partial remission, or no progression were randomized to receive either maintenance therapy, or no further treatment or placebo. However, the remaining 10 trials randomized patients before adjuvant therapy, and did not inform the readers of how many patients had progression in each group after adjuvant therapy. Patients who had progression after adjuvant treatment will often receive further chemotherapy treatments rather than continue on to maintenance therapy and, thus, they may not be appropriate to remain in these trials. Also, the percentage of patients with progression after adjuvant therapy and the subsequent choices for managements may be not balanced between the two groups in each trial, which would potentially impact the final effect magnitude of the maintenance therapy. Moreover, as there was no maintenance-alone arm in these studies, it is impossible to determine the benefit of concurrent and maintenance agent compared with agent alone given as maintenance treatment. The interventions that were included in these eight trials are topotecan [2, 7], bevacizumab [14-21], lonafarnib [39], enzastaurin [41], nintedanib [37, 38, 49]], veliparib [22], and trebananib [40]. Third, patients' QoL outcomes are important for patients and clinicians to weigh the benefits and harms of maintenance therapy. However, only 11 of 26 trials reported QoL and the use of measurement tools varies. In the AGO-OVAR 16 study [24], QoL results varied depending on the tool used where the changes from baseline favoured the experimental group using EORTC QoL-C30 score, favoured the control group using the QLQ-OV28 score, and showed no statistical difference between the two groups using the EQ-5D-3L. Fourth, the main four histological subtypes of EOC are serous (including high-grade and low-grade), endometrioid, mucinous, and clear cell. Different histological subtypes may have differential sensitivities to certain maintenance therapies. However, only the two trials of bevacizumab had subgroup analyses for different histological subtypes and showed that patients with low-grade serous or clear cell tumours [15, 18-20], or with non-serous tumours [14, 16, 17, 21] did not benefit from bevacizumab. However, each group in the subgroup analysis had less than 110 patients and there was not a preplanned sample size calculation for the subgroup analysis in these two trials, respectively. It is possible that the sample size may be too small to identify the difference. Fifth, no RCT or subgroup analysis focuses on patients with stage II only. Sixth, the PAOLA-1 trial investigated the efficacy of olaparib, but all patients received bevacizumab [12]. To date, there is no evidence that taking bevacizumab with adjuvant chemotherapy and as maintenance therapy after chemotherapy has a greater survival benefit than taking it solely as maintenance therapy after adjuvant chemotherapy. Moreover, the GOG-0218 trial did not find PFS or OS benefit in patients taking bevacizumab with adjuvant chemotherapy compared with adjuvant chemotherapy alone [14, 16, 17, 21]. Additionally, the authors of the PAOLA-1 trial realized the potential contamination bias due to the lack of an arm with olaparib monotherapy in their discussion section. Thus, we cannot recommend bevacizumab plus olaparib as a combination maintenance therapy in the target patients.

CONCLUSIONS

At the present time, for patients with newly diagnosed EOC, there is evidence to support olaparib, niraparib, bevacizumab, and veliparib as an option for maintenance therapy. It is expected that the OS outcomes of olaparib, niraparib, and veliparib will become clearer as these studies mature. After ongoing trials are completed, the effectiveness of these maintenance therapy options is expected to become clearer.

Table 4-1. Trial and patient characteristics (study order is based on the latest publication year and alphabetical by first author's last name under each subheading)

Author year (Trial name)	RCT phase; Country	N; Mean/ Median (range) age (y)	Experimental group (EG) vs. Control group (CG)	FIGO stage	Histological feature	Size of residual disease
1. Consolidation therapy with chemotherapy						
van der Burg 2014	III; Netherlands	112; 58 (30 to 80)	Pts without progressive disease after receiving either paclitaxel + cisplatin or paclitaxel + carboplatin for 6 cycles of weekly intervention or 3 cycles of 3-weekly: **EG:** Paclitaxel 175 mg/m^2, + cisplatin 75 mg/m^2 or + carboplatin AUC=6 IV 3-weekly, 6 cycles	II: 4% III: 68% IV: 28%	Serous: 70% Endometrioid: 13% Mucinous: 4% Clear cell: 5% Other: 8%	≤1 cm: 45% >1 cm: 55%
		122; 56 (21 to 82)	**CG:** Paclitaxel 175 mg/m^2, + cisplatin 75 mg/m^2 or + carboplatin AUC=6 IV 3-weekly, 3 cycles	II: 10% III: 61% IV: 29%	Serous: 57% Endometrioid: 14% Mucinous: 4% Clear cell: 2% Other: 23%	≤1 cm: 46% >1 cm: 54%
Markman 2009, 2003 (SWOG-9701/GOG-178)	III; USA	150; 58	Pts with CR following 5 to 6 cycles of platinum + paclitaxel-based Tx: **EG:** Paclitaxel 175 mg/m^2 IV 4-weekly, 12 cycles	III: 86% IV: 14%	NR	NR
		146; 59	**CG:** Paclitaxel 175 mg/m^2 IV 4-weekly, 3 cycles	III: 86% IV: 14%		
Pecorelli 2009 (After-6 protocol 1)	III; Italy	101; 59 (19-78)	Pts with CR after 6 cycles of paclitaxel + platinum-based Tx: **EG:** Paclitaxel 175 mg/m^2 IV 3-weekly, 6 cycles	II: 15% III: 78% IV: 6% Unknown: 1%	Serous: 70% Endometrioid: 12% Mucinous: 2% Clear cell: 1% Other: 15%	0 cm: 52% ≤1 cm: 9% 1-2 cm: 11% >2 cm: 22% Unknown: 6%
		99; 58 (35-76)	**CG:** Observation	II: 14% III: 79% IV: 6% Unknown: 1%	Serous: 73% Endometrioid: 15% Mucinous: 1% Clear cell: 3% Other: 8%	0 cm: 52% ≤1 cm: 10% >1-2 cm: 10% >2 cm: 19% Unknown: 9%
Bolis 2006	II; Italy	64; 56 (30-72)	Pts with CR after first-line therapy with surgery plus platinum-based Tx: **EG:** Epidoxorubicin 120 mg/m^2 IV 3-weekly, 4 cycles	IIC: 6% III: 81% IV: 13%	Serous: 56% Other: 44%	0 to <1 cm: 42% >1 cm: 52% NOP: 6%
		74; 56 (29-75)	**CG:** Observation	IIC: 3% III: 92% IV : 5%	Serous: 55% Other: 45%	0 to <1 cm or: 43% >1 cm: 45% NOP: 12%
Nicoletto 2004	II; Italy	60; 55 (38-76)	Pts with CR after surgery and first-line Tx: **EG:** 5-fluorouracil 500 mg/m^2 IV for 5 days then cisplatin 100 mg/m^2 at Day 6th and 7th, 4-weekly, 3 cycles	IC: 5% IIB-C: 21% III-IV: 74%	Serous: 74% Endometrioid: 13% Mucinous: 0% Clear cell: 3% Other: 10%	≤2 cm: 84% >2 cm: 16%
		61; 55 (16-73)	**CG:** Observation	IC: 20% IIB-C: 28% III-IV: 52%	Serous: 52% Endometrioid: 25% Mucinous: 7% Clear cell: 3% Other: 13%	≤2 cm: 90% >2 cm: 10%

Piccart 2003 (EORTC 55875)	III; Belgium, France, Italy, Netherlands, Poland	76; 55 (34-75)	Pts with CR following IV platinum-based Tx: **EG:** Cisplatin 90 mg/m^2 IP 3-weekly, 4 cycles	IIB/C: 4% III: 96%	Serous: 68% Other: 32%	1 cm: 34% >1 cm: 47% NOP: 17%
		76; 55 (30-74)	**CG:** Observation	IIB/C: 4% III: 96%	Serous: 57% Other: 43%	1 cm: 46% >1 cm: 37% NOP: 17%
Pfisterer 2006 (AGO-OVAR 7)	III; France, Germany	658; 60 (20 to 81)	Pts after adjuvant paclitaxel + carboplatin (but no details of pts' response to the adjuvant Tx): **EG**: topotecan 1.25 mg/m^2 IV for Days 1-5, 3-weekly, 4 cycles	II: 9% III: 72% IV: 19%	Serous: 71% Endometrioid: 9% Mucinous: 3% Unknown: 17%	≤1 cm: 62% >1 cm: 29% Unknown:9%
		650; 60 (20 to 81)	**CG**: Observation	II: 8% III: 76% IV: 16%	Serous: 71% Endometrioid: 8% Mucinous: 4% Unknown: 14%	≤1 cm: 61% >1 cm: 30% Unknown: 9%
De Placido 2004 (MITO-1)	III; Italy	137; 55 (22-73)	Pts without progressive disease after adjuvant paclitaxel + carboplatin: **EG**: Topotecan 1.5 mg/m^2/d IV for Days 1-5, 3-weekly, 4 cycles	IC: 12% II: 15% III: 66% IV 8%	NR	0 cm: 47% ≤1 cm: 20% >1 cm: 33
		136; 56 (29-74)	**CG**: Observation	IC: 14% II: 10% III: 65% IV: 11%		0 cm: 46% ≤1 cm: 20% >1 cm: 34%
2. Maintenance therapy with biological therapy						
2.1. Patients randomized after the first-line therapy with surgery and adjuvant chemotherapy						
2.1.1. Alpha-interferon						
Alberts 2006	III; USA	35; 56 (31 to 71)	Pts with CR after an adjuvant Tx containing cisplatin (≥400 mg/m^2) or carboplatin (≥1200 mg/m^2): **EG:** Alpha-interferon 50 × 10^6 IU IP Weekly, 6 cycles	III: 100%	Serous: 34% Endometrioid: 6% Mucinous: 3% Other: 14% Unknown: 43%	NR
		35; 53 (26 to 72)	**CG:** Observation	III: 100%	Serous: 34% Endometrioid: 14% Mucinous: 0% Other: 9% Unknown: 43%	
Hall 2004	III; UK	149; 58 (31-76)	Pts without progression after postoperative Tx: **EG:** Interferon-alpha 2a 4.5 mega-units subcutaneously 3 days per week to disease progression, in response to toxicity, or patient request	I: 7% II: 14% III: 63% IV: 15%	Serous: 45% Endometrioid: 18% Mucinous: 7% Clear cell: 3% Other: 27%	0 cm: 15% <2 cm: 30% 2-5 cm: 16% >5 cm: 24% Unknown:15%
		149; 57 (33-78)	**CG:** Observation	I: 8% II: 13% III: 64% IV: 15%	Serous: 48% Endometrioid: 23% Mucinous: 8% Clear cell: 3% Other: 18%	0 cm: 17% <2 cm: 34% 2-5 cm: 9% >5 cm: 27% Unknown:13%
2.1.2. EGFR inhibitor—Erlotinib						
Vergote 2014	III;	420; 59 (19-85)	Pts without progression after debulked surgery and 6-9 cycles of first-line platinum-based Tx: **EG:** Erlotinib 150 mg PO QD to 2 years	I: 8% II: 7% III: 65%	Serous: 66% Endometrioid: 6% Mucinous: 2%	NR

	Europe, Australia, New Zealand			IV: 20%	Clear cell: 6% Other: 20%	
		415; 59 (27-84)	**CG:** Observation	I: 6% II: 8% III: 70% IV: 16%	Serous: 58% Endometrioid: 9% Mucinous: 2% Clear cell: 6% Other: 25%	
2.1.3. Anti-idiotypic CA-125 antibody						
2.1.3.1. Abagovomab						
Sabbatini 2013 (MIMOSA)	III; USA	593; 56 (46 to 67)	Pts with CR after debulking surgery and 6-8 cycles of taxane- and platinum-based Tx: **EG:** Abagovomab subcutaneously 2-weekly for 3 injections, then 4-weekly to 21 months	III: 87% IV: 13%	Serous: 82% Endometrioid: 6% Mucinous: 1% Other: 11%	0 cm: 48% ≤1 cm: 33% >1 cm: 19%
		295; 56 (45 to 67)	**CG:** Placebo to 24 months	III: 86% IV: 14%	Serous: 83% Endometrioid: 7% Mucinous: 1% Other: 9%	0 cm: 47% ≤1 cm: 32% >1 cm: 21%
2.1.3.2. Oregovomab						
Berek 2009, Berek 2008, Berek 2004	III; USA	251; 59 (28 to 84)	Pts with CR after debulked surgery and carboplatin and paclitaxel first-line Tx**:** **EG:** Oregovomab 2 mg IV, 4-weekly for 3 cycles, then 12-weekly to 5 years	I: 0% II: 1% III: 92% IV: 7%	Serous: 80% Endometrioid: 5% Mucinous: 1% Clear cell: 4% Other: 10%	<1 cm: 89% 1-2 cm: 9% >2 cm: 2% Unknown: 0%
		120; 59 (32 to 85)	**CG:** Placebo	I: 1% II: 0% III: 93% IV: 7%	Serous: 73% Endometrioid: 12% Mucinous: 1% Clear cell: 2% Other: 12%	<1 cm: 90% 1-2 cm: 9% >2 cm: 0% Unknown: 1%
2.1.4. Poly ADP ribose polymerase (PARP) inhibitor						
2.1.4.1. Olaparib						
Moore 2018 (SOLO1 trial)	III; 15 countries[a]	260; >18	Pts with *BRCA1/2* or both *BRCA1/2* with CR or PR after surgery and platinum-based Tx: **EG:** Olaparib 300 mg PO BID, median 24.6 months	III: 85% IV: 15%	Serous: 95% Endometrioid: 3% Mixed serous and endometriod: 2%	NR
		131; >18	**CG:** Placebo, median 13.9 months	III: 80% IV: 20%	Serous: 99% Mixed serous and endometriod: 1%	
Ray-Coquard 2019 (PAOLA-1/ENGOT-OV25)	III; 11 countries[b]	537; 61 (32 to 87)	Pts with CR or PR after surgery and platinum-based Tx + bevacizumab (4 months): **EG:** Olaparib 300 mg PO BID to 24 months + bevacizumab 15 mg/kg IV 3-weekly to 11 months	III: 70% IV: 30%	Serous: 97% Endometrioid: 2% Other: 1%	≤1 cm: 60% >1 cm: 33% NOP: 7%
		269; 60 (26 to 85)	**CG:** Placebo for olaparib + bevacizumab 15 mg/kg IV 3-weekly to 11 months	III: 69% IV: 31%	Serous: 94% Endometrioid: 3% Other: 3%	≤1 cm: 59% >1 cm: 33% NOP: 8%
2.1.4.2. Niraparib						
Gonzalez-Martin 2019	III; 20 countries[c]	487; 62 (32 to 85)	Pts with CR or PR after surgery and platinum-based Tx: **EG:** Niraparib 200-300 mg PO daily to 3 years	III:65% IV: 35%	Serous: 96% Endometrioid: 2% Other: 2%	NR

(PRIMA/ENGOT-OV26/GOG-3012)		246; 62 (33 to 88)	**CG:** Placebo	III:64% IV: 36%	Serous: 94% Endometrioid: 4% Other: 2%	
		247; 58 (32 to 83)	Pts with HRD with CR or PR after surgery and platinum-based Tx: **EG:** Niraparib 200-300 mg PO daily to 3 years	III:65% IV: 35%	Serous: 95% Endometrioid: 2% Other: 3%	
		126; 58 (33 to 82)	**CG:** Placebo	III:62% IV: 38%	Serous: 92% Endometrioid: 5% Other: 3%	
2.1.5. VEGFR tyrosine kinase inhibitor						
2.1.5.1. Pazopanib						
Vergote 2019, Friedlander 2018, Harter 2016, du Bois 2014, (AGO-OVAR 16)	III; Europe, Asia, North America, Australia	472; 56 (25 to 85)	Pts without progression after surgery and ≥5 cycles platinum-taxane-based Tx: **EG:** Pazopanib 800 mg/d PO QD to 24 months	II: 9% III: 75% IV: 16%	Serous: 72% Endometrioid: 6% Mucinous: 5% Clear cell: 4% Other: 13%	NR
		468; 57 (20 to 85)	**CG:** Placebo to 24 months	II: 9% III: 74% IV: 17%	Serous: 75% Endometrioid: 5% Mucinous: 3% Clear cell: 3% Other: 14%	
Kim 2018[d] (East Asian study plus subgroup of AGO-OVAR 16)	For East Asian study: II; China, Korea	177; 52 (22 to 75)	Pts without progression after surgery and first-line Tx: **EG:** Pazopanib 800 mg/d PO QD to 24 months	II: 16% III: 68% IV: 21%	Serous: 59% Endometrioid: 6% Mucinous: 10% Clear cell: 3% Other: 16%	≤1 cm: 41% >1 cm: 47% Unknown: 12%
		173; 55 (27 to 86)	**CG:** Placebo to 24 months	II: 15% III: 71% IV: 14% Unknown: 1%	Serous: 61% Endometrioid: 5% Mucinous: 14% Clear cell: 5% Other: 15%	≤1 cm: 39% >1 cm: 40% Unknown: 21%
2.1.5.2. Sorafenib						
Hainsworth 2015	II; USA	43; 63 (31 to 78)	**EG:** Paclitaxel 175 mg/m^2 + carboplatin AUC=6+, 3-weekly, 6 cycles and sorafenib 400 mg PO BID for 18 weeks concurrently with chemotherapy [e]	III: 77% IV:18% Other:5%	NR	NR
		42; 62 (42 to 80)	**CG:** Paclitaxel 175 mg/m^2 + carboplatin AUC=6+, 3-weekly, 6 cycles, then observation	III: 67% IV: 33%		
Herzog 2013	IIB; Europe, Asia, USA, Canada	123; 57 (30 to 84)	Pts with CR after debulked surgery and platinum/taxane: **EG:** Sorafenib 400 mg PO, BID to 3 years	III or IV: 100%	Serous: 64% Mucinous: 5% Clear cell: 7% Other:24%	≤1 cm: 85% >1 cm: 8% Unknown: 7%
		123; 54 (28 to 81)	**CG:** Placebo to 3 years	III or IV: 100%	Serous: 65% Mucinous: 2% Clear cell: 3% Other: 30%	≤1 cm: 85% >1 cm: 8% Unknown: 7%
2.2. Patients randomized after the first-line therapy with surgery but before adjuvant chemotherapy						
2.2.1. Anti-VEGF monoclonal antibody—Bevacizumab						

Gonzalez-Martin 2019, Oza 2015, Stark 2013, Perren 2011 (ICON7)	III; Europe, Canada, Australia, New Zealand	764; 57 (24 to 80)	**EG:** Paclitaxel 175 mg/m^2 + carboplatin AUC=5/6 + bevacizumab 7.5mg/kg, IV 3-weekly, 6 cycles; then bevacizumab 7.5mg/kg, 3-weekly, 12 cycles	I/IIA: 9% IIB/C: 9% III: 68% IV: 14%	Serous: 69% Endometrioid: 8% Mucinous: 2% Clear cell: 9% Other:12%	0 cm: 47% ≤1 cm: 25% >1 cm: 26% NOP: 2%
		764; 57 (18 to 81)	**CG:** Paclitaxel 175 mg/m^2 + carboplatin AUC=5/6, IV 3-weekly, 6 cycles; then observation	I/IIA: 10% IIB/C: 9% III: 68% IV: 13%	Serous: 69% Endometrioid: 7% Mucinous: 2% Clear cell: 8% Other: 14%	0 cm: 49% ≤1 cm: 23% >1 cm: 26% NOP: 2%
Tewari 2019, Norquist 2018, Monk 2013, Burger 2011 (GOG-0218)	III; USA, Canada, South Korea, Japan	623; 60 (22 to 89)	**EG1:** Paclitaxel 175 mg/m^2 + carboplatin AUC=6, IV 3-weekly, 6 cycles; with bevacizumab 15 mg/km IV added from cycle 2 through 22	III: 74% IV: 26%	Serous: 84% Endometrioid: 4% Mucinous: 1% Clear cell: 3% Other: 8%	Among III Pts: ≤1 cm: 47% >1 cm: 53%
		625; 60 (24 to 88)	**EG2:** Paclitaxel 175 mg/m^2 + carboplatin AUC=6, IV 3-weekly, 6 cycles; with bevacizumab 15 mg/km IV added from cycle 2 through 6 + placebo added in cycle 7 through 22	III: 74% IV: 26%	Serous: 83% Endometrioid: 2% Mucinous: 1% Clear cell: 4% Other: 10%	Among III Pts: ≤1 cm: 44% >1 cm: 56%
		625; 60 (25 to 86)	**CG:** Paclitaxel 175 mg/m^2 + carboplatin AUC=6, IV 3-weekly, 6 cycles; with placebo added in cycle 2 through 22	III: 76% IV: 24%	Serous: 87% Endometrioid: 3% Mucinous: 1% Clear cell: 2% Other: 7%	Among III Pts: ≤1 cm: 46% >1 cm: 54%
2.2.2. Poly ADP ribose polymerase (PARP) inhibitor—Veliparib						
Coleman 2019 (VELIA/GOG-3005)	III; 11 countries[f]	382; 62 (30 to 85)	**EG1:** Paclitaxel 175 mg/m^2 + carboplatin AUC=6, 3-weekly, 6 cycles and veliparib 150 mg PO BID for 6 cycles concurrently with chemotherapy. Pts without progression continued veliparib 400 mg BID to 30 cycles (but all the pts were analyzed together)	III: 77% IV: 23%	NR	0 cm: 44% ≤1 cm: 20% >1 cm: 29% Unknown: 7%
		383; 62 (22 to 88)	**EG2:** Paclitaxel 175 mg/m^2 + carboplatin AUC=6, 3-weekly, 6 cycles and veliparib 150 mg PO BID for 6 cycles at the same time and Pts without progression continued placebo to 30 cycles	III: 75% IV: 25%		0 cm: 43% ≤1 cm: 20% >1 cm: 32% Unknown: 5%
		375; 62 (33 to 86)	**CG:** Paclitaxel 175 mg/m^2 + carboplatin AUC=6, 3-weekly, 6 cycles and placebo matched to EG	III: 78% IV: 22%		0 cm: 44% ≤1 cm: 21% >1 cm: 29% Unknown: 6%
2.2.3. Farnesyltransferase inhibitor—Lonafarnib						
Meier 2012	II; Germany	53; 61 (21 to 80)	**EG:** Paclitaxel 175 mg/m^2 + carboplatin AUC=5 + lonafarnib 100 mg PO Bid, 3-weekly, 6 cycles; then lonafarnib 200 mg PO Bid to 6 months after chemotherapy completion	IIB-III: 83% IV: 17%	Serous: 66% Endometrioid: 11% Mucinous: 2% Other: 21%	NR
		52; 56 (41 to 74)	**CG:** Paclitaxel 175 mg/m^2 + carboplatin AUC=5, IV 3-weekly, 6 cycles; then observation	IB-III: 81% IV: 19%	Serous: 71% Endometrioid: 8% Mucinous: 8% Other: 13%	
2.2.4. Protein kinase C-beta inhibitor—Enzastaurin						

Vergote 2013	II; Belgium, Germany, Spain, Poland, USA	69; 54 (28 to 80)	**EG:** Paclitaxel 175 mg/m^2 + carboplatin AUC=5 IV plus enzastaurin 1125 mg PO on day before paclitaxel and carboplatin, followed by oral enzasturin 500 mg PO daily, 3-weekly, 6 cycles; then oral enzastaurin 500 mg PO daily to 3 years	IIA to IIIB: 17% IIIC AND IV: 83%	NR	NR
		73; 55 (25 to 84)	**CG:** Paclitaxel 175 mg/m^2+ carboplatin AUC=5 IV + placebo PO. 3-weekly, 6 cycles; then placebo	IIA to IIIB: 21% IIIC AND IV: 79%		
2.2.5. Triple angiokinase inhibitor—Nintedanib						
Ray-Coquard 2019, Du Bois 2016 (AGO-OVAR 12)	III; Germany, Norway, France, Italy, Austria, Spain, Netherlands, Slovakia	911; 58 (23 to 84)	**EG:** Carboplatin AUC= 5 + paclitaxel 175 mg/m^2 IV plus nintedanib 200 mg PO BID on days 2-21, 6 cycles; then nintedanib 200 mg PO BID up to 120 weeks	IIB: 11% III: 65% IV: 24%	Serous: 72% Endometrioid: 9% Mucinous: 3% Clear cell: 2% Other: 14%	NR
		455; 58 (21 to 79)	**CG:** Carboplatin AUC= 5 + paclitaxel 175 mg/m^2 IV plus placebo 3-weekly, 6 cycles; then placebo up to 120 weeks	IIB: 10% III: 66% IV: 24%	Serous: 70% Endometrioid: 9% Mucinous: 3% Clear cell: 3% Other: 15%	
Ferron 2019 [Abstract] (CHIVA)	II; France	188; ≥18	**EG:** Paclitaxel 175 mg/m^2 + carboplatin AUC=5 IV 3-weekly, 6 cycles plus nintedanib 200 mg PO BID on day 2-21 at cycles 1, 2, 5 and 6; then up to 2 years.	III to IV	NR	NR
			CG: Paclitaxel 175 mg/m^2 + carboplatin AUC=5 IV 3-weekly, 6 cycles plus placebo; then placebo			
2.2.6. Angiopoietin inhibitor—Trebananib						
Vergote 2019 (TRINOVA-3/ENGOT-ov2/GOG-3001)	III; 14 countries[g]	678; 59 (51 to 66)	**EG:** Paclitaxel 175 mg/m^2 + carboplatin AUC=5 IV 3-weekly, 6 cycles plus trebananib 15 mg/kg intravenous weekly; then up to 18 months	III: 72% IV: 27% Unknown: 1%	Serous: 77% Endometrioid: 3% Other:20%	≤1 cm: 57% >1 cm: 43%
		337; 59 (51 to 66)	**CG:** Paclitaxel 175 mg/m^2 + carboplatin AUC=5 IV 3-weekly, 6 cycles plus placebo	III: 76% IV: 24%	Serous: 78% Endometrioid: 3% Other:19%	≤1 cm: 56% >1 cm: 44%

Abbreviations: AUC = area under the curve; BID = twice a day, CA-125 = cancer antigen 125, Chemo = chemotherapy, CG = control group; CR = complete remission/complete response, EG = experimental group; EGFR = epidermal growth factor receptor, FIGO = the International Federation of Gynecology and Obstetrics, HRD = homologous-recombination deficiency, IP = intraperitoneal, IV = intravenous, NA = not assessed, NOP = Not operated, NR = not reported, PARP = poly ADP ribose polymerase, PO = by mouth, PR = partial response/partial remission , Pts = patients, QD = once a day, RCT = randomized controlled trial, Tx = treatment, UK = United Kingdom, USA = United States, VEGF = vascular endothelial growth factor.

[a] Fifteen countries: Australia, Brazil, Canada, China, France, Israel, Italy, Japan, Netherlands, Poland, Russia, South Korea, Spain, United Kingdom, United States.

[b] Eleven countries: Austria, Belgium, Denmark, Finland, France, Germany, Italy, Japan, Monaco, Spain, Sweden.

[c] Twenty countries: Belgium, Canada, Czechia, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Norway, Poland, Russia, Spain, Sweden, Switzerland, Ukraine, United Kingdom, United States.

[d] This paper was accepted by the journal and was published online in October 2015, and included east Asian patients from AGO-OVAR 16.

[e] The authors stated that patients without progression continued sorafenib to 12 months, but all patients were analyzed together. Since the results were not statistically significant (Table 4-2), we kept this study with Herzog 2013 under ***2.1.5.2. Sorafenib.***

[f] Eleven countries: Australia, Brazil, Denmark, Israel, Japan, New Zealand, Poland, South Korea, Spain, United Kingdom, United States (this information is derived from https://clinicaltrials.gov/ based on trial ID of NCT 02470585).
[g] Fourteen countries: Austria, Belgium, Canada, China, Denmark, Germany, Italy, Japan, Netherlands, Russia, South Korea, Spain, United Kingdom, United States.

Table 4-2. Survival, adverse events, and quality of life outcomes (study order is based on the latest publication year and alphabetical of the first author's last name under each subheading)

Author year (Trial name)	Intervention: Experimental group (EG) vs. Control group (CG)	PFS Follow-up time: Median time /survival rate; HR (95% CI), p-value	OS Follow-up time: Median time/survival rate, HR (95% CI), p-value	Grade 3 or higher adverse effects[a]				Quality of life (QOL)
1. Maintenance therapy with chemotherapy								
1.1 Patients randomized after the first-line therapy with surgery and adjuvant chemotherapy								
van der Burg 2014	**EG** (n=112): Paclitaxel + cisplatin/ carboplatin 6 cycles vs. **CG** (n=122): Paclitaxel + cisplatin/ carboplatin 3 cycles	At median 10.3 years: 19.3 mo (95% CI, 17.7 to 20.9) vs. 17.1 mo (95% CI, 14.0 to 20.2); p=0.46	At median 10.3 years: 44.9 mo (95% CI, 35.1 to 54.6) vs. 46.9 mo (95% CI, 40.8 to 53.1); p=0.60	NR				NR
Markman 2009, 2003 (SWOG-9701/GOG-178)	**EG** (n=150): Paclitaxel monthly cycle to 12 mo vs. **CG** (n=146): Paclitaxel to 3 mo	F-up (NR): 22 mo vs. 14 mo; HR=0.68; p<0.01	F-up (NR): 53 mo vs. 48 mo; HR=0.88; p=0.40	Hematologic Neurologic	EG (n=149) 5% 6%	CG (n=136) 10% 1%	p-value 0.11 0.02	NR
Pecorelli 2009 (After-6 Protocol 1)	**EG** (n=101): Paclitaxel to 4.5 mo vs. **CG** (n=99): Observation	At median 3.6 years: 34 mo (95% CI, 19 to 49) vs. 30 mo (95% CI, 17 to 53) At 2 years PFS rate: 59% (95% CI, 49% to 69%) vs. 54% (95% CI, 43% to 64%); HR=0.94; 95% CI, 0.62 to 1.41; p=0.68	At median 3.6 years: 77 (95% CI, 62 to ∞) vs. NR At 24 mo (unplanned interim analysis): 87% (95% CI, 80% to 94%) vs. 90% (95% CI. 84% to 97%); p=0.13	NR				NR
Bolis 2006	**EG** (n=64): Epidoxorubicin to 3 mo vs.	NR	At 3 years: 79% vs. 79%; p=0.93 At 5 years:	Anemia Neutropenia	EG (n=64) 16% 58%	CG NR	p-value NA	NR

	CG (n=74): Observation		58% vs. 54%; p=0.95	TCP Nausea/Vomiting	8% 2%			
Nicoletto 2004	**EG** (n=60): 5-Fluorouracil and cisplatin to 3 mo vs. **CG** (n=61): Observation	At median 3 years: 68 mo (1.4 to 170) vs. 73 mo (1.6 to 169); 62.1% vs. 62.3%; HR=NR; p=0.41	At median 3 years: 87 mo vs. 89 mo; 82.0% vs. 80.3%; HR=NR; p=0.66	Neutropenia TCP Nausea/Vomiting	EG (n=60) 2% 2% 44%	CG NR	p-value NA	NR
Piccart 2003 (EORTC 55875)	**EG** (n=76): Cisplatin to 3 mo vs. **CG** (n=76): Observation	At median 8 years: 51% vs. 45%; HR=0.89; 95% CI, 0.59-1.33; p=0.58	At median 8 years: 52% vs. 46%; HR=0.82; 95% CI, 0.52 to 1.29; p=0.39	Neuropathy[b]	EG (n=76) 15%	CG NR	p-value NA	NR
1.2. Patients were randomized after the first-line therapy with surgery but before adjuvant chemotherapy								
Pfisterer 2006 (AGO-OVAR 7)	**EG** (n=658): Topotecan 3-weekly, 4 cycles vs. **CG** (n=650): Observation	At median 3.5 years: 18.2 mo (95% CI, 16.6 to 20.7) vs. 18.5 mo (95% CI, 16.8 to 19.9); HR=0.97; 95% CI, 0.85 to 1.10; p= 0.69	At median 3.5 years: 43.1 mo (95% CI, 37.6 to 48.7) vs. 44.5 mo (95% CI, 39.0 to 51.5); HR=1.01; 95% CI, 0.86 to 1.18; p= 0.89	Anemia Neutropenia TCP Nausea Vomiting Sensory	EG (n=658) 18% 76% 27% 4% 3% 6%	CG (n=650) 7% 55% 5% 4% 2% 5%	p-value: <0.01 <0.01 <0.01 0.63 0.54 0.78	1154 (88%) of patients were assessed in the QOL analysis by using the global health score. There was no statistically significant difference between two groups during treatment or follow-up.
De Placido 2004 (MITO-1)	**EG** (n=137): Topotecan 3-weekly, 4 cycles vs. **CG** (n=136): Observation	At median 2.3 years: 18.2 mo vs. 28.4 mo; HR=1.18; 95% CI, 0.86 to 1.63; p=0.83	At median 2.3 years: p=0.30	Anemia Neutropenia TCP Nausea/ Vomiting	EG (n=112) 9% 58% 23% 4%	CG NR	p-value NA	NR
2. Maintenance therapy with biological therapy								
2.1. Patients randomized after the first-line therapy with surgery and adjuvant chemotherapy								
2.1.1. Alpha-interferon								
Alberts 2006	**EG** (n=35): interferon-alpha vs. **CG** (n=35): Observation	At median 12.3 years: 47 mo (95% CI, 18 to 160) vs. 94 mo (95%, 21 to 102); p=0.56	At median 12.3 years: Not reach vs. 87 mo; p=0.09	Nausea Vomiting	EG (n=35) 14% 14%	CG NR	p-value NA	NR
Hall 2004	**EG** (n=149): Interferon-alpha 2a vs. **CG** (n=149): Observation	At median 27 mo: 10.3 mo vs. 10.4 mo; HR=0.96; 95% CI, 0.75 to 1.22; p=0.73	At median 27 mo: 27 mo vs. 32.7 mo; HR=1.06; 95% CI, 0.82 to 1.38; p=0.65	NR				NR
2.1.2. EGFR inhibitor—Erlotinib								
Vergote 2014	**EG** (n=420): Erlotinib to 24 mo vs. **CG** (n=415): Observation	At median 4.3 years: 12.7 mo vs. 12.4 mo; HR=1.05; 95% CI, 0.90 to 1.23; p=0.53	At median 4.3 years (second interim analysis): 50.8 mo vs. 59.1 mo; HR=0.99; 95% CI, 0.81 to 1.20; p=0.90	NR for the seven AE flagged for concern by the Working Group.				426 (51%) Pts completed assessment at 1 year. Global health/QOL scores showed a significant overall difference between the two groups (P=0.01) and favoured CG. The EORTC QLQ-C30 found

								statistically significant differences at the 5% level in symptom levels and favoured CG.
2.1.3. Anti-idiotypic CA-125 antibody								
2.1.3.1. Abagovomab								
Sabbatini 2013 (MIMOSA)	**EG** (n=593): Abagovomab to 21 mo vs. **CG** (n=295): Placebo	RFS at 2 years: 13.4 mo (10.8 to 13.8) vs. 13.4 mo (10.8 to 16.2); HR=1.099; 95% CI, 0.919 to 1.315; p=0.30	At 2 years: 80% in both arms; HR=1.150; 95% CI, 0.872 to 1.518; p=0.32	Any SAE	EG (n=593) 24%	CG (n=295) 24%	p-value NS	NR
2.1.3.2. Oregovomab								
Berek 2009, Berek 2008, Berek 2004	**EG** (n=251): Oregovomab to 60 mo vs. **CG** (n=120): Placebo	At median 29 mo: Median TTR: 10.3 mo (95% CI, 9.7 to 13.0) vs. 12.9 mo (95% CI, 10.1 to 17.4); p=0.29	For Berek 2009 (phase III RCT) at median 29 mo: OS data were immature and the trial was stopped because of the results of Berek 2008 (phase II). For Berek 2008 at 5 years: 57.5 mo vs. 48.6 mo; HR=0.72; 95% CI, 0.41 to 1.25); p=0.28	Any SAE	EG (n=249) 14%	CG (n=118) 19%	p-value 0.22	There was no difference in QOL for the two groups in the overall analysis or the subdomains by using EORTC QLQ-C30 tool.
2.1.4. Poly ADP ribose polymerase (PARP) inhibitor								
2.1.4.1. Olaparib								
Moore 2018, (SOLO1 trial)	**EG** (n=260): Olaparib to 24.6 mo vs. **CG** (n=131): Placebo to 13.9 mo	At 3 years: 60% vs. 27%; HR=0.3; 95% CI, 0.23 to 0.41; p<0.01 Sensitivity analysis of investigators' assessment: 49.9 mo vs. 13.8 mo; p<0.01)	At 3 years (interim analysis): 84% vs. 80%; HR=0.95; 95% CI, 0.60 to 1.53; p>0.05	Anemia Neutropenia TCP Nausea Vomiting Any AE	EG (n=260) 22% 9% 1% 1% 0.4% 39%	CG (n=130) 2% 5% 2% 0% 1% 18%	p-value <0.01 0.16 0.42 0.25 0.12 <0.01	362 (93%) completed the assessment at 2 years by FACT-O. The estimated between-group difference in change was 3 (not clinically meaningful because <10).
Ray-Coquard 2019 (PAOLA-1/ENGOT-OV25)	**EG** (n=537): Olaparib to 24 mo + bevacizumab to 11 mo vs. **CG** (n=269): Placebo to 24 mo + bevacizumab to 11 mo	At median 2 years: 22.1 mo vs. 16.6 mo; HR=0.59; 95% CI, 0.49 to 0.72; p<0.01	At median 2 years: Data were not matured	Fatal AE Anemia Neutropenia TCP Nausea Vomiting Headache	EG (n=535) 0.2% 17% 6% 2% 2% 1% 0.4%	CG (n=267) 1.5% <1% 3% 0.4% 1% 2% 0.7%	p-value 0.03 <0.01 0.07 0.08 0.30 0.24 0.57	744 (92%) completed the assessment at 2 years. There was no clinically significant difference in QOL between the two groups by using EORTC QLQ-C30.
2.1.4.2. Niraparib								
Gonzalez-Martin 2019 (PRIMA/ENGOT-OV26/GOG-3012)	**EG** (n=487): Niraparib to 36 mo vs. **CG** (n=246): Placebo	At median 13.8 mo: 13.8 mo vs. 8.2 mo; HR=0.62; 95% CI, 0.50 to 0.76; p<0.01	Interim analysis: At 2-year OS: 84% vs. 77%; HR=0.70; 95% CI, 0.44 to 1.11; p>0.05	Tx-related death Tx-related AE Anemia	EG (n=484) 0.4% 65% 31%	CG (n=244) 0.4% 7% 2%	p-value 1.00 <0.01 <0.01	There was no difference in QOL between the two groups by using FOSI, EQ-5D-5L, and EORTC QLQ-C30/OV28 tools.

				Neutropenia TCP Nausea Vomiting Headache	13% 29% 1.2% 1% 0.4%	1% 0.4% 0.8% 1% 0%	<0.01 <0.01 0.62 1.00 0.32	
2.1.5. VEGFR tyrosine kinase inhibitor								
2.1.5.1. Pazopanib								
Vergote 2019, Friedlander 2018, Harter 2016, du Bois 2014 (AGO-OVAR 16)	**EG** (n=472): Pazopanib to 24 mo vs. **CG** (n=468): Placebo	At median 24.3 mo: 17.9 mo (95% CI, 15.9 to 21.8) vs. 12.3 mo (95% CI, 11.8 to 17.7); HR=0.77; 95% CI, 0.64 to 0.91; p<0.01	At median 24.3 mo (second interim analysis): HR=1.08; 95% CI, 0.87 to 1.33; p=0.50 At 7 years (final analysis): HR=0.96; 95% CI, 0.81 to 1.15; p=0.64	Neutropenia TCP Any AE stopped Tx	EG (n=477[c]) 10% 3% 22%	CG (n=461) 2% 1% 3%	p-value <0.01 0.03 <0.01	752 (80%) Pts completed assessment at 25 months. Changes from baseline showed significant difference favoured EG by EORTC QOL-C30 score (5.5 points; 95% CI, 0.7 to 10.4; p=0.03); favoured CG by QLQ-OV28 (8.1 points; 95% CI, 3.6 to 12.5; p<0.01); no difference between two groups (0.018 points; 95% CI -0.033 to 0.069; p=0.49) by EQ-5D-3L.
Kim 2015[d] (East Asian study plus subgroup of AGO-OVAR 16)	**EG** (n=177): Pazopanib to 24 mo vs. **CG** (n=173): Placebo	At median 24.3 mo: 17.9 mo vs. 21.5 mo; HR=1.11; 95% CI, 0.82 to 1.52; p=0.49	From AGO-OVAR 16: At median 24.3 months (second interim analysis): HR=1.71; 95% CI, 1.01 to 2.88; p=0.047 At 7 years (final analysis): HR=1.33; 95% CI, 0.86 to 2.05; p=NS	Neutropenia TCP Vomiting Any AE	EG (n=179) 13% 5% 0.6% 64%	CG (n=174) 2% 2% 0% 16%	p-value <0.01 0.13 0.31 <0.01	NR
2.1.5.2. Sorafenib								
Hainsworth 2015	**EG** (n=43): Sorafenib with adjuvant Tx, and then to 1 year vs. **CG** (n=42): Observation after Adjuvant Tx	At median 3 years: 15.4 mo vs.<16.3 mo; HR= 1.09; p=0.38	At 3 years: 36.5 mo vs. NR, p=0.12	Anemia Neutropenia TCP Nausea/Vomiting	EG (n=43) 16% 26% 21% 7%	CG (n=42) 12% 31% 7% 7%	p-value 0.59 0.61 0.06 1.00	NR
Herzog 2013	**EG** (n=123): Sorafenib to 36 mo vs. **CG** (n=123): Placebo	At 2.5 years: 12.7 mo vs. 15.7 mo; HR=1.09; 95% CI, 0.72 to 1.63; p=NS	At 2.5 years: Median time: NR; HR=1.48; 95% CI, 0.69 to 3.23; p=NS	Vomiting Sensory neuropathy	EG (n=123) 3% 1.6%	CG (n=123) 0 2.4%	p-value 0.04 0.65	NR
2.2. Patients randomized after the first-line therapy with surgery but before adjuvant chemotherapy								
2.2.1. Anti-*VEGF* monoclonal antibody—Bevacizumab								
Gonzalez-Martin 2019, Oza 2015, Stark 2013, Perren 2011 (ICON7)	**EG** (n=764): Bevacizumab with adjuvant Tx, and then up to 12 cycles vs.	At median 4.1 years: RMST: 29.2 mo (95% CI, 27.7 to 30.7) vs. 27.6 mo (95% CI, 26.1	At median 4.1 years: RMST: 45.5 mo (95% CI, 44.2 to 46.7) vs. 44.6 mo (95% CI, 44.32 to 45.9);	Neutropenia TCP Any event	EG (n=745) 17% 3% 491 (66)	CG (n=753) 15% 2% 419 (54)	p-value 0.29 0.21 <0.01	At week 54, 1079 (71%) pts were assessed by EORTC QLQ-C30 and EORTC QLQ-OV28. The mean global QOL score 6.4 higher in the CG group (p<0.01

	CG (n=764): Observation after adjuvant Tx	to 29.2); HR=0.93; 95% CI, 0.83 to 1.05; p=NS	HR=0.99; 95% CI, 0.85 to 1.14; p=NS					clinically significant too). At week 76, 374 (24%) were assessed and no difference was found between two groups (score in EG=72.6 vs. CG=75.9; p=0.43)
Tewari 2019, Norquist 2018, Monk 2013, Burger 2011 (GOG-0218)	**EG1** (n=623): Bevacizumab with adjuvant Tx from cycle 2 to cycle 22 vs. **CG** (n=625): Placebo with and after adjuvant Tx	At median 17.4 mo: 14.1 mo vs. 10.3 mo; HR=0.72; 95% CI, 0.63 to 0.82; p<0.01	At median 17.4 mo: 39.7 mo vs. 39.3 mo; HR=0.92; 95% CI, 0.73 to 1.15; p=0.45 At median 102.9 mo: 43.4 mo vs. 41.1 mo; HR=0.96; 95% CI, 0.85 to 1.09; p=0.53	Fatal AE Neutropenia	EG (n=608) 2.3% 63%	CG (n=601) 1.0% 58%	p-value 0.08 0.08	1388 (74%) Pts completed assessment at 6 months by FACT-O TOI. There were no significant differences across the three treatment groups.
	EG2 (n=625): Bevacizumab with adjuvant Tx from cycle 2 to cycle 6, and placebo from cycle 7 to 22 vs. **CG** (n=625)	At median 17.4 months: 11.2 vs. 10.3; HR=0.91; 95% CI, 0.80 to 1.04; p=0.16	At median 17.4 months: 38.7 mo vs. 39.3 mo; HR=1.04; 95% CI, 0.83 to 1.30; p=0.76. At median 102.9 months: 40.8 mo vs. 41.1 mo; HR=1.06; 95% CI, 0.94 to 1.20; p=0.34	Neutropenia Fata AE	EG2 (n= 607) 63% 1.6%	CG (n=601) 58% 1.0%	p-value 0.08 0.36	
2.2.2. Poly ADP ribose polymerase (PARP) inhibitor—Veliparib								
Coleman 2019 (VELIA/GOG-3005)	**EG1** (n=382): Veliparib to 36 cycles vs. **CG** (n=131): Placebo	At median 28 mo: 23.5 mo (95% CI, 19.3 to 26.3) vs. 17.3 mo (95% CI, 15.1 to 19.1); HR=0.68; 95% CI, 0.56 to 0.83; p<0.01	At median 28 mo: Data were not matured	Any AE Neutropenia TCP Nausea Vomiting	EG1 (n=377) 88% 58% 28% 8% 4%	CG (n=371) 77% 49% 8% 3% 2%	p-value <0.01 0.01 <0.01 <0.01 0.11	60% of pts completed the assessment up to 2 years by NFOSI-18. No clinical significance was found between groups.
	EG2 (n=383): Veliparib to 36 cycles vs. **CG** (n=131): Placebo	At median 28 mo: 15.2 mo vs. 17.3 mo; HR=1.07; 95% CI, 0.90 to 1.29; p>0.05		Any AE Neutropenia TCP Nausea Vomiting	EG2 (n=376) 88% 62% 31% 4% 4%	CG (n=371) 77% 49% 8% 3% 2%	p-value <0.01 <0.01 <0.01 <0.01 >0.05	
2.2.3. Farnesyltransferase inhibitor—Lonafarnib								
Meier 2012	**EG** (n=53): Lonafarnib with adjuvant Tx; then lonafarnib to 6 mo vs. **CG** (n=52): Observation after adjuvant Tx	F-up (NR): 14.2 mo (95% CI, 11.0 to 16.5) vs. 17.8 mo (95% CI, 13.5 to 29.9); HR=1.28; 95% CI, 0.83 to 2.0; p= 0.27	F-up (NR): 34.4 mo (95% CI, 25.9 to 47.7) vs. 47.3 mo (95% CI, 33.3 to ∞); HR=1.61; 95% CI, 0.91 to 2.50; p= 0.08	TCP Nausea Vomiting Polyneuropathy sensory	EG (n=52) 8% 10% 8% 6%	CG (n=51) 2% 2% 2% 0%	p-value 0.36 0.21 0.36 0.08	NR
2.2.4. Protein kinase C-beta inhibitor—Enzastaurin								
Vergote 2013	**EG** (n=69): Enzastaurin with	At median 17.5 mo:	NR	Anemia	EG (n=67) 10%	CG (n=72) 7%	p-value 0.53	NR

	adjuvant Tx, and then to 3 years vs. **CG** (n=73): Placebo	18.9 mo (95% CI, 13.8 to ∞) vs. 15.2 mo (95% CI, 11.0 to 18.9); HR= 0.80; 95% CI, 0.50 to 1.29; p= 0.37		Neutrophils TCP	58% 3%	57% 3%	NS NS	
2.2.5. Triple angiokinase inhibitor—Nintedanib								
Ray-Coquard 2019[e], Du Bois 2016 (AGO-OVAR 12)	**EG** (n=911): Nintedanib with adjuvant Tx and then up to 120 weeks vs. **CG** (n=455): Placebo	At median 5 years: 17.6 mo (95% CI, 16.6 to 20.7) vs. 16.6 mo (95% CI, 13.9 to 19.7); HR=0.86; 95% CI, 0.75 to 0.98; p=0.03	At median 5 years: 62.0 mo (95% CI, 58.3 to not estimable) vs. 62.8 mo (95% CI, 55.4 to not estimable); HR=0.99; 95% CI, 0.83 to 1.17; p=0.86	Tx-related death Anemia Neutropenia TCP Vomiting Nausea Peripheral neuropathy	EG (n=902) 0.3% 14% 42% 18% 3% 4% 4%	CG (n=450) 0.2% 7% 36% 6% 2% 3% 5%	p-values NS <0.01 0.03 <0.01 NS NS NS	896 patients were assessed for quality of life analysis. QOL was assessed using the EORTC QLQ-C30. Overall, QOL was not adversely affected during treatment with nintedanib.
Ferron 2019 [Abstract] (CHIVA)	**EG** (n=124): Nintedanib from cycles 1, 2, 5, 6 to 2 years vs. **CG** (n=64): Placebo	F-up (NR): 14.4 mo (95% CI, 12.2 to 15.4) vs. 16.8 mo (95% CI 13.3 to 21.4); HR=1.50; p=0.02	F-up (NR): 37.7 mo (95% CI 29.8 to 41.0) vs. 44.1 mo (95% CI, 32.7 to not reach); HR=1.54; p=0.053	Any AE	EG (n=NR) 92%	CG (n=NR) 71%	p-values NA	NR
2.2.6. Angiopoietin inhibitor—Trebananib								
Vergote 2019 (TRINOVA-3/ENGOT-ov2/GOG-3001)	**EG** (n=678): Trebananib with adjuvant Tx and then to 18 mo vs. **CG** (n=337): Placebo	At median 27.4 mo: 15.9 mo (95% CI, 15.0 to 17.6) vs. 15.0 mo (95% CI, 12.6 to 16.1); HR=0.93; 95% CI, 0.79 to 1.09; p=0.36	At median 27.4 mo: Data were not matured	Fatal AE Anemia Neutropenia TCP Nausea Vomiting Peripheral neuropathy Any AE	EG (n=675) 3% 12% 48% 9% 3% 2% 3% 76%	CG (n=336) 0.3% 13% 51% 8% 2% 2% 4% 71%	p-values <0.01 0.65 0.37 0.59 0.35 1.00 0.40 0.09	About 90% of patients completed questionnaires. The mean changes in the FACT-O and FACT-O OCS, and health utility states from assessment of EQ-5D and EQ-5D visual analogue scale were not statistically significantly different between two groups.

Abbreviations: AE = adverse event, CA-125 = cancer antigen 125, CG = control group, CI = confidence interval, DFS = disease-free survival, EG = experimental group, EGFR = epidermal growth factor receptor, EORTC = European Organisation for Research and Treatment of Cancer, EQ-5D-3L = EuroQoL-5 dimensions-3 levels, FACT-O = the Functional Assessment of Cancer Therapy-Ovarian Cancer, FACT-O OSC = the Functional Assessment of Cancer Therapy-Ovarian Cancer-specific Scale; FOSI = Functional Assessment of Cancer Therapy Ovarian Symptom Index, F-up = follow up time, HR = hazard ratio, HRD = homologous-recombination deficiency, mo = months, n = sample size, NA = not applicable, NFOSI-18 = National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Ovarian Symptom Index-18, NR = not reported, NS = not significant, OS = overall survival, PFS = progression-free survival, Pts = patients, QLQ-C30 = Quality of Life Questionnaire - Cancer30, QLQ-OV28 = Quality of Life Questionnaire ovarian cancer module, QOL = quality of life, RCT = randomized controlled trial, RFS = relapse-free survival, RMST = restricted mean survival time, SAE = serious adverse event, TCP = Thrombocytopenia, TOI = trial outcome index, TTR = time to relapse, Tx = treatment, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor, vs. = versus.

[a] We calculated p-value by using STATA 15 software (TX: StataCorp LP) if the original authors did not report it.

[b] Patients with Grade 2 or 3 adverse effects were calculated together.

[c] The authors indicated that six patients randomly assigned to the placebo arm who took pazopanib in error.

[d] This paper was accepted by the journal and was published online in October 2015, and included east Asian patients from AGO-OVAR 16.
[e] This trial reported that the median survival time was 62.0 versus 62.8 months for intervention and control group respectively. But it also reported HR = 0.99 with 95% CI of 0.83 to 1.17. From the face value, HR should >1 rather than <1. Thus it may be an error. However, it would not cause any problem for us to make recommendations because it is very close to 1 and not statistically significant.

Table 4-3. Subgroup analysis for *BRCA1/2* mutation and HRD status on survival outcomes

			PFS	OS

Author year (Trial name)	*BRCA1/2* mutation status	Treatment : Experimental group (EG) vs. Control group (CG)	Median time/survival rate, HR (95% CI), p-value	Median time/survival rate, HR (95% CI), p-value
2. Maintenance therapy with biological therapy				
2.1. Patients randomized after the first-line therapy with surgery and adjuvant chemotherapy				
2.1.4. poly ADP ribose polymerase (PARP) inhibitor				
2.1.4.1. Olaparib				
Moore 2018 (SOLO1 trial)	*BRCA1* (n=279)	**EG** (n=188): Olaparib to median 24.6 mo vs. **CG** (n=91): Placebo	At 3 years: HR=0.40; 95% CI, 0.29 to 0.56; p<0.05	NR
	BRCA2 (n=101)	**EG** (n=62): Olaparib to median 24.6 mo vs. **CG** (n=39): Placebo	HR=0.20; 95% CI, 0.10 to 0.38; p<0.05 **Interaction test: p>0.05[a]**	
Ray-Coquard 2019 (PAOLA-1/ENGOT-OV25)	*BRCA1/2* (n=237)	**EG** (n=NR): Olaparib to 24 mo + bevacizumab to 11 mo vs. **CG** (n=NR): Placebo	At 2 years: 37.2 mo vs. 21.7 mo; HR=0.31; 95% CI, 0.20 to 0.47; p<0.05	
	Non-*BRCA1/2* (n=569)	**EG** (n=NR): Olaparib to 24 mo + bevacizumab to 11 mo vs. **CG** (n=NR): Placebo	18.9 mo vs. 16.0 mo; HR=0.71; 95% CI, 0.58 to 0.88; p<0.05 **Interaction test: p<0.01[a]**	
	HRD (n=387)	**EG** (n=NR): Olaparib to 24 mo + bevacizumab to 11 mo vs. **CG** (n=NR): Placebo	At 2 years: 37.2 mo vs. 17.7 mo; HR=0.33; 95% CI, 0.25 to 0.45; p<0.05	
	Non-HRD (n=419)	**EG** (n=NR): Olaparib to 24 mo + bevacizumab to 11 mo vs. **CG** (n=NR): Placebo	16.9 mo vs. 16.0 mo; HR=0.92; 95% CI, 0.72 to 1.17; p>0.05 **Interaction test: p<0.01[a]**	
2.1.4.2. Niraparib				
Gonzalez-Martin 2019 (/ENGOT-OV26/GOG-3012)	For HRD Pts (n=373)	**EG** (n=247): Niraparib to 36 mo vs. **CG** (n=126): Placebo	At median 13.8 mo: 21.9 mo vs. 10.4 mo; HR=0.43; 95% CI, 0.31 to 0.59; p<0.01	Interim analysis: At 2-year OS: 91% vs. 85%; HR=0.61; 95% CI, 0.27 to 1.39; p>0.05
	For non-HRD Pts (n=249)	**EG** (n=169): Niraparib to 36 mo vs. **CG** (n=80): Placebo	At median 13.8 mo: 8.1 mo vs. 5.4 mo; HR=0.68; 95% CI, 0.49 to 0.94; p<0.01 **Interaction test: p=0.05[a]**	Interim analysis: At 2-year OS: 81% vs. 59%; HR=0.51; 95% CI, 0.27 to 0.97; p<0.05 **Interaction test: p>0.05[a]**
	For Pts with HRD: *BRCA1/2* (n=223)	**EG** (n=152): Niraparib to 36 mo vs. **CG** (n=71): Placebo	At median 13.8 mo: 22.1 mo vs. 10.9 mo; HR=0.40; 95% CI, 0.27 to 0.62; p<0.05	NR
	Non-*BRCA1/2* (n=150)	**EG** (n=95): Niraparib to 36 mo vs. **CG** (n=55): Placebo	19.6 mo vs. 8.2 mo; HR=0.50; 95% CI, 0.31 to 0.83; p<0.05 **Interaction test: p>0.05[a]**	
2.1.5. VEGFR tyrosine kinase inhibitor				
2.1.5.1. Pazopanib				
Vergote 2019, Friedlander 2018, Harter 2016, du Bois 2014 (AGO-OVAR 16)	*BRCA1/2* (n=97)	**EG** (n=46): Pazopanib to 24 mo vs. **CG** (n=51): Placebo	At median 24.3 mo: 30.2 mo (95% CI, 17.7 to Not reached) vs. 30.3 mo (95% CI, 23.7 to Not reached); HR=1.36; 95% CI, 0.66 to 2.82; p=0.41	NR
	Non-*BRCA1/2* (n=567)	**EG** (n=289): Pazopanib to 24 mo vs. **CG** (n=278): Placebo	At median 24.3 mo: 17.7 mo (95% CI, 13.2 to 20.9) vs. 14.1 mo (95% CI, 11.7 to 17.7); HR=0.77; 95% CI, 0.62 to 0.97; p=0.02 **Interaction test: p=0.38**	NR

Kim 2018 (East Asian study plus subgroup of AGO-OVAR 16)	*BRCA1/2* (n=41)	**EG** (n=13): Pazopanib to 24 mo vs. **CG** (n=28): Placebo	At median 24.3 mo: 18.0 mo (95% CI, 10.8 to Not reached) vs. 17.0 mo (95% CI, 9.2 to Not reached); HR=0.94; 95% CI, 0.34 to 2.65; p=NS	NR
	Non-*BRCA1/2* (n=215)	**EG** (n=116): Pazopanib to 24 mo vs. **CG** (n=99): Placebo	At median 24.3 mo: 17.5 mo (95% CI, 14.0 to 23.1) vs. Not reached (95% CI, 18.0 to Not reached); HR=1.30; 95% CI, 0.87 to 1.94); p=NS[b]	
2.2. Patients randomized after the first-line therapy with surgery but before adjuvant chemotherapy				
2.2.1. Anti-*VEGF* monoclonal antibody—Bevacizumab				
Tewari 2019, Norquist 2018 (Only including EG—throughout and CG patients) (GOG-0218)	Mutation Pts (about 74% with *BRCA1/2*) (n=228)	**EG1** (n=NR): Bevacizumab from cycle 2 to 22 vs. **CG** (n=NR): Placebo from cycle 2 to 22	At median 17.4 mo: 19.6 mo vs. 15.4 mo; HR=0.95; 95% CI, 0.71 to 1.26; p=NS	At median 102.9 mo: 62.2 vs. 62.0; HR, NR; p=NS
	No mutation Pts (n=581)	**EG1** (n=NR): Bevacizumab from cycle 2 to 22 vs. **CG** (n=NR): Placebo from cycle 2 to 22	At median 17.4 mo: 15.7 mo vs. 10.6 mo; HR=0.71; 95% CI, 0.60 to 0.85; p<0.01 **Interaction test: p=0.10**	At median 102.9 mo: 43.4 mo vs. 40.4; HR, 0.907; p=NS
2.2.2. Poly ADP ribose polymerase (PARP) inhibitor—Veliparib				
Coleman 2019 (VELIA/GOG-3005)	*BRCA1/2* (n=200)[b]	**EG1** (n=108): Veliparib to 36 cycles vs. **CG** (n=92): Placebo	At median 28 mo: 34.7 mo vs. 22.0 mo; HR=0.44; 95% CI, 0.28 to 0.68; p<0.01	Data are not matured
	Non-*BRCA1/2* (n=499)	**EG1** (n=245): Veliparib to 36 cycles vs. **CG** (n=254): Placebo	HR=0.80; 95% CI, 0.64 to 1.00; p=0.05 **Interaction test: p<0.05**[a]	
	BRCA1/2 (n=190)[b]	**EG2** (n=98): Veliparib to 6 cycles, then placebo vs. **CG** (n=92): Placebo	At median 28 mo: 21.1 mo vs. 22.0 mo; HR=1.22; 95% CI, 0.82 to 1.80; p>0.05	
	Non-*BRCA1/2* (n=497)	**EG2** (n=243): Veliparib to 6 cycles, then placebo vs. **CG** (n=254): Placebo	NR	
	HRD (n=421)	**EG1** (n=214): Veliparib to 36 cycles vs. **CG** (n=207): Placebo	At median 28 mo: 31.9 mo vs. 20.5 mo HR=0.57; 95% CI, 0.43 to 0.76; p<0.01	
	Non-HRD (n=249)	**EG1** (n=125): Veliparib to 36 cycles vs. **CG** (n=124): Placebo	HR=0.81; 95% CI, 0.60 to 1.09; p>0.05 **Interaction test: p>0.05**[a]	
	HRD (n=413)	**EG2** (n=206): Veliparib to 6 cycles, then placebo vs. **CG** (n=207): Placebo	At median 28 mo: 18.1 mo vs. 20.5 mo; HR=1.10; 95% CI, 0.86 to 1.41; p>0.05	
	Non-HRD (n=247)	**EG2** (n=123): Veliparib to 6 cycles, then placebo vs. **CG** (n=124): Placebo	NR	

Abbreviations: CG = control group, CI = confidence interval, EG = experimental group, HR = hazard ratio, HRD = homologous-recombination deficiency, mo = months, n = sample size, NR = not reported, NS = not significant, OS = overall survival, PFS = progression-free survival, pts = patients, VEGF = vascular endothelial growth factor, VEGFR = vascular endothelial growth factor receptor, vs. = versus.

[a] The p-value was calculated from the data provided in the paper.

[b] The sample size calculation was powered to test PFS for the BRCA-mutation cohort.

Table 4-4. Subgroup analysis for different stages/risks on survival outcomes

Author year (Trial name)	Stage status	Treatment : Experimental group (EG) vs. Control group (CG)	PFS Median time/survival rate, HR (95% CI), p-value	OS Median time/survival rate, HR (95% CI), p-value	Quality of life (QOL)
1. Consolidation therapy with chemotherapy					
1.2. Patients randomized after the first-line therapy with surgery but before adjuvant chemotherapy					
Pfisterer 2006 (AGO-OVAR 7)	Stratum 1: stage IIB-III with residual ≤1 cm (n=762)	**EG** (n=379): Topotecan 3-weekly, 4 cycles vs. **CG** (n=383): Observation	At median 3.5 years: 26.4 mo (95% CI, 22.5 to 30.1) vs. 28.6 mo (95% CI, 24.0 to 33.2); HR=1.02; 95% CI, 0.85 to 1.22; p=0.84	At median 3.5 years: Not reached (95% CI, 52.6 to unknown) vs. 56.5 mo (95% CI, 54.1 to ∞); HR=1.08; 95% CI, 0.85 to 1.38; p=0.51	NR
	Stratum 2: stage IIB-III with residual >1 cm, or stage IV (n=546)	**EG** (n=279): Topotecan 3-weekly, 4 cycles vs. **CG** (n=267): Observation	At median 3.5 years: 13.1 mo (95% CI, 12.0 to 14.8) vs. 13.1 mo (95%ci, 11.7 to 14.6); HR=0.93; 95% CI, 0.78 to 1.12); p=0.45[a]	At median 3.5 years: 27.2 mo (95% CI, 23.9 to 33.7) vs. 28.6 mo (95% CI, 24.7 to 32.6); HR=0.96; 95% CI, 0.78 to 1.18; p=0.71[a]	
2. Maintenance therapy with biological therapy					
2.1. Patients randomized after the first-line therapy with surgery and adjuvant chemotherapy					
2.1.4. poly ADP ribose polymerase (PARP) inhibitor					
2.1.4.1. Olaparib					
Moore 2018 (SOLO1 trial)	Stage III (n=325)	**EG** (n=220): Olaparib to median 24.6 mo vs. **CG** (n=105): placebo, median 13.9 mo	At 3 years: HR=0.32; 95% CI, 0.24 to 0.44; p<0.05	NR	NR
	Stage IV (n=66)	**EG** (n=40): Olaparib to median 24.6 mo vs. **CG** (n=26): placebo, median 13.9 mo	At 3 years: HR=0.49; 95% CI, 0.25 to 0.94; p<0.05 **Interaction test: p>0.05[b]**		
2.1.4.2. Niraparib					
Gonzalez-Martin 2019 (PRIMA/ENGOT-OV26/GOG-3012)	Stage III (n=476)	**EG** (n=318): Niraparib to 30 mo vs. **CG** (n=158): Placebo	At median 13.8 mo: HR=0.54; 95% CI, 0.42 to 0.70; p<0.05	NR	NR
	Stage IV (n=257)	**EG** (n=169): Niraparib to 30 mo vs. **CG** (n=88): Placebo	HR=0.79; 95% CI, 0.55 to 1.12; p>0.05 **Interaction test: p>0.05[a]**		
2.2. Patients randomized after the first-line therapy with surgery but before adjuvant chemotherapy					
2.2.1. Anti-VEGF monoclonal antibody—Bevacizumab					
Gonzalez-Martin 2019, Oza 2015, Stark 2013, Perren 2011 (ICON7)	High-risk Pts: stage III with residual >1 cm or inoperable, and stage IV (including 6% inoperable pts) (n=502)	**EG** (n=248): Bevacizumab with adjuvant Tx, and up to 12 cycles vs. **CG** (n=254): Observation after adjuvant Tx	At median 4.1 years, RMST: 20.0 mo (95% CI, 18.1 to 21.8) vs. 15.9 mo (95% CI, 14.1 to 17.7); HR=0.73 (95% CI, 0.61 to 0.88; p<0.05	At median 4.1 years, RMST: 39.3 mo (95% CI, 37.0 to 41.7) vs. 34.5 mo (95% CI, 32.0 to 37.0); HR=0.78; 95% CI 0.63 to 0.97; p=0.03	At week 76, 70 (14%) Pts was assessed by EORTC QLQ-C30 and EORTC QLQ-OV28. No significant difference was found between EG and CG (76.7 vs. 72.4; p=0.36) for Global QOL score.
	Non-high-risk Pts: Stage III with residual ≤1 cm	**EG** (n=516): Bevacizumab with adjuvant Tx, and up to 12 cycles vs. **CG** (n=510): Observation after adjuvant Tx	At median 4.1 years, RMST: 33.7 mo (95% CI, 31.9 to 35.5) vs. 33.8 mo (95% CI, 31.8 to 35.7);	At median 4.1 years, RMST: 48.4 mo (95% CI, 47.0 to 49.9) vs. 49.7 mo (95% CI 48.3 to	At week 76, 374 (24%) was assessed and EG had a lower score than CG (71.5 vs. 76.5;

	or stage I-II (n=1026)		HR=1.03; 95% CI, 0.88 to 1.21; p=NS **Interaction test: p<0.01**	51.1); HR=1.14; 95% CI, 0.93 to 1.40; p=0.20 **Interaction test: p=0.01**	p=0.02) for Global QOL score.
Tewari 2019, Burger 2011 (GOG-0218)	Stage III with residual ≤1 cm (n=434)	**EG1** (n=216): Bevacizumab from cycle 2 to 22 vs. **CG** (n=218): Placebo with and after adjuvant Tx from cycle 2 to 22	At median 1.5 years: HR=0.62; 95% CI 0.47 to 0.82;p<0.05	At 102.9 mo: For stage III patients, **EG1** (n=458) vs. **CG** (n=472): 44.3 mo vs. 44.2 mo; HR=1.05; 95% CI, 0.91 to 1.22[c]; P=NS.	NR
	Stage III with residual>1 cm (496)	**EG1** (n=242): Bevacizumab from cycle 2 to 22 vs. **CG** (n=254): Placebo with and after adjuvant Tx from cycle 2 to 22	At median 1.5 years: HR=0.76; 95% CI 0.60 to 0.93;p<0.05 **Interaction test: p>0.05 to compare with stage III with residual ≤1 cm[b]**		
	Stage IV (n=318)	**EG1** (n=165): Bevacizumab from cycle 2 to 22 vs. **CG** (n=153): Placebo with and after adjuvant Tx from cycle 2 to 22	At median 1.5 years: HR=0.70; 95% CI 0.53 to 0.90;p<0.05 **Interaction test: p>0.05 to compare with stage III with residual ≤1 cm; p>0.05 to compare with stage III with residual >1 cm[b]**	At median 8.6 years: 42.8 mo vs. 32.6 mo; HR=0.75; 95% CI 0.59 to 0.95; p<0.05 **Interaction test: p<0.05[b]**	
2.2.2. Poly ADP ribose polymerase (PARP) inhibitor—Veliparib					
Coleman 2019 (VELIA/GOG-3005**)**	Stage III (n=587)	**EG** (n=295): Veliparib up to 24 mo vs. **CG** (n=292): placebo	At 28 mo: HR=0.67; 95% CI, 0.54 to 0.84; p<0.05	Data are not matured	NR
	Stage IV (n=167)	**EG** (n=87): Veliparib up to 24 mo vs. **CG** (n=82): placebo	At 28 mo: HR=0.79; 95% CI, 0.54 to 1.17; p>0.05 **Interaction test: p>0.05[b]**		
2.2.3. Farnesyltransferase inhibitor—Lonafarnib					
Meier 2012	Stage IIB and III with residual ≤1 cm (n=NR)	**EG** (n=NR): Lonafarnib with adjuvant Tx; then lonafarnib to 6 mo vs. **CG** (n=NR): Observation after adjuvant Tx	F-up (NR): 18.8 mo (95% CI, 11.1 to 32.6) vs. 25.3 mo (95% CI, 13.5 to 43.1); HR=1.02; 95% CI, 0.59 to 1.77; p= 0.27	Data are not matured	NR
	Stage III with residual >1 cm and stage IV (n=NR)	**EG** (n=NR): Lonafarnib with adjuvant Tx; then lonafarnib to 6 mo vs. **CG** (n=NR): Observation after adjuvant Tx	F-up (NR): 11.5 mo (95% CI, 7.4 to 14.2) vs. 16.4 mo (95% CI, 10.3 to 40.4); HR=0.36; 95% CI, 0.15 to 0.84; p= 0.01 **Interaction test does not need to calculate as lonafarnib led to worse PFS**	F-up (NR): 20.6 mo (95% CI, 13.1 to 31.0) vs. 43.4 mo (95% CI, 15.7 to unestimated); HR=0.32; 95% CI, 0.13 to 0.80; p= 0.01	
2.2.5. Triple angiokinase inhibitor—Nintedanib					
Ray-Coquard 2019, Du Bois 2016[1] (AGO-OVAR 12)	High-risk Pts: stage III with residual >1 cm or inoperable,	**EG** (n=355): Nintedanib with adjuvant Tx then up to 120 weeks vs. **CG** (n=172): Placebo	At median 5 years: 12.7 mo (95% CI, 11.3 to 13.9) vs. 11.3 mo (95% CI, 11.1 to 13.9); HR=1.03; 95% CI, 0.84 to 1.27; p=NS	At median 5 years: 40.4 mo (95% CI, 36.2 to 46.5) vs. 42.7 mo (95% CI, 33.0 to 52.8); HR=1.14; 95% CI, 0.89 to 1.45; p=NS	NR

	and stage IV (n=527)				
	Non-high-risk Pts: Stage III with residual ≤1 cm or stage I-II (n=839)	**EG** (n=556): Nintedanib with adjuvant Tx then up to 120 weeks vs. **CG** (n=283): Placebo	At median 5 years: 27.7 mo (95% CI, 23.6 to 30.0) vs. 21.7 mo (95% CI, 16.8 to 24.8); HR=0.77; 95% CI, 0.64 to 0.93; p<0.05 **Interaction test: p=0.04**	At median 5 years: NE (95% CI, NE to NE) vs. NE (95% CI, 62.8 to NE); HR=0.89; 95% CI, 0.70 to 1.13; p=NS	
2.2.6. Angiopoietin inhibitor—Trebananib					
Vergote 2019 (TRINOVA-3/ENGOT-ov2/GOG-3001)	Stage IIIA/B (n=89)	**EG** (n=61): Trebananib with adjuvant Tx and then to 18 mo vs. **CG** (n=28): Placebo	At median 27.4 mo: HR=0.76; 95% CI, 0.39 to 1.49; p>0.05	Data are not matured	NR
	Stage IIIC/IV (n=925)	**EG** (n=616): Trebananib with adjuvant Tx and then to 18 mo vs. **CG** (n=309): Placebo	HR=0.96; 95% CI, 0.81 to 1.14; p>0.05[a]		

Abbreviations: CI = confidence interval, EORTC = European Organisation for Research and Treatment of Cancer, HR = hazard ratio, mo = months, n = sample size, NE = not estimated, NR = not reported, NS = not significant, OS = overall survival, QLQ-OV28 = Quality of Life Questionnaire ovarian cancer module, PFS = progression-free survival, Pts = patients, QLQ-C30 = Quality of Life Questionnaire - Cancer30, RMST = restricted mean survival time, Tx = treatment, vs. = versus.

[a] Since there is no statistically significant difference between two groups for all the trial population and for stage subgroup, there is no need to calculate interaction test for this subgroup analysis.

[b] The p-value from interaction test was calculated from the data provided in the paper.

[c] There must be an error because OS was 44.3 months for EG and 44.2 months for CG, the HR should be <1. Since the OS value are almost the same, HR should be very close to 1, and p-value should be not significant, this error will not impact the conclusions of this trial and our recommendation. Also, due to this error, we do not calculate p-value for the interaction test.

Table 4-5. Subgroup analysis for histological types on survival outcomes

Author year (Trial name)	Histological type	Intervention: Experimental group (EG) vs. Control group (CG)	PFS	OS
			Median time/survival rate, HR (95% CI), p-value	Median time /survival rate, HR (95% CI), p-value
2. Maintenance therapy with biological therapy				
2.2. Patients randomized after the first-line therapy with surgery but before adjuvant chemotherapy				
2.2.1. Anti-*VEGF* monoclonal antibody—Bevacizumab				
Gonzalez-Martin 2019, Oza 2015, Stark 2013, Perren 2011 (ICON7)	Low-grade serous tumours (n=80)	**EG** (n=31): Bevacizumab with adjuvant Tx then up to 12 cycles vs. **CG** (n=49): Observation after adjuvant Tx	NR	At median 4.1 years, RMST: 50.5 mo (95% CI, 43.9 to 57.0) vs. 50.4 mo (95% CI, 45.6 to 55.2); Difference=0.1; 95% CI, -7.9 to 8.0; p=NS.
	Clear cell tumours (n=159)	**EG** (n=82): Bevacizumab with adjuvant Tx then up to 12 cycles vs. **CG** (n=77): Observation after adjuvant Tx		At median 4.1 years, RMST: 47.6 mo (95% CI 43.6 to 51.6) vs. 48.0 mo (95% CI 43.9 to 52.2); Difference=-0.4; 95% CI, -6.1 to 5.3; p=NS[b]
Tewari 2019, Burger 2011 (GOG-0218)	Serous tumours (n=1065)	**EG1** (n=524): Bevacizumab from cycle 2 to 22 vs. **CG** (n=541): Placebo	At median 17.4 mo: HR=0.70; 95% CI, 0.57 to 0.82; p<0.05	At 102.9 mo: HR=0.99; p=NS
	Non-serous tumours (n=183)	**EG1** (n=99): Bevacizumab from cycle 2 to 22 vs. **CG** (n=84): Placebo	At median 17.4 mo: HR=0.71; 95% CI, 0.48 to 1.08; p=NS **Interaction test: p>0.05[a]**	At 102.9 mo: HR=0.91; p=NS[b]
2.2.6. Angiopoietin inhibitor—Trebananib				
Vergote 2019 (TRINOVA-3/ENGOT-ov2/GOG-3001)	Serous tumours (n=787)	**EG** (n=525): Trebananib with adjuvant Tx and then to 18 mo vs. **CG** (n=262): Placebo	At median 27.4 mo: HR=0.92; 95% CI, 0.76 to 1.11; p>0.05	Data are not mature
	Non-serous tumours (n=220)	**EG** (n=148): Trebananib with adjuvant Tx and then to 18 mo vs. **CG** (n=72): Placebo	HR=1.07; 95% CI, 0.76 to 1.52; p>0.05[b]	

Abbreviations: CI = confidence interval, HR = hazard ratio, mo = months, n = sample size, NR = not reported, NS = not significant, OS = overall survival, PFS = progression-free survival, RMST = restricted mean survival time, Tx = treatment, vs. = versus.

[a] The p-value from interaction test was calculated from the data provided in the paper.

[b] Since there is no statistically significant difference between two groups for all the trial population and for stage subgroup, there is no need to calculate interaction test for this subgroup analysis.

Table 4-6. Options for recommended maintenance therapy agents in patients with newly diagnosed stage III or IV EOC[a]

Medication agent	Usage and maintenance time[b]	Patient population		
		With *BRCA1/2* mutation	With HRD	Without HRD
Olaparib[c] (PARP inhibitor)	300 mg PO BID for up to 2 years or until progression	Yes	Unclear	Unclear
Niraparib[c] (PARP inhibitor)	200-300 mg PO QD for 3 years	Yes	Yes	Yes
Veliparib[c,d] (PARP inhibitor)	150 mg PO BID for 6 cycles at adjuvant therapy, and then 400 mg BID up to 12 cycles	Yes	Yes	Unclear
Bevacizumab[d] (Anti-VEGF monoclonal antibody)	7.5mg/kg, IV 3-weekly for 6 cycles at adjuvant therapy and then up to 12 cycles or until progression	Yes for high-risk[e]	Yes for high-risk[e]	Yes for high-risk[e]

Abbreviations: BID = twice a day, EOC = epithelial ovary, fallopian tube, or primary peritoneal carcinoma, HRD = homologous-recombination deficiency, PO = by mouth, PARP = Poly ADP ribose polymerase, QD = once a day, VEGF = vascular endothelial growth factor

[a] We are unable to specify the patient population by histological types for different maintenance therapy recommendations. The majority of patients in the eligible studies are high-grade serous. A few studies had subgroup analyses for non-serous types, but no study had pre-planned sample size calculation for subgroup analysis, and all of them were not statistically significant (Table 4-5 in Section 4).

[b] These data are derived from the eligible trials. Patients should stop taking maintenance therapy if they have disease progression. Further research is needed to investigate which maintenance time is most appropriate.

[c] At present, there are no results for overall survival for this agent.

[d] It is unclear if bevacizumab or veliparib can reach the similar effects of PFS and OS reported in the trials when patients received it just after adjuvant chemotherapy without disease progression because in the present two trials, patients took it concurrently with adjuvant therapy and continuously as maintenance therapy.

[e] High-risk patients were defined as stage III with residual >1 cm, inoperable stage III, or stage IV EOC (totally 30 [6%] inoperable stage III or IV patients).

Consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the Patients' Consultation Group, the GDG Expert Panel, and the PEBC RAP (Appendix 2). The results of these evaluations and the Working Group's responses are described below.

Patients' Consultation Group

Six patients/survivors/caregivers representatives in the Patients' Consultation Group reviewed the draft document and provided their comments in a teleconference. Their main comments were: (1) Overall survival (OS) is a critical outcome and a strong recommendation should be made only when there is an OS benefit for a therapeutic agent. (2) They wanted to know whether their QoL would be impacted after taking or not taking a maintenance therapy. The Working Group incorporated the Patient Consultation Group comments into the Justification for Recommendation section under each recommendation in Section 2.

Expert Panel Review and Approval

Of the nine members of the Expert Panel, eight cast votes and one abstained, for a total of 89% response in January 2020. Of those that cast votes, eight approved the document but required revision based on their comments (100%). Especially for Recommendation 2, some of them preferred "Recommendation" rather than "Weak Recommendation". 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. In Section 2, in front of Recommendations, the Working Group stated that "The target patients are those that at the baseline had complete remission, partial remission, or stable disease after adjuvant chemotherapy. They may not have disease related symptoms, thus, it may be difficult to identify the difference in QoL before and after maintenance therapy." I am unsure about this statement. I think that QoL is very important for maintenance therapy. We wish to evaluate how much of a decrement in QoL might be with maintenance therapy versus placebo/observation.	We agree with the reviewer's comment, and have removed this statement.
2. I think the Working Group should re-think whether olaparib is effective in patients with HRD in Table 4-6. Perhaps this should be changed to "unclear". This table appears to provide a recommendation for olaparib monotherapy in HRD, despite the fact that the data	During the Internal Review process, The PAOLA-1 trial was published in full [12]. We agree with the reviewer's comment, and have changed "Yes" to "Unclear".

have only been presented in abstract form and all patients on this study had concurrent bevacizumab (PAOLA-1 trial). At minimum, a footnote needs to be provided for this.	
3. In the SOLO1 trial under Key Evidence section, the Working Group stated, "the interim analysis for OS did not reach a statistically significant difference (84% vs. 80%; HR, 0.95; 95% CI, 0.60 to 1.53)". The way this is written seems to mislead the reader that this advantage is not meaningful. This should be stated as "data to support an OS advantage are immature".	We do not know whether the final OS result will indicate the benefit. Thus, we have changed that sentence to "the final OS data are not mature".
4. Could a stronger recommendation for olaparib be made based on the SOLO1 trial?	Since final OS data are not matured and based on above patients' opinion, we do not think it is appropriate to make a strong recommendation for olaparib now. However, PEBC have an annual assessment process for all PEBC guidelines. If the new evidence appears to support a change in our recommendations, we will update this guideline as soon as possible.
5. In the SOLO1 trial for olaparib and PRIMA trial for niraparib, to report interim analysis result for OS would mislead the readers. This should be stated as "data of OS are immature".	We have revised those sentences based on reviewer's comment.
6. In the SOLO1 trial, the benefit of PFS is clear and also at three years and seems to be maintained for the second PFS. You may need to mention this additional surrogate for Recommendation 2.	In the SOLO1 trial, the second PFS (the time from randomization to second disease progression or death) is beyond the scope of this guideline. Thus, we did not report it.
7. In the PRIMA trial for niraparib, there is an error. There was a non-HRD subgroup in the paper: "In the subgroup of patients with homologous-recombination proficiency, the median duration of progression-free survival was 8.1 months in the niraparib group and 5.4 months in the placebo group (hazard ratio, 0.68; 95% CI, 0.49 to 0.94). In this population, the interim overall survival analysis showed an estimated probability of survival at 24 months of 81% in the niraparib group and 59% in the placebo group (hazard ratio, 0.51; 95% CI, 0.27 to 0.97)."	We have added this result and revised corresponding data in tables and text. Also, we can recommend niraparib in patients with HRD and without HRD as well.
8. Under Recommendation 4, in the GOG-0218 trial, since there was no statistical difference between EG2 and CG for PFS or OS, there is no evidence to support that maintenance therapy should begin at the start of adjuvant therapy. I do not agree with this statement. This could read, "there is uncertainty about the utility of bevacizumab concurrently with cytotoxic	Based on the reviewer's comment, we have changed the sentence into "Since there was no statistical difference between EG2 and CG for PFS or OS, there is uncertainty about the utility of bevacizumab

chemotherapy", however, since no patients on either study were treated with chemotherapy alone followed by maintenance bevacizumab, this statement cannot be qualified.	concurrently with cytotoxic chemotherapy".
9. The ICON7 trial showed significant OS benefit in the pre-planned subgroup of high risk for use of bevacizumab. Can we make a strong recommendation?	Although this trial had a pre-planned subgroup analysis for patients with high-risk ovarian cancer, it did not calculate sample size separately for this subgroup analysis to guarantee the results from a statistical perspective. Also, in the Justification section, we clarified that the study design for maintenance therapy is not optimal. It should be designed as SOLO1 trial: only patients that did not have disease progression should be randomized into maintenance or placebo group. Thus, the Working Group decided not to make a strong recommendation.

RAP Review and Approval

Three RAP members, including the PEBC's Scientific Director, reviewed and approved this document in February 2020 after the following modifications in Table 5-2. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2. If the comments are similar as those from Expert Panel members in Table 5-1, they are not listed again to avoid duplication.

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

Comments	Responses
1. I find the wording confusing. The document title is about maintenance therapy and here the word consolidation is used. This should be clarified.	We have added "consolidation therapy" into the title.
2. Introduction part in Section 4 is key to setting up the inquiry. There should be more detail around the history of treatment leading up to the current inquiry, the rationale for testing maintenance and a bit about the biology.	We have added more information from a clinical perspective.
3. There is only one conference abstract regarding tamoxifen with big data error (Goel 2017). Thus, I think it should be included, but should not be analyzed.	We have deleted that paragraph and explained the reason under Methods section based on reviewer's comment.
4. It seems that the three notes before Recommendations, Key Evidence, and Justification in Section 2 is unnecessary	We have deleted the original three notes, and added two new notes based on other reviewers' comments.

because these contents are covered where it should be under certain Justification parts.	
5. Please clarify the patient population. Do all the patients have surgery? Do all the patients have chemotherapy after surgery? What is the difference between biological therapy and targeted therapy? Please keep consistence across the document.	We focus on patients with newly diagnosed stage II, III, or IV ovarian cancer after first-line surgery and adjuvant therapy. Yes, all the patients should have chemotherapy after surgery. Patients who needed neoadjuvant therapy before surgery were qualified for this guideline as well. We have added this information into "Target Population". Based on our exclusion criteria of "Studies recruited >20% recurrent (including relapsed, drug-sensitive, drug-resistant, drug-persistent, and drug-refractory patients), inoperable, or stage I patients but did not have a subgroup analysis for patients with newly diagnosed EOC on stage II to IV.", if the study recruited ≤20% of inoperable patients, it is still eligible to be included. According to the definitions from National Cancer Institute (https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet). The targeted therapy can be part of biological therapy. In order to reduce confusion of understanding of these terms, we have removed "biological therapy" out of this report because we already have subheadings for different catergories, such as "Poly ADP ribose polymerase inhibitor".
6. Under "Consolidation therapy with chemotherapy" These trials seem similar in approach. Was a formal meta-analysis considered?	Those trials used different agents, different doses, or different frequency, and that is why we did not perform a meta-analysis.
7. In Section 2, I am wondering about the rationale for grouping these agents. The same class, such as "poly ADP ribose polymerase inhibitor" appeared in different categories.	Under maintenance therapy, some trials randomized patients before adjuvant therapy, and others randomized patients after adjuvant therapy. Ideally, patients who do not have disease progression after adjuvant therapy should be randomized into maintenance therapy or placebo group. Within each category, we classified recommendations into two groups: the agents that we recommended and the agents that we did not recommend. We have reworded the subheadings to make them clearer for readers.
8. Under Recommendation 4 in Section 2, I think OS when first presented should be presented in a consistent manner i.e., %, HR, CI, p-value.	Sometimes, the paper did not provide these values, and we are unable to calculate for them. Thus, the reported data may be not in a consistent manner.

9. This guideline focuses on consolidation and maintenance use rather than adjuvant and maintenance use. Why did you recommend bevacizumab and veliparib with adjuvant therapy, and then as a maintenance therapy respectively?	In trials for bevacizumab (ICON7 and GOG-0218) and veliparib (VELIA/GOG-3005), patients were randomized after surgery before adjuvant therapy. There is no arm to use bevacizumab or veliparib in patients without disease progression after adjuvant therapy. We have discussed this limitation in the Discussion section in Section 4. That is why we have four categories for maintenance therapy (please see Response 7. in this table).
10. Since the recommendations are all weak, I think paragraph 1 under discussion could be expanded upon. Here clinical experience can be introduced here while respecting the methodology of evidence synthesis	We have added more discussion from a clinical perspective under the Discussion section in Section 4.
11. I would strongly recommend an attempt at streamlining the information presented in Section 2 and the readability of the tables. Clarify the numbers of articles included, which ones, and its alignment with the tables.	We have reworded and reorganized Section 2, clarified the individual study's name to match it in tables, and revised the tables to improve the readability.
12. I find the key evidence listed in Section 2 too detailed. It would be preferable to serve as sign posts for the reader to refer to the results section for more detail. For example, in Recommendation 1, the "bottom line" is there is no benefit, so sharing the details of the HR, and duration of therapy here is not really helpful and detract the reader's effort in following the recommendation where the numbers are more relevant in convincing the reader to follow the recommendation. In Recommendation 4, subgroup analysis for histological types found no benefit for low grade serous and clear cell tumors. Recommendation 4, key evidence bullet on GOG 0218. Suggest the statement is easier to absorb if it is stated that there is no difference in OS, PFS, QoL benefits between EG1 and EG2 but more Grade 3 or higher neutropenia in EG 1.	Some readers like to have more details in Key Evidence in Section 2, and then they do not go to Section 4 to read the details. We have shortened some sentences, and removed all non-significant data out in Section 2.
13. In Table 4-2, the document presents the evidence based on whether randomization took place after adjuvant chemotherapy. I may have missed it, but a statement somewhere to explain the different power of inference/bias that this makes would be instructive to the reader.	Please see the Response 7. in this table. We discuss this point under Discussion section in Section 4.
14. Table 4-2 Is "Median time" equal to median duration of follow-up?	We have added "Follow-up time" in Table 2.

15. In Table 2, I would encourage giving more space to the intervention, PFS, and OS columns so the data align with the group. I think giving the HR and p-values their own line, allowing the CI to be on one line is well worth the space. It will make the data that is painstakingly compiled more accessible for the reader.	In Table 4-1, we already have details for interventions in each study. Since we prefer to show four outcomes (PFS, OS, adverse effect, and QoL) in one table, we do not have space to give HR, p-value, 95% CI an own line.
16. The trial numbers are inconsistent in Figure, Tables, and the text in Section 2.	We have double-checked all the numbers and revised them. Additionally, the PAOLA-1 trial was published as a full-text article instead of only a conference abstract after we sent this report to RAP Review. Thus, we have changed the corresponding numbers in Figure, Tables, and the text.
17. The recommendation statements are quite long. Is it possible to replace "newly diagnosed SII, III or IV …. and completion of first-line systemic therapy" with "the target population", so the statement is shorter, and the additional conditions (e.g. with homologous recombination deficiency, or with complete or partial remission) easier to pick out from the statement?	We have added a note prior to Recommendations in Section to indicate "the target patients" represents "patients with newly diagnosed stage II, III, or IV EOC". However, since patients were randomized before or after adjuvant therapy in different trials, we are unable to add "completion of first-line systemic therapy" into definition of "the target patients".
18. It is unclear to me why "ongoing trials" is needed to justify the recommendation. In general, I would recommend ways of simplifying/shortening these sections and only include statement that is unique for that particular recommendation. Where common principles apply to multiple recommendations, include this in Section 1.	Based on the reviewer's comment, we have added one note prior to Recommendations in Section 2. Thus, we do not to repeat the same justification in different Recommendations. To simplify Section 2, we also agree to remove "ongoing trials" statement from justification part.

EXTERNAL REVIEW

Targeted Peer Review

Four targeted peer reviewers from Canada who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Two agreed to be the reviewers. One response was received (Appendix 1). Results of the feedback survey are summarized in Table 5-3. The main comments from targeted peer reviewer 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=1)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.			1		

2. Rate the guideline presentation.			1		
3. Rate the guideline recommendations.			1		
4. Rate the completeness of reporting.				1	
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1		
6. Rate the overall quality of the guideline report.				1	
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			3		
8. I would recommend this guideline for use in practice.			3		
9. What are the barriers or enablers to the implementation of this guideline report?	These guidelines will require updating frequently in the coming 1-3 years as data about overall survival mature from the relevant trials of maintenance therapy.				

Table 5-4. Summary of the Working Group's responses to comments from targeted peer reviewer.

Comments	Responses
1. Using the term "recommendation NOT to use the agent" is comfusing. I wasn't sure what that meant and it took a minute of going through the information to understand it. So the subsections Summarizing Recommendations would be easier to follow if broken into Recommend and DO NOT Recommend.	We have reworded the terms that the reviewer pointed out. We have highlighted subheadings for consolidation and maintenance therapy by blue respectively. Under maintenance therapy, we presented recommended agents first, and non-recommended agents were followed. We also have drawn a diagram to show the recommended agents for different target patients, which may be easy for readers to catch the main points from this guideline.
2. The guidelines do not discuss histological type and disease grade. Firstly, this is important as disease biology is not much better defined and these cancers need to be treated as unique diseases. This is also important for the trials of maintenance therapy using PARP inhibitors, in particular niraparib as molecular criteria were not needed, where disease subtype was a consideration for study enrolment.	At the project plan stage, we did not plan to discuss disease grade, but we did subgroup analyses for BRCA1/2 and HRD status, different stages/risks, and histological types in Tables 4-3, 4-4, and 4-5. We also discussed histological types as the fourth limitation under DISCUSSION.
3. The guidelines over emphasize the risk of toxicity with PARP inhibitors, particularly as discussed in the justification sections. While it is true that toxicity did occur on trial with the use of full doses, and as such are reported in toxicity tables, this can be easily mitigated by dose interuption and modification and the vast majority of patients are able to be on maintenance PARP inhibitors without any or very few side effects.Qol data suppport this.	When make recommendations, we need to balance benefits and harms including QoL under Justification section for each recommendation.

4. These guidelines also seem to undervalue the impact of very long PFS. A weak recommendation to use maintenance PARP inhibitors in BRCA mutated cases is completely out of step with clinical practice, and patient goals and desires, and suggests this treatment has little/marginal value. While OS is not reported, it is pending due to the fact that median OS was not reached at last reporting, underscoring the fact that these patient are living long and well. Is there no intemediate strength recommendation? A weak recommendation may lead some uninformed practitioners to not pursue maintenance therapy for BRCA patients, or this may reduce the testing for BRCA mutations, when quite clearly PARP inhibitor in this population in particular is the biggest advance we have had so far.	After discussing with Expert Panel members, the Working Group members have changed "Weak Recommendations" to "Recommendation" for olaparib due to the large benefit showed in supplemental materials (The sensitivity analysis of investigator-assessed PFS showed the difference was 36.1 months [49.9 months vs. 13.8 months; p<0.01] between two groups). The strength of recommendation will be reconsidered when OS data are available.
5. It is very odd/unexpected that the recommendation for *BRCA* mutated cases is the same as for all comers…again this is out of step with clinical priorities. If there is one subtype of this cancer that deserves to be treated with PARP inhibitors, it is *BRCA* mutated cancers. Not emphasized in this guideline, but known to the reviewers, is the fact that PARPi use early in the disease trajectory has yeilded the best results, therefore, these guidelines fall flat in this important area.	Since we did subgroup analysis for *BRCA*1/2 mutation and HRD status, we did our best to incorporate this information. Also, in Table 4-6, we have a column for patients with *BRCA* mutation.
6. In past, I have seen flow diagrams with Ontario guidelines. How should oncologists proceed? What sequence to follow in treating patients? Test everyone for *BRCA*? If BRCA consider olaparib? If Not *BRCA*, what do to?	We have added a diagram in Section 1 to show the recommended agents for different target patients.
7. While complete in reviewing the history or maintenance and "consolidation" therapy, I feel the final recommendations need to be refined.	After External Review process, we have summarized the main comments from Target Reviewer and Professional Consultation, and responded and modified the final recommendation sections. Before we post this guideline on the Ontario Health's CCO website, it should be approved by >75% of the Working Group members and Expert Panel members.

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 the gynecologic oncologists and medical oncologists in the PEBC database who showed interest in ovarian cancer, and the clinical experts whom the Working Group members recommended were contacted by email to inform them of the survey. One hundred and one professionals in Ontario were contacted. Ten (10%) responses were received and the results 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.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				5 (50%)	5 (50%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			2 (20%)	2 (20%)	6 (60%)
3. I would recommend this guideline for use in practice.			1 (10%)	5 (50%)	4 (40%)
4. What are the barriers or enablers to the implementation of this guideline report?	1) There is no demonstrated OS benefit. It is unclear whether that will demonstrate a difference between OS and PFS later on. 2) Finances: until CCO picks up the cost, few patients will be able to receive these recommended agents. 3) I would also like to see updated recommendations based on OS data from SOLO-1 as soon as these are available.				

Table 5-6. Summary of the Working Group's responses to comments from professional consultants.

Comments	Responses
1. There are a lot more drugs than I have seen in previous guidelines. I prefer to have a summary table listing drugs recommended in this guideline. Intended Users could include health care administrators, policy makers	We have added a diagram in Section 1 to make this guideline easy to follow for the readers. The Target Users of PEBC's guidelines are set up to clinicians in Ontario in general. However, the health care administrators and policy makers can apply this guideline in their contexts.
2. For olaparib, although it is true that OS is not yet mature, the magnitude of difference in PFS is larger than any study in ovarian cancer in the past 10 years. A weak recommendation on the part of CCO feels a little odd. On a practical level, the format of these guidelines is not user friendly for the average clinician.	Please see the response for comment 4 in Table 5-4.
3. Can you get the same benefit by using a PARP inhibitor after first recurrence as maintenance?	This question is beyond the scope of this guideline, but we refer you to another PEBC's guideline 4-3 version 4 *Systemic Therapy for Recurrent Epithelial Ovarian Cancer*.
4. In Justification for Recommendation 1: reference is made to "more costly" (also Recommendations 4, 7, 9) but there was no analysis or qualification in the Results sections	The cost-effectiveness analysis is beyond the scope of the PEBC's document. However, the additional maintenance therapy must add more costs, and that is why we mentioned this point when we made recommendations.
5. The term of "first-line surgery" is odd.	We have revised this term to "the first-line therapy with surgery" based on the reviewer's comment.

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.

Appendix 1. Strength of Recommendations for this Guideline (modified based on GRADE [10])

Strength	Definition
Recommendation to use the intervention	The guideline Working Group* believes the benefits of the maintenance therapy in newly diagnosed stage II, III, or IV ovarian cancer patients clearly outweigh the harms for nearly all patients and the group is confident to support the recommended action.
Weak recommendation to use the intervention	The guideline Working Group* believes the benefits and harms of the maintenance therapy in the target population are closely balanced or are more uncertain but still adequate to support the recommended action.
No recommendation for the intervention	The guideline Working Group* is uncertain whether the benefits and harms of the maintenance therapy in the target population are balanced and does not recommend a specific action.
Weak recommendation against the intervention	The guideline Working Group* believes the benefits and harms of the maintenance therapy in the target population are closely balanced or are more uncertain but still adequate to support the recommended action.
Recommendation against the intervention	The guideline Working Group* believes the harms of the maintenance therapy in the target population clearly outweigh the benefits for nearly all patients and the group is confident to support the recommended action.
	The factors considered in the above judgments include desirable and undesirable effects of the maintenance therapy, the certainty of evidence, patient preference, health equity, acceptability, feasibility, and generalizability in Ontario.

*The guideline Working Group includes one medical oncologist, three gynecologic oncologists, and one guideline methodologist.

Appendix 2. Affiliations and conflict of interest declarations

(1). Members of the Working Group

Name	Affiliation	Declarations of interest
Hal Hirte	Division of Medical Oncology, Juravinski Cancer Center, McMaster University, Hamilton, Ontario, Canada	Astra Zeneca and Merck advisory board member; Participated in SOLO-1 and ICON7 trials.
Xiaomei Yao, Health Research Methodologist	Program in Evidence-Based Care, Ontario Health (Cancer Care Ontario), Department of Oncology, McMaster University, Hamilton, Ontario, Canada	None declared
Sarah E. Ferguson	Department of Obstetrics and Gynecology, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada	None declared
Taymaa May	Department of Obstetrics and Gynecology, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada	None declared
Laurie Elit	Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, Canada	2018-2019: 1) coinvestigator of clinical utility of BRCA testing—Grant from Astra Zeneca 2) Astra Zeneca advisory board member. 2017-2018: coinvestigator of clinical utility of BRCA testing—Grant from Astra Zeneca

(2). Members of the Patients' Consultation Group

Name	Declarations of interest
Bob Tuck	None
Lauri Petz	None
Patricia Sevean	None
Lise Craig	None
Marissa Myers	None
Minna Allarakhia	None

(3). Ovarian Cancer Guideline Development Group

Name, Expertise	Affiliation	Declarations of interest
Limor Helpman	Department of Obstetrics and Gynecology, Juravinski Cancer Center, McMaster University, Hamilton, Ontario, Canada	Been a principal investigator for SOLO1, SOLO2, SOLO3, LIGHT (Astra Zeneca – Olaparib), PRIMA (Tesaro – Niraparib)
Josee-Lyne Ethier	Department of Oncology, Kingston Health Sciences Centre Cancer Centre of Southeastern Ontario, Queen's University, Kingston, Ontario, Canada	Received $500 or more in a single year to act in a consulting capacity from Astra Zeneca (speaker) and Merck (advisory board); received other financial or material support from Astra Zeneca (conference travel); been a local principal investigator for LIGHT trial (Astra Zeneca) and Merck trials (MK-7339, MK-7902)
Liat Hogen	Department of Obstetrics and Gynecology, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada	None
Stephanie Lheureux	Cancer Clinical Research Unit, Princess Margaret Cancer Centre, Toronto, Ontario, Canada	Received $500 or more in a single year to act in a consulting capacity from Merck and Astra Zeneca; been a principal investigator of different clinical trials including clinical trials in ovarian cancer; published an editorial, commentary, or other clear opinion regarding any of the objects of study (Epithelial ovarian cancer: Evolution of management in the era of precision medicine. Lheureux S, Braunstein M, Oza AM. CA Cancer J Clin. 2019 May 17. doi: 10.3322/caac.21559. [Epub ahead of print] Review. Epithelial ovarian

		cancer. Lheureux S, Gourley C, Vergote I, Oza AM. Lancet. 2019 Mar 23;393(10177):1240-1253. doi: 10.1016/S0140-6736(18)32552-2. Review.)
Neesha Dhani	Cancer Clinical Research Unit, Princess Margaret Cancer Centre, Toronto, Ontario, Canada	Received honorarium from AstraZeneca to present updates on parp inhibitors in ovarian cancer in community medical oncology setting; been a site-principal investigator of an industry sponsored international study evaluating role of olaparib in BRCA-mutated pancreatic cancer (POLO trial); published advice or guidance regarding the objects of study in a public capacity (Dhani N, Oza A. Targeting Angiogenesis: Taming the Medusa of Ovarian Cancer. Hematol Oncol Clin North Am. 2018 Dec;32(6):1041-1055)
Stephen Welch	Division of Medical Oncology, Western University, London, Ontario, Canada	Received honoraria for speaking from Astra Zeneca (Advisory Board); been a local principal investigator for Astra Zeneca, Merck, Tesaro, Clovis
Allison Ball	Department of Obstetrics and Gynecology, Royal Victoria Regional Health Centre, University of Toronto, Toronto, Ontario, Canada	Received honorarium for speaking from Astra Zeneca; been a principal investigator for the OVC.2 study
Lilian Gien	Department of Obstetrics and Gynecology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada	None

Helen Mackay	Division of Medical Oncology and Hematology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada	Received $500 or more in a single year to act in a consulting capacity from Merck (Advisory Board)

(4). Members of the Report Approval Panel

Name, Expertise	Affiliation	Declarations of interest
Rebecca Wong	Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada	None
Marko Simunovic	Department of Surgery, Juravinski Cancer Centre, Hamilton, Ontario, Canada	None
Jonathan Sussman, Radiation Oncologist	Department of Oncology, Juravinski Cancer Centre, Hamilton, Ontario, Canada	None

(5). Targeted Peer Reviewer

Name, Expertise	Affiliation	Declarations of interest
Anna Tinker	Ovarian Cancer Research Program, Cheryl Brown Ovarian Cancer Outcomes Unit, Division of Medical Oncology, University of British Columbia, Vancouver, British Columbia	Grant funding from Asta Zeneca

Appendix 3. Literature Search Strategy

1). Databases: **Embase, EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Health Technology Assessment, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 2003 to October 4, 2019

Search Strategies:

#	Searches
1	exp Ovarian Neoplasms/
2	exp ovary tumor/
3	(ovar$ adj6 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$ or metasta$)).mp.
4	(fallopian tube adj4 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$ or metasta$)).mp.
5	(primary peritoneal adj4 (cancer$ or neoplas$ or adenocarcinom$ or carcinom$ or malignan$ or tumo?r$ or metasta$ or metasta$)).mp.
6	or/1-5
7	drug therap$.mp. or exp Drug Therapy/ or exp antineoplastic agent/ or exp chemotherapy/ or chemotherapy, adjuvant/ or consolidation chemotherapy/ or antineoplastic combined chemotherapy protocols/ or molecular targeted therapy/
8	((systemic or biolog$ or target$ or immun$ or hormon$ or vaccin$ or maintenance) adj2 (therap$ or treatment$)).mp.
9	exp Immunotherapy/ or immunotherap$.tw.
10	chemotherap$.tw.
11	(adriamycin or carboplatin$ or cisplatin$ or platin$ or platamin or neoplatin or cismaplat or cis-diamminedichloroplatinum or cisdiamminedichloroplatinum or cyclophosphamide or doxorubicin or epirubicin or gemcitabine$ or irinotecan or isosfamide or paclitaxel$ or taxane or etoposide or platinum).tw.
12	MEK$ inhibitor$.tw.
13	(PD-325901 or Selumetinib or AZD6244 or PD184352 or PD-184352 or CI-1040 or PD035901 or TAK-733 or TAK733).tw.
14	(binimetinib or MEK162 or MEK-162 or ARRY-162 or ARRY-438162).tw.
15	(trametinib or GSK1120212 or GSK-1120212 or mekinist).tw.
16	(cobimetinib or cotellic or XL518 or GDC-0973 or XL-518).tw.
17	exp "Poly(ADP-ribose) Polymerase Inhibitors"/

18	exp "Poly(ADP-ribose) Polymerase Inhibitors"/ or PARP$.tw.
19	(olaparib or AZD 2281 or AZD2281 or Lynparza or AZD221).tw.
20	(veliparib or ABT888 or talazoparib or BMN673 or nintedanib or iniparib or oregovomab or abagovomab or CA-125 or MUC16 or pazopanib or niraparib or MK4827 or MK-4827).mp.
21	(rucaparib or PF-01367338 or AG014699 or AG-014699).tw.
22	(rapamune or rapamycin or sirolimus or I2190A or I-2190A or AY 22989 or AY 22-989).tw.
23	(cediranib or recentin or AZD2171 or AZD-2171).tw.
24	Antibodies, Monoclonal, Humanized/ or (bevacizumab or avastin).tw.
25	mTOR inhibitor$.tw.
26	(temsirolimus or CCI 779 or CCI-779 or Torisel).tw.
27	(everolimus or afinitor or certican or RAD001 or (RAD adj1 "001") or (SDZ adj1 RAD) or SDZ-RAD).tw.
28	(deforolimus or ridaforolimus or MK8669 or MK-8669 or AP23573 or AP-23573).tw.
29	BRAF inhibitor$.tw.
30	PLX8394.tw.
31	(vemurafenib or RG7204 or RG-7204 or R05185426 or PLX4032 or PLX-4032 or zelboraf).tw.
32	(dabrafenib or tafinlar or GSK2118436 or GSK-2118436).tw.
33	(tumo?r-infiltrating lymphocyte$ therap$ or TIL$ therap$).tw.
34	exp Cytokines/ad, ae, de, re, tu, to [Administration & Dosage, Adverse Effects, Drug Effects, Therapeutic Use, Toxicity]
35	(interleukin-2 or IL-2 or interferon or IFN-alfa or immune checkpoint inhibitor$).tw.
36	(thalidomide or sedoval or thalomid or revlimid or lenalidomide or CC5013 or CC-5013 or IMiD$).tw.
37	(S-3APG or pomalidomide or pomalyst or imnovid or CC-4047 or CC4047).tw.
38	bacille calmette-guerin.tw.
39	(tamoxifen or tomaxithen or zitazonium or soltamox or novaldex or nolvadex or ICI47699 or ICI-47699 or ICI46474 or ICI-46474 or ICI46,474 or ICI-46,474 or fareston).tw.
40	(Fulvestrant or faslodex or ZM 182780 or ZM-182780 or ICI182780 or ICI-182780 or ICI182,780 or ICI-182,780).tw.
41	(letrozole or femara or CGS-20267 or CGS20267).tw.
42	(anastrozole or arimidex or ICI D1033 or ICID1033 or ZD-1033 or ZD1033).tw.
43	(examestane or aromasin or FCE-24304 or FCE24304).tw.

44	(cystorelin or dirigestran or factrel or GnRH or Gn-RH or gonadoliberin or gonadorelin or luliberin or gonadotropin-releasing hormone or kryptocur or LFRH or ((LH-FSH or LHFSH or LH or FSH) adj releasing hormone) or luteinizing hormone-releasing hormone or LH-RH or LHRH or LHFSHRH).tw.
45	((angiogenesis or aromatase or VEGF$ or VEGFR$ or PDGFR$) adj2 inhibitor:).mp.
46	(topotecan or hycamtamine or hycamtin or NSC-609699 or NSC609699 or SKF104864A or SKF-104864A or SKF-104864-A or FOLFOX$ or oxaliplatin or eloxatin or docetaxel or taxotere or RP-56976 or trabectedin or ecteinascidin or yondelis or ET-743 or NSC 684766).tw.
47	or/7-46
48	exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or ((exp Clinical Trial/ or Prospective Study/ or Prospective Studies/) and Random$.tw.) or exp Randomized Controlled Trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or exp "Randomized Controlled Trial (Topic)"/ or "Phase 3 Clinical Trial (Topic)"/ or "Phase 4 Clinical Trial (Topic)"/ or ((exp Clinical Trials as Topic/ or exp "Clinical Trial (Topic)"/) and random$.tw.) or Random Allocation/ or Randomization/ or Single-Blind Method/ or Double-Blind Method/ or Single Blind Procedure/ or Double Blind Procedure/ or Triple Blind Procedure/ or Placebos/ or Placebo/ or ((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or (placebo? or (allocat$ adj2 random$)).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.
49	(RCT$ or random$).tw.
50	48 or 49
51	(systematic adj (review: or overview:)).mp.
52	(meta-analy: or metaanaly:).mp.
53	(pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
54	(exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
55	(cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
56	(reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
57	or/51-56
58	(selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
59	(stud: adj1 select:).ab.
60	(58 or 59) and review.pt.

61	57 or 60
62	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.
63	Animal/ not Human/
64	(editorial or note or letter erratum or short survey).pt. or letter/ or case study/
65	or/62-64
66	(6 and 50) or (6 and 47 and 61)
67	66 not 65
68	limit 67 to english language [Limit not valid in CDSR; records were retained]
69	(201707: or 201708: or 201709: or 201710: or 201711: or 201712: or 2018:).dc. or (201707: or 201708: or 201709: or 201710: or 201711: or 201712: or 2018:).dd.
70	68 and 69
71	remove duplicates from 70

2). Database: PubMed January 2018 to October 4, 2019

Search Strategies:

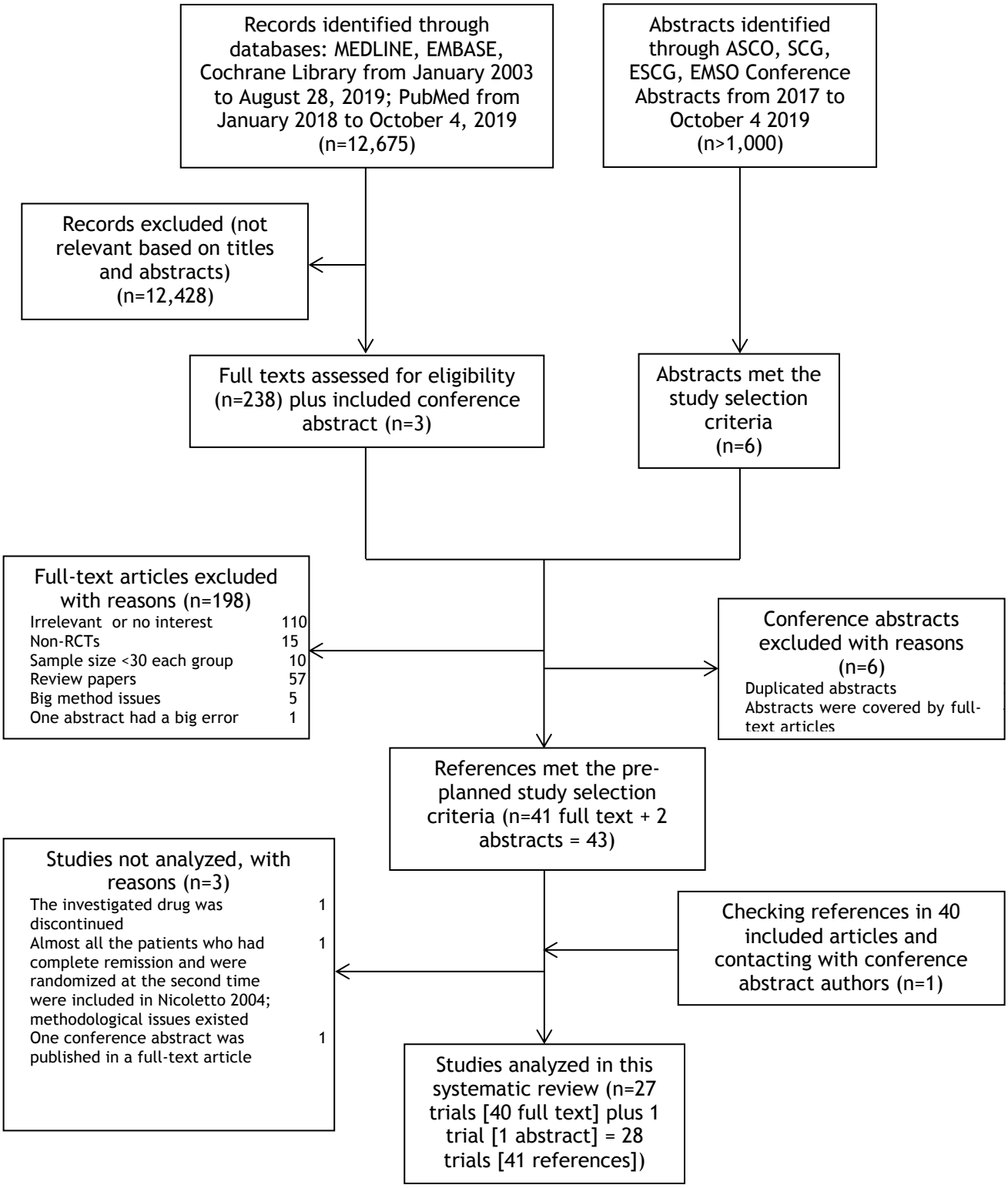
(1) "ovarian Neoplasms/drug therapy"[Mesh] OR "Ovarian Neoplasms/immunology"[Mesh] OR "Ovarian Neoplasms/mortality"[Mesh] OR "Ovarian Neoplasms/pharmacology"[Mesh] OR "Ovarian Neoplasms/therapy"[Mesh] AND ((Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb]) AND ("2017/01/01"[PDAT] : "2020/12/31"[PDAT]))

(2) (ovarian[Title] OR ovary[Title]) AND (cancer[Title] OR tumour[Title] OR tumor[Title] OR carcinoma[Title] OR neoplasm[Title] OR adenocarcinoma[Title]) AND maintenance[Title/Abstract] AND ("2017/01/01"[PDAT] : "2020/12/31"[PDAT])

(3) (((ovarian[Title] OR ovary[Title]) AND (cancer[Title] OR tumour[Title] OR tumor[Title] OR carcinoma[Title] OR neoplasm[Title] OR adenocarcinoma[Title])) AND (randomized[Title/Abstract] OR randomised[Title/Abstract] OR trial[Title/Abstract] OR phase[Title/Abstract])) AND ("2017/01/01"[PDAT] : "2020/12/31"[PDAT])

3). PROSPERO database: To October 4, 2019
Search Strategies: “ovarian” OR “ovary”

Appendix 4. Modified PRISMA flow diagram



Appendix 5. Risk of bias assessment

Trial name; Author year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall[a]
1. Maintenance therapy with chemotherapy							
. Patients were randomized after the first-line therapy with surgery and adjuvant chemotherapy							
van der Burg 2014	Unclear	Unclear	High	High for PFS, adverse effects; Low for OS	Low	Low	High
Markman 2009, Markman 2003 (SWOG-9701/GOG-178)	Low	Unclear	High	High for PFS, adverse effects; Low for OS	Low	Low	Moderate
Pecorelli 2009 (After-6 protocol 1)	Low	Unclear	High	High for PFS, adverse effects; Low for OS	Low	Low	Moderate
Bolis 2006	Low	Low	High	High for PFS, adverse effects; Low for OS	Low	Moderate	Moderate
Nicoletto 2004	Unclear	Unclear	High	High for PFS, adverse effects; Low for OS	Low	Low	High
Piccart 2003	Low	Unclear	High	High for PFS, adverse effects; Low for OS	Low	Low	Moderate
. Patients were randomized after the first-line therapy with surgery but before adjuvant chemotherapy							
Pfisterer 2006 (AGO-OVAR 7)	Low	Low	High	High for PFS, adverse effects, QoL; Low for OS	Low	Low	Moderate
De Placido 2004 (MITO-1)	Low	Low	High	High for PFS, adverse effects, QoL; Low for OS	Low	Low	Moderate
2. Maintenance therapy							
2.1. Patients were randomized after the first-line therapy with surgery and adjuvant chemotherapy							
2.1.1. Alpha-interferon							
Alberts 2006	Unclear	Unclear	High	High for PFS, adverse effects; Low for OS	Low	unclear	High
Hall 2004	Unclear	Unclear	High	High for PFS, adverse effects; Low for OS	Low	Low	High

2.1.2. EGFR inhibitor—Erlotinib							
Vergote 2014	Low	Unclear	High	Unclear for PFS, adverse effects; Low for OS	Low	Low	Moderate
2.1.3. Monoclonal antibody targeted CA-125							
2.1.3.1. Abagovomab							
Sabbatini 2013 (MIMOSA)	Low	Unclear	Low	Unclear for PFS, adverse effects, QoL; Low for OS	Low	Low	Moderate
2.1.3.2. Oregovomab							
Berek 2009, Berek 2008, Berek 2004	Low	Low	Low	Unclear for TTR, adverse effects, QoL; Low for OS	Low	Low	Low
2.1.4. poly ADP ribose polymerase (PARP) inhibitor—Olaparib							
1.1.4.1. Olaparib							
Moore 2018, (SOLO1 trial)	Low	Low	Low	Unclear for PFS, adverse effects, QoL; Low for OS	Low	Low	Low
Ray-Coquard 2019 (PAOLA-1/ENGOT-OV25)	Low	Low	Low	Low for PFS; Unclear for adverse effects, QoL; Low for OS	Low	Low	Low
2.1.4.2. Niraparib							
Gonzalez-Martin 2019 (PRIMA/ENGOT-OV26/GOG-3012)	Low	Low	Low	Unclear for PFS, adverse effects, QoL; Low for OS	Low	Low	Low
2.1.5. VEGFR tyrosine kinase inhibitor							
2.1.5.1. Pazopanib							
Vergote 2019, Friedlander 2018, Harter 2016, du Bois 2014 (AGO-OVAR 16)	Low	Unclear	Low	Unclear for PFS, adverse effects, QoL; Low for OS	Low	Low	Moderate
Kim 2018 (East Asian study plus subgroup of AGO-OVAR 16)	Unclear	Unclear	Low	Unclear for PFS, adverse effects	Low	Low	Moderate
2.1.5.2. Sorafenib							

Hainsworth 2015	Unclear	Unclear	High	High for PFS, adverse effects, QoL; Low for OS	Low	Low	High
Herzog 2013	Low	Unclear	Low	Unclear for PFS, adverse effects; Low for OS	Low	Low	Moderate
2.2. Patients were randomized after the first-line therapy with surgery but before adjuvant chemotherapy							
2.2.1. Anti-VEGF monoclonal antibody—Bevacizumab							
Martin 2019, Oza 2015, Stark 2013, Perren 2011 (ICON7)	Low	Low	High	High for PFS, adverse effects, QoL; Low for OS	Low	Low	Moderate
Tewari 2019, Norquist 2018, Monk 2013, Burger 2011 (GOG-0218)	Low	Unclear	Low	Unclear for PFS, adverse effects, QoL; Low for OS	Low	Low	Moderate
2.2.2. Poly ADP ribose polymerase (PARP) inhibitor—Veliparib							
Coleman 2019 (VELIA/GOG-3005)	Low	Unclear	Low	Unclear for PFS, adverse effects, QoL; Low for OS	Low	Low	Moderate
2.2.3. Farnesyltransferase inhibitor—Lonafarnib							
Meier 2012	Low	Low	High	High for PFS, adverse effects; Low for OS	Low	Low	Moderate
2.2.4. Protein kinase C-beta inhibitor—Enzastaurin							
Vergote 2013	Low	Unclear	Low	Unclear for PFS, adverse effects	Low	Low	Moderate
2.2.5. Triple angiokinase inhibitor—Nintedanib							
Ray-Coquard 2019, Du Bois 2016 (AGO-OVAR 12)	Low	Low	Low	Unclear for PFS, adverse effects, QoL	Low	Low	Low
2.2.6. Angiopoietin inhibitor—Trebananib							
Vergote 2019 (TRINOVA-3/ENGOT-ov2/GOG-3001)	Low	Unclear	Low	Unclear for PFS , adverse effects	Low	Low	Moderate

Abbreviations: EGFR = epidermal growth factor receptor, OS = overall survival, PFS = progression-free survival, QoL = quality of life, TTR = time to relapse, VEGF = vascular endothelial growth factor.

[a] For the study having several outcomes, if different outcomes have different results for one domain, we will accept the highest risk of bias for this domain. If a study has less than two “Unclear” domains, we treat it as “Low” risk of bias for the overall study assessment; if it has two “Unclear” and two “High” risk of bias, we treat it as “High”; and we treat others as “Moderate”.

Appendix 6. Ongoing trials (Oct 5 2019)

Primary investigator (country)	Title	Study design, sample size (age)	Protocol ID	Estimated study completion date
Jacobus Pfisterer (Denmark, Finland, France, Germany, Norway, Sweden)	Evaluation of Optimal Treatment Duration of Bevacizumab Combination With Standard Chemotherapy in Patients With Ovarian Cancer (BOOST)	Phase III RCT, 800 (≥18 years)	NCT01462890	November 2021
Amanda Fader (United States)	Letrozole With or Without Paclitaxel and Carboplatin in Treating Patients With Stage II-IV Low-grade Serous Carcinoma of the Ovary or Peritoneum	Phase III RCT, (≥18 years)	NCT04095364	February 2028
Ales Horacek (Czechia, Germany, Poland)	Phase II Study DCVAC/OvCa Added to First Line Carboplatin and Paclitaxel Newly Diagnosed Epithelial Ovarian Carcinoma	Phase II RCT, 99 (≥18 years)	NCT02107937	December 2023
Philipp Harter and Carol Aghajanian (United Sates, Austria, Belgium, Bulgaria, Canada, Denmark, Finland, France, Germany, Hungary, Italy, Japan, Korea, Romania, Spain, Turkey)	Durvalumab Treatment in Combination With Chemotherapy and Bevacizumab, Followed by Maintenance Durvalumab, Bevacizumab and Olaparib Treatment in Advanced Ovarian Cancer Patients.	Phase III RCT, 1056 (≥18 years and >20 in Japan)	NCT03737643	July 2025
Bradley Monk and Jonathan Ledermann (United States, Australia, Belgium, Estonia, Hungary, Ireland, Italy, Japan, Korea, Russia, Singapore, Slovakia, Taiwan)	Avelumab and Talazoparib in Untreated Advanced Ovarian Cancer (JAVELIN OVARIAN PARP 100)	Phase III RCT, 720 (≥18 years)	NCT03642132	May 2026
NA (United States, Belgium, Canada, Czech Republic, Denmark,	A Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on	Phase III RCT, 620 (≥18 years)	NCT02655016	February 2020

Finland, France, Germany, Hungary, Ireland, Israel, Italy, Norway, Poland, Russia, Spain, Sweden, Switzerland, Ukraine, United Kingdom)	Front-Line Platinum Based Chemotherapy			
NA (China)	A Study of ZL-2306 (Niraparib) as Maintenance Treatment Following First-line Chemotherapy in Patients With Advanced Ovarian Cancer	Phase III RCT, 381 (≥18 years)	NCT03709316	June 2021
Beth Zaharoff (United States)	Phase 2, A Study of Niraparib Combined With Bevacizumab Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy	Phase II RCT, 90 (≥18 years)	NCT03326193	September 2021
NA (Belgium, Canada, Israel, Japan, Korea, Poland, Russia, Spain)	Study of Chemotherapy With Pembrolizumab (MK-3475) Followed by Maintenance With Olaparib (MK-7339) for the First-Line Treatment of Women With *BRCA* Non-mutated Advanced Epithelial Ovarian Cancer (EOC) (MK-7339-001/KEYLYNK-001/ENGOT-ov43)	Phase III RCT, 1086 (≥18 years)	NCT03740165	August 2025
Luisa Manning (United States)	Phase 2 Trial of Maintenance Vigil for High Risk Stage IIIb-IV Ovarian Cancer (VITAL)	Phase II RCT, 91 (≥18 years)	NCT02346747	January 2020
Paul DiSilvestro and Kathleen Moore (United States, Australia, Brazil, Canada, China, France, Israel, Italy, Japan, Korea, Netherlands, Poland, Russia, Spain, United Kingdom)	Olaparib Maintenance Monotherapy in Patients With *BRCA* Mutated Ovarian Cancer Following First Line Platinum Based Chemotherapy.	Phase III RCT, 451 (≥18 years)	NCT01844986	June 2023
Bradley Monk and Rebecca Kristeleit (United	A Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance	Phase III RCT,	NCT03522246	December 2030

States, Australia, Canada, Italy, New Zealand, Russia, Spain, United Kingdom)	Treatment Following Response to Front-Line Platinum-Based Chemotherapy	1012 (≥18 years)		
E Pujade-Lauraine (United States, Australia, Brazil, Canada, China, France, Germany, Israel, Italy, Japan, Korea, Netherlands, Poland, Russia, Spain, United Kingdom)	Olaparib Treatment in *BRCA* Mutated Ovarian Cancer Patients After Complete or Partial Response to Platinum Chemotherapy	Phase III RCT, 327 (≥18 years)	NCT01874353	June 2021
Bradley Monk and Jonathan Ledermann (United States, Bulgaria, Canada, Estonia, Germany, Hong Kong, Hungary, Ireland, Italy, Japan, Korea, Latvia, Mexico, Netherlands, Poland, Romania, Russia, Singapore, Slovakia, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom)	Avelumab in Previously Untreated Patients With Epithelial Ovarian Cancer (JAVELIN OVARIAN 100)	Phase III RCT, 998 (≥18 years)	NCT02718417	May 2019
Beth Zaharoff (United States, Belgium, Denmark, Finland, France, Romania, Spain)	A Phase 3 Comparison of Platinum-Based Therapy With TSR-042 and Niraparib Versus Standard of Care Platinum-Based Therapy as First-Line Treatment of Stage III or IV Nonmucinous Epithelial Ovarian Cancer	Phase III RCT, 960 (≥18 years)	NCT03602859	July 2023
Isabelle Ray Coquard (Austria, Belgium, Denmark, Finland, France,	Platine, Avastin and Olaparib in 1st Line (PAOLA-1)	Phase III RCT, 612 (≥18 years)	NCT02477644	June 2022

Germany, Italy, Japan, Monaco, Spain, Sweden)				
Alexandra Leary (France)	Immunotherapy With Neo-adjuvant Chemotherapy for OVarian Cancer	Phase II RCT, 66 (≥18 years)	NCT03249142	September 2021
NA (China)	A Study of the Efficacy and Safety of Bevacizumab in Chinese Women With Newly Diagnosed, Previously Untreated Stage III or Stage IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Phase III RCT, 100 (≥18 years)	NCT03635489	February 2021
Domenica Lorusso (Italy)	Trial of Carboplatin-Paclitaxel-Bevacizumab vs. Carboplatin-Paclitaxel-Bevacizumab-Rucaparib vs. Carboplatin-Paclitaxel-Rucaparib in Patients With Advanced (Stage III B-C-IV) Ovarian, Primary Peritoneal and Fallopian Tube Cancer.	Phase II RCT, 234 (≥18 years)	NCT03462212	March 2023
Paul DiSilvestro,Kathleen Moore (USA)	Olaparib Maintenance Monotherapy in Patients With *BRCA* Mutated Ovarian Cancer Following First Line Platinum Based Chemotherapy. (SOLO-1)	Phase III, RCT, 450 (≥18 years)	NCT01844986	June 2023
Yuanguang Meng, Weidong Han (China)	Lower Dose Decitabine (DAC)-Primed TC (Carboplatin-Paclitaxel) Regimen in Ovary Cancer	Phase II-III, RCT 500 18-80 years old	NCT02159820	June 2024
Yolanda Garcia (Spain)	Neoadjuvant Therapy in Advanced Ovarian Cancer With Avastin	Phase II, RCT 71 (≥18 years)	NCT01847677	May 2019
Larry J Copeland (USA)	Paclitaxel, Polyglutamate Paclitaxel, or Observation in Treating Patients With Stage III or Stage IV Ovarian Epithelial, Peritoneal Cancer, or Fallopian Tube Cancer	Phase III, RCT 1100 Child, Adult, Older Adult	NCT00108745	January 2022
NA (USA)	A Study of Atezolizumab Versus Placebo in Combination With Paclitaxel, Carboplatin, and Bevacizumab in Participants With Newly-Diagnosed Stage III or Stage IV Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Phase III, RCT 1300, (≥18 years)	NCT03038100	December 2021

Seiko Yamada (USA)	Metformin and Chemotherapy in Treating Patients With Stage III-IV Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Phase II, RCT 160 (≥18 years)	NCT02122185	February 2022

Abbreviation: NA = not available, RCT = randomized controlled trial.

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